Vinod H. Nargund
Derek Raghavan
Howard M. Sandler
Editors

Urological Oncology

Second Edition

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Editors
Vinod H. Nargund, PhD, FRCSED, FRCSUrol, FEBU
Department of Urology
Homerton University Hospital &
Formerly St. Bartholomew's Hospital
London
UK

Derek Raghavan, MD, PhD, FRACP, FACP, FASCO
Levine Cancer Institute
Carolinas HealthCare System
Charlotte, NC
USA

Howard M. Sandler, MD, MS, FASTRO
Radiation Oncology
Cedars Sinai Cancer Center
Los Angeles, CA
USA

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Dedicated to our patients and teachers

Preface to Second Edition

We are delighted to present the second edition of *Urological Oncology* for our readership. When we collaborated with our fine team of authors initially, we felt that there was a need for a simple handbook focused on the interface between science and practical management that would allow the less experienced clinician or one with less specific knowledge of urological malignancies to understand clinical management practices and the basis for their implementation. We were gratified by the impact of the first edition of *Urological Oncology* and by the high level of feedback from readers requesting an update.

With this second edition, we have sought to maintain the didactic and easy-to-assimilate format and at the same time improve domains that might have been covered in more detail and include data from recent practice-changing clinical trials, innovations in laboratory diagnostics, surgery, radiation oncology, systemic therapy, and palliative/supportive care.

Medicine is changing at an ever-increasing pace, with a shifting focus on value rather than volume and an astounding amount of complex molecular and biostatistical information, daunting even to the most experienced clinician. We hope that our second edition will enable all to place these advances in the context of existing practices, so as to encourage more tailored management of patients. The second edition remains again compact, concise, and comprehensive.

We thank our contributors, staff at Springer, and, most of all, our readers, who have made this new edition possible.

September 2014

Vinod H. Nargund
Derek Raghavan
Howard M. Sandler

Preface to First Edition

I keep six honest serving men
(They taught me all I knew);
Their names are What and Why and When
And How and Where and Who.
Rudyard Kipling ("The Elephant's Child," in The Just-So Stories, 1902)

Clinical knowledge is based on three components: meticulous observation, detailed recording, and an understanding of basic science relevant to the clinical situation. The first two come with apprenticeship and the last one with personal research or inquisitive reading. It is the last component that is the basis for this book. Although most general urology books contain a fair amount of urological oncology, most of them are written by urologists for urologists. There is an increasing realization, however, that a multidisciplinary approach is required for the management of all cancers, including urological cancers. In particular, there is a need for surgeons and oncologists to have an integrated strategy for the management of complex cancer cases. A multidisciplinary team will include anesthetists, radiologists, minimally invasive surgeons, intensivists, nutritionists, and support and social work staff in addition to the cancer clinicians. We aim, in this book, to provide this integrated approach as it has contributions from specialists from these different disciplines. All these specialists should have a role in the management of patients to provide them with optimal chances of recovery. They have also a key role in counseling patients in a coordinated way, for otherwise, patients would gain piecemeal information of variable quality from a number of sources, including the Internet. The media and the Internet have increased cancer awareness among patients, who demand more and more answers to questions such as: What caused my cancer? How can I prevent a recurrence? Will my children get it? How do I get the best up-to-date treatment for my cancer?

Patients have a greater understanding that there may be choices in the management of their condition, and oncologists, both surgical and medical, have to listen to and include the patient's views in the decision-making process. We hope this book will assist in both the management and the counseling of patients with urological cancer. The book also includes chapters on basic science, research, and trials related to urological cancers, which will help those students with an interest in research. Relevant surgical anatomy and other details of basic science are included wherever necessary.

Initially, this book was intended to be a pocket guide on adult urological cancer, but it quickly metamorphosed into a minitextbook. The authorship is truly international and therefore reflects a consensus approach to investigation and treatment across the world. The text is didactic and should provide the basis for further reading from journals or more detailed review papers. The book is aimed at residents and urological specialists at all levels of training in urology and oncology.

London, UK — Vinod H. Nargund
Cleveland, OH — Derek Raghavan
Ann Arbor, MI — Howard M. Sandler

Contents

Contributors

Adam Alleemudder, MBChB, BSc, MRCS (Ed) Department of Urology, Barts and The Royal London Hospital, London, UK

Ravishankar Rao Baikady, FRCA Department of Anaesthesia, The Royal Marsden Hospital, London, UK

Sohail Ibrahim Baithun, MB, FRCP Department of Histopathology, King Hospital, Busaiteen, Bahrain

Eric Barret, MD Department of Urology, Institut Montsouris- Universite Paris Descartes, Paris, France

Yakup Bostanci, MD Department of Urology, New York University Hospital, NYU, New York, NY, USA

Ronald M. Bukowski, MD Department of Solid Tumor Oncology, Cleveland Clinic Foundation Taussig Cancer Center, Cleveland, OH, USA

John Buscombe, MD, FRCP Department of Nuclear Medicine, Addenbrookes Hospital, Cambridge, UK

R.S.K. Chaganti, PhD Department of Medicine and Cell Biology Program, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Seungjean Chai, MD Department of Solid Tumor Oncology and Investigational Therapeutics, Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC, USA

Lewis Chan, FRACS, DDU Department of Urology, Concord Repatriation General Hospital, Concord, Australia

Shern L. Chew, BSc, MB, BChir, MD, FRCP Department of Endocrinology, The London Clinic, London, UK

Bob Djavan, MD, PhD Department of Urology, VA University Hospital, New York, NY, USA

Tanya Barauskas Dorff, MD Department of Medicine, USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA

Albert A. Edwards, FRCR Department of Oncology, St. Luke's Cancer Centre, Royal Surrey County Hospital, Guildford, UK

Darren R. Feldman, MD Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

David J. Feuer, FRCP Department of Palliative Medicine, Barts Health NHS Trust and Homerton Hospital NHS Foundation Trust, West Smithfield, London, UK

Sophie D. Fossa, MD, PhD Department of Surgery, Oslo University Hospital, Montebello, Oslo, Norway

Nicos Fotiadis, MD, FRCR, EBIR Department of Interventional Oncology, The Royal Marsden NHS Foundation Trust, London, UK

Gary Frenette, MD, PhD Department of Solid Tumor Oncology, Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC, USA

Matthew D. Galsky, MD Department of Medicine/Oncology, Tisch Cancer Institute/Mount Sinai School of Medicine, New York, NY, USA

L. Michael Glodé, MD Division of Medical Oncology, Department of Medicine, University of Colorado, Aurora, CO, USA

Veronica Greener, BSc, MBBS, MRCP, MD Department of Endocrinology, Chelsea and Westminster Hospital, London, UK

T.R. Leyshon Griffiths, BSc, MD, FRCSEd Department of Cancer Studies and Molecular Medicine, University of Leicester, Leicester, UK

Sounak Gupta, MBBS, PhD Department of Anatomic Pathology, The Cleveland Clinic, Cleveland, OH, USA

Donna E. Hansel, MD, PhD Department of Pathology and Laboratory Medicine Institute, Cleveland Clinic, Cleveland, OH, USA

Axel Heidenreich, MD, PhD Department of Urology, University Hospital Aachen, Aachen, Germany

Thomas Hermanns, MD Division of Urology, Department of Surgical Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada

Simon Horenblas, MD, PhD, FEBU Department of Urology, Netherlands Cancer Institute, Amsterdam, Netherlands

Bo Hu, PhD Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH, USA

Ray K. Iles, PhD, CBiol, FSB, FRSC The Eric Leonard Kruse Foundation for Health Research, An Scoil, Monzievaird, CRIEFF, Perth and Kinross, Scotland, UK

Benjamin L. Jackson, MBchB (hons), FRCS (urol) Department of Urology, University Hospitals Leicester, Leicester, UK

Audrey E.T. Jacques, MDDS, BSc, MRCP, FRCR Department of Radiology, Guy's and St. Thomas Hospital, London, UK

Günter Janetschek, MD Department of Urology and Andrology, Paracelsus Medical University, Salzburg, Austria

Jana Jeyakumar, MRCP, MBBS Department of Medicine, Barts and The London NHS Trust, London, UK

Prashanth Kanagarajah, MD Department of Urology, University of Miami-Miller School of Medicine, Miami, FL, USA

Michael W. Kattan, PhD Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH, USA

Amir Kazzazi, MD Department of Urology, New York University Hospital, NYU, New York, NY, USA

Bridget F. Koontz, MD Department of Radiation Oncology, Duke University Medical Center, Durham, NC, USA

Cynthia Kuk, MSc Division of Urology, Department of Surgery, Mount Sinai Hospital, University Health Network, Toronto, ON, Canada

Priyadarshi Kumar, MB, BS, MRCS, MD, FRCS Department of Urology, Lancashire Teaching Hospitals, NHS Foundation Trust, Lancashire, UK

Robert W. Laing, FRCP Department of Oncology, St. Luke's Cancer Centre, Royal Surrey County Hospital, Guildford, UK

Elaine T. Lam, MD Division of Medical Oncology, Department of Medicine, University of Colorado, Aurora, CO, USA

Stephen E.M. Langley, FRCS Department of Urology, Royal Surrey County Hospital, Guildford, UK

Abigail Lee Department of Morbid Anatomy, The Royal London Hospital, Barts Health NHS Trust, London, UK

Irwin H. Lee, MD, PhD Kaiser Permanente, Rohnert Park, CA, USA

W. Robert Lee, MD Department of Radiation Oncology, Duke University Medical Center, Durham, NC, USA

Hing Yip Leung, MBChB, PhD, FRCS(Urol.) Department of Urology, Beatson Institute for Cancer Research, Institute for Cancer Sciences, University of Glasgow, Glasgow, Strathclyde, UK

Karen W.E. Lord, PhD Department of Palliative Care, University Hospital of Leicester NHS Trust, Leicester, UK

Lukas Lusuardi, MD, FEBU Department of Urology and Andrology, Paracelsus Medical University, Salzburg, Austria

Eamonn R. Maher, BSc, MD, FRCP, FMedSci Department of Medical Genetics, University of Cambridge, Cambridge, UK

John Mahoney, MD Department of Solid Tumor Oncology and Investigational Therapeutics, Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC, USA

Kim Mammen, MS, MCh, FRCS, FACS Department of Urology, Christian Medical College and Hospital, Ludhiana, India

Murugesan Manoharan, MD Department of Urology, University of Miami-Miller School of Medicine, Miami, FL, USA

Rajesh Mehta, MBBS, BSc, FRCA Department of Anesthesia, The Royal London Hospital, Barts Health NHS Trust, London, UK

J. Killian Mellon, MD, FRCS Department of Cancer Studies and Molecular Medicine, University of Leicester, Leicester, UK

Maria Carmen Mir, MD Department of Urology, Cleveland Clinic, Cleveland, OH, USA

Alex J. Mitchell, MBBS, BMedSci, MSc Department of Cancer Studies and Molecular Medicine, University of Leicester, Leicester, UK

Mark R. Morris, PhD, BSc Department of Biology, Chemistry and Forensic Science, University of Wolverhampton, Wolverhampton, UK

Ghulam Nabi, MS, MD, MCh, FRCS (Urol) Department of Urology, Ninewells Hospital, University of Dundee, Dundee, Scotland, UK

Vinod H. Nargund, PhD, FRCSEd, FRCSUrol, FEBU Department of Urology, Homerton University Hospital, London, UK

Jan Oldenburg, MD, PhD Department of Oncology, Oslo University Hospital, Oslo, Norway

Ali Panah, MRCS Department of Urology, Homerton University Hospital NHS Trust, London, UK

Gilles Pasticier, MD Department of Urology, Service d'urologie A-Hopital Pellegrin Place, University Hospital Pellegrim, Bordeaux, France

Jacek Pinski, MD, PhD Department of Medicine, USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA

Melanie Powell, MB, BS, MD, FRCP, FRCR Department of Clinical Oncology, Barts Health NHS Trust, St. Bartholomew's Hospital, London, UK

Shirish G. Prabhudesai, MBBS, MS, MRCS Department of Radiology, St Bartholomew's and The Royal London Hospital, London, UK

Derek Raghavan, MD, PhD, FRACP, FACP, FASCO Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC, USA

Bhavan Prasad Rai, MBBS, MRCSEd Department of Urology, Medical Research Institute, Ninewells Hospital and Medical School, Dundee, Scotland, UK

Prabhakar Rajan, MA, MBBChir, PhD, MRCS Department of Cancer Research, University of Glasgow, Glasgow, Strathclyde, UK

Andrew J. Richards, MBBS, FRACS Department of Urology, Prince of Wales University, Randwick, Australia

Christopher Ricketts, PhD Medical and Molecular Genetics, IBR, University of Birmingham, Birmingham, UK

Brian I. Rini, MD Department of Solid Tumor Oncology, Cleveland Clinic Foundation Taussig Cancer Center, Cleveland, OH, USA

Anju Sahdev, MBBS, MRCP, FRCR Department of Imaging King George V Block, St. Bartholomew's Hospital, London, UK

Howard M. Sandler, MD, MS, FASTRO Department of Radiation Oncology, Cedars Sinai Cancer Center, Los Angeles, CA, USA

Amlesh Seth, MBBS, MS, DNB, MCh(Urol) Department of Urology, All India Institute of Medical Sciences, New Delhi, India

Jonathan Shamash, MD, FRCP Medical Oncology, St. Bartholomew's Hospital, London, UK

Andrew J. Stephenson, MD, FACS, FRCS Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH, USA

Clare Sweeney, MBBS MRCSEd, FRCS (Urol) Department of Urology, Medical Research Institute, Ninewells Hospital and Medical School, Dundee, Scotland, UK

Paul Symonds, MD, FRCP Department of Cancer Studies and Molecular Medicine, University of Leicester, Leicester, UK

Chandran Tanabalan, MRCS Department of Urology, Homerton University Hospital NHS Trust, London, UK

Raj Thuraisingham, MD, FRCP Department of Renal Medicine and Transplantation, Royal London Hospital, London, UK

Alexandre Zlotta, MD, PhD, FRCSC Division of Urology, Department of Surgery, Mount Sinai Hospital, University Health Network, Toronto, ON, Canada

Chapter 1
Normal Cell

Ray K. Iles

Knowledge of normal cell biology is crucial for understanding the function of a normal cell and its deregulation in cancer. This chapter describes briefly the cellular and molecular features of a normal and malignant human cell with particular reference to genitourinary cancers.

Cell Structure and Function

Cell (*plasma*) *membrane* is a bilayer consisting of amphipathic phospholipids, a polar hydrophilic head (phosphatidyl choline) and a lipid hydrophobic tail (commonly two long chain fatty acids). The phospholipids spontaneously form an effective bilayer barrier impermeable to most water-soluble molecules; the barrier also defines cellular internal environment. The membrane exchanges are regulated by proteins embedded within the lipid bilayer. *Cytoskeleton* is a complex network of structural proteins that regulates not only the shape of the cell but its ability to traffic internal cell organelles. The major components are microtubules, intermediate filaments, and microfilaments. *Cytoplasm* contains organelles and defines the interior of the cell. Although a fluid compartment, the organelles are held within a scaffolding or cytoskeleton that regulates the passage and direction in which the interior solutes and storage granules flow.

Basement membrane (BM) is a specialized form of extracellular matrix (ECM) that has been recognized as a key regulator of cell behaviour. In addition to structural support and cell compartmentalization, BM sends a signal to the cells about the extracellular microenvironment, thereby regulating cell behaviours [1]. The role of BM in

R.K. Iles, PhD, CBiol, FSB, FRSC
The Eric Leonard Kruse Foundation for Health Research, An Scoil, Monzievaird, CRIEFF, Perth and Kinross, Scotland, UK
e-mail: ray.iles@anglia.ac.uk

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angiogenesis is described later. The *nucleus* is an organelle containing the human genome and it is bound by two bilayer lipid membranes. The outer of the two is continuous with the endoplasmic reticulum (ER). Nuclear pores are present in the membranes, allowing the passage of nucleotides and DNA interacting proteins in and messenger RNA (mRNA) out. *Nucleoli* are dense areas within the nucleus rich in proteins and RNA chiefly concerned with the synthesis of ribosomal RNA (rRNA) and ribosomes.

The *endoplasmic reticulum* (ER) is interconnecting branching tubules or flattened sacs (cisternae) of lipid membrane bilayer. It may contain ribosomes on the surface [rough endoplasmic reticulum (RER) when present, or smooth endoplasmic reticulum (SER) when absent]. ER is the site of production of transmembrane proteins and lipid and proteins for secretion or for other organelles. *Ribosomes* are complexes of protein and RNA that translate mRNA into a primary sequence of amino acids of a protein peptide chain. This chain is synthesized into the ER where it is first folded and modified into mature peptides.

The *Golgi apparatus* is characterized as a stack of flattened cisternae from which, vesicles bud off from the thickened ends. The primary processed peptides of the ER are exported to the Golgi for maturation into functional proteins (e.g. glycosylation of proteins, which are to be excreted, occurs here) before packaging into secretory granules and cellular vesicles, which bud off the end. *Lysosomes* are dense cellular vesicles containing acidic digestive enzymes.

Mitochondria are semiautonomous organelles responsible for cellular energy metabolism, free radical generation, and apoptosis [2]. They have two lipid bilayer membranes and a central matrix. The *outer membrane* contains gated receptors for the import of raw materials [pyruvate and adenosine diphosphate (ADP)] and the export of precursor of amino acids and sugars (oxaloacetate) and adenosine triphosphate (ATP). Proteins of the Bcl-2-Bax family are incorporated in this membrane and can release cytochrome C that triggers apoptosis [3]. The *inner membrane* is infolded (cristae) to increase its effective surface area, and it contains transmembrane enzyme complexes of the electron transport chain, generating an H^+ ion gradient. *The inner matrix* contains the enzymes of the Krebs' cycle. Mitochondria also possess several copies of their own DNA in a circular genome and thereby maintain genomic independence from the nucleus [4].

Mutations in mitochondrial DNA (mtDNA) have been identified in renal cell carcinoma (RCC) and prostate cancer. In RCC there is evidence to suggest alterations of mtDNA (mutation of the *ND1* gene) and mRNA coding for the subunit *ND3* gene [5, 6]. In prostate cancer there is evidence of mtDNA deletions that increase with advanced age [7]. The knowledge of cancer related mitochondrial abnormalities may help in devising novel anticancer therapies.

Cell Dynamics

The cell component proteins and organelles are continually being formed and degraded. Old cellular proteins are mopped up by a small cofactor molecule called ubiquitin. Ubiquitination acts as a signal for destruction, and a complex containing more than three ubiquitin molecules is rapidly degraded by a macromolecule called

26S proteasome. Failure to remove worn protein can result in the development of chronic debilitating disorders. This is well demonstrated in von Hippel–Lindau (VHL) disease, which is caused by mutation of the *VHL* gene (3p26-p25). There is increased activity in hypoxia inducible factors 1 and 2 (HIF-1 and HIF-2) with *VHL* gene mutation [8]. The HIFs are transcription factors in angiogenesis and tumor growth. The VHL protein is thought to form an E3 ligase (ubiquitin-activating enzyme) [8].

Cytoskeleton

As its name suggests cytoskeleton is a cellular skeleton and is made of protein. The major cytoskeleton components are microtubules, intermediate fi laments, and microfilaments. *Microtubules* are made up of polymerized α and β tubulin and continuously changing length. They form a "highway" transporting organelles through the cytoplasm. Two motor microtubule-associated proteins- dynein and kinesin allow antegrade and retrograde movements. During the *interphase*, the microtubules are rearranged by the microtubule-organizing center (MTOC), which provides a structure on which the daughter chromosomes can separate.

Intermediate filaments form a network around the nucleus and extend to the periphery of the cell. They make cell-to-cell contacts with the adjacent cells via desmosomes and basement matrix via hemidesmosomes. Their function appears to be in structural integrity, being prominent in cellular tissues under stress. The intermediate filament fiber proteins are specific; for example, keratin is intermediate fibers only found in epithelial cells, whereas vimentin is only found in mesothelial (fibroblastic) cells.

Microfilaments

The muscle contractile actin and myosin filaments are also present throughout the nonmuscle cells, as truncated myosins (e.g., myosin 1), in the cytosol (forming a contractile actomyosin gel) beneath the plasma membrane. The calcium-dependent actin-binding proteins modulate the behaviour of microfilaments. Alterations in the cell's actin architecture are also controlled by the activation of small ras-like guanosine triphosphate (GTP)-binding proteins rho and rac. These are important in the rearrangement of the cell during division, and dysfunctions of these proteins are associated with malignancy.

Intercellular Connections

The cytoskeleton and plasma membrane interconnect, and extracellular domains form junctions between cells to form tissues—tight, adherent, and gap junctions.

Tight junctions (TJs) (zonula occludens) hold cells together with the proteins called c*laudins*. They show selective tissue expression and regulate what small ions may pass through the gaps between cells. These are particularly important in the lining urothelium as they create a physiological barrier between urine and blood [9]. Increased urinary concentration of hepatocyte growth factor/scatter factor (HGF/SF) is associated with high grade and muscle invasive bladder cancer [10, 11]; HGF/SF and interleukin-8 disrupt tight junctions and have been thought to cause progression of transitional cell carcinoma (TCC) [12]. *Adherent junctions* (zonula adherens) are continuous on the basal side of cells and contain cadherins. Cadherins comprise a family of calcium-dependent transmembrane cell-to-cell adhesion molecules, and reduced expression of subclass E-cadherin is associated with increased urothelial tumor recurrence and invasiveness [13].

Similarly aberrations in E-cadherin are associated with prostate cancer progression [14]. *Desmosomes* are apposed areas of thickened membranes of two adjacent cells attached to intermediate filaments of cytokeratin. Desmosomal adhesion inhibits invasive behaviour of cancer cells. Invasive TCCs show decreased desmosomal density compared to noninvasive TCCs [15]. *Gap junctions* allow substances to pass directly between cells without entering the extracellular fluids.

Cell Adhesion Molecules

Adhesion molecules and adhesion receptors are essential for tissue structure organization. Differential expression of such molecules is implicit in the processes of cell growth and differentiation, such as wound repair and embryogenesis. There is increasing evidence to suggest that the adhesion properties of neoplastic cells play a key role in the development and progression of cancer [16]. Some of these molecules are involved in cell signalling and tumor suppression. There are four major families of adhesion molecules: cadherins, integrins, the immunoglobulin superfamily, and the selectins. The role of *cadherins* has already been described (zonula adherens). At desmosomal junctions cadherins mediate cell-to-cell connection. Integrins are essential for cell attachment, control cell migration, cell cycle progression, and programmed cell death. They are formed of α and β subunits that dimerize to yield different heterodimers, each with distinct ligand binding and signalling properties. They principally bind to extracellular matrix components such as fibrinogen, elastase, and laminin. Their intracellular domains connect to the actin cytoskeleton. They also affect migration, proliferation, and survival of both normal and neoplastic cells. The $\alpha_6\beta_4$ integrin is associated with collagen VII on the basement membrane of urothelium forming a hemidesmosomal anchoring complex, which acts as an effective barrier to cell migration [17]. Loss of the $\alpha_6\beta_4$ integrin is associated with collagen VII, which explains the defects in the loss of the urothelial barrier in bladder cancer [18].

The *immunoglobulin* superfamily cell adhesion molecules (CAMs) contain domain sequences, which are immunoglobulin-like in structures. The neural CAM (N-CAM) is found predominantly in the nervous system mediating a homophilic

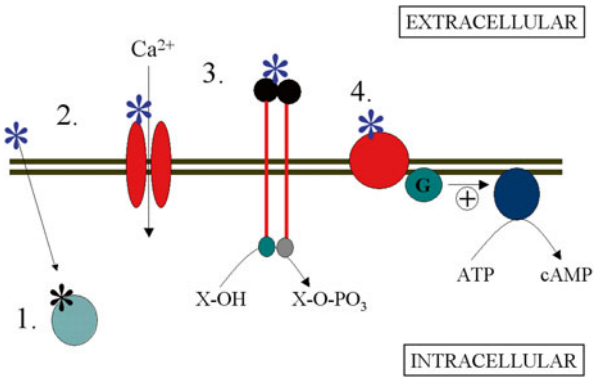

Fig. 1.1 Illustration of the sites of cellular connections and the adhesion molecules found at the interface between the cell and a basement membrane and between cells. Diagrammatic illustration of the four types of receptor found in a cell: *1* cytoplasmic, *2* Ion channel, *3* enzyme linked, *4* G protein linked. (*represents receptor ligand)

(like with like) adhesion. Their function in the urinary tract is not completely understood. The *selectins*, unlike most adhesion molecules that bind to other proteins, interact with carbohydrate-ligands and mucin complexes on leukocytes and endothelial cells (vascular and hematological systems).

Receptors

Cellular interpretation and translation of extracellular signals into an appropriate response is achieved through a diversity of receptors (Fig. 1.1). These signals could be soluble factors (e.g., chemicals, polypeptides, proteins, sugars), a ligand bound to another cell, or the extracellular matrix itself [19]. The receptors then transduce these extracellular signals across the cell wall to activate intracellular pathways, thereby bringing desired change [19]. There are three types of intercellular signalling: autocrine (cells respond to the substances secreted by themselves), paracrine (cells respond to signalling substance from adjacent cells); and endocrine (cells from distant sites). The malignant cells use signalling systems in all possible combinations.

Secondary Messengers

Cyclic AMP, IP3/DAG, and Ca^{2+} Ions

Cyclic adenosine monophosphate (cAMP) is derived from ATP. It functions in intracellular signal transduction (e.g., effects of hormones like glucagon and adrenaline). It activates protein kinases and regulates the passage of Ca^{2+} through ion channels. The G-protein–coupled transmembrane receptors (GPCs) form one of the largest families of cell receptors. G-protein complexes activate inner membrane-bound phospholipase complexes. These in turn cleave membrane phospholipid—polyphosphoinositide (PIP2)—into inositol triphosphate (IP3) (water soluble)

diacylglycerol (DAG) (lipid soluble). The former interacts with gated ion channels in the ER, causing a rapid release of Ca^{2+}, and the latter remains at the membrane, activating a serine/threonine kinase, protein kinase C.

Protein Phosphorylation

Although phosphorylation of the cytoplasmic secondary messengers is often a consequence of secondary activation of cAMP, Ca^{2+} and DAG, the principal route for the protein phosphorylation cascades is from the dimerization of surface protein kinase receptors. The tyrosine kinase receptors phosphorylate each other when ligand binding brings the intracellular receptor components in to close proximity. The inner membrane and cytoplasmic targets of these activated receptor complexes are Ras, protein kinase C, and ultimately the mitogen-activated protein (MAP) kinase, Janus Stat pathways (family of intracellular tyrosine kinase), or phosphorylation of IκB, causing it to release its DNA-binding protein nuclear factor κB (NF-κB). These intracellular signalling proteins usually contain conserved noncatalytic regions called the Serc homology regions 2 and 3 (SH2 and SH3). The SH2 region binds to phosphorylated tyrosine. The SH3 domain has been implicated in the recruitment of intermediates, which activate Ras proteins. Like G proteins, Ras (and its homologous family members Rho and Rac) switches between inactive GDP-binding state and active GTP-binding states. This starts a phosphorylation cascade of the MAP kinase, Janus-Stat protein pathways, which ultimately activate a DNA binding protein. This protein undergoes a conformational change, enters the nucleus, and initiates transcription of specific genes.

Free Radicals

A free radical is any atom or molecule containing one or more unpaired electrons, making it more reactive than the native species. They have been implicated in a large number of human diseases. The hydroxyl (OHO) radical is by far the most reactive species, but the others can generate more reactive species as breakdown products. When a free radical reacts with a nonradical, a chain reaction ensues resulting in direct tissue damage by lipid peroxidation of membranes. Hydroxyl radicals can cause mutations by attacking DNA. Interestingly ionising radiation used in cancer treatment can activate this mechanism by the interaction with water molecules.

Superoxide dismutases O2O (SOD) convert superoxide to hydrogen peroxide. Glutathione peroxidases are major enzymes that remove hydrogen peroxide generated by SOD in cytosol and mitochondria. Free radical scavengers bind reactive oxygen species (ROS). α-Tocopherol, urate, ascorbate, and glutathione remove free radicals by reacting in a direct and noncatalytic way. There is a growing evidence that cardiovascular diseases and cancer can be prevented by a diet rich in substances that diminish oxidative damage. Principal dietary antioxidants include vitamins C and E, β-carotene, and flavonoids.

Heat Shock Proteins

Heat shock proteins (HSPs) are induced by heat shock and other chemical and physical stresses [20], and their functions include the export of proteins in and out of specific cell organelles, acting as molecular chaperones (the catalysis of protein folding and unfolding), and the degradation of proteins (often by ubiquitination pathways). The unifying feature, which leads to the activation of HSPs, is the accumulation of damaged intracellular protein. Tumors have an abnormal thermotolerance, which is the basis for the observation of enhanced cytotoxic effect of chemotherapeutic agents in hyperthermic subjects. The HSPs are expressed in a wide range of human cancers and are implicated in cell proliferation, differentiation, invasion, metastasis, cell death, and immune response [20]. Although HSP detection by immunocytochemistry has been an established practice, serum detection of HSP and its antibodies is still a new research area. Various types of HSP have been demonstrated in urogenital cancers including kidney, prostate, and bladder. For example, HSP27 expression in prostate cancer indicates poor clinical outcome [21, 22].

Programmed Cell Death

In necrotic cell death external factors damage the cell with influx of water and ions leading to the swelling and rupture of cellular organelles. Cell lysis induces acute inflammatory responses *in vivo* (Table 1.1). In apoptosis, cell death occurs through the deliberate activation of constituent genes whose function is to cause their own demise. Necrosis lacks the features of apoptosis and is an uncontrolled process. Another process is autophagy (self eating) which is lysosome mediated catabolic process. Apoptotic cell death has the following characteristic morphological features:

- Chromatin aggregation, with nuclear and cytoplasmic condensation into distinct membrane-bound vesicles, which are termed apoptotic bodies
- Organelles remain intact
- Cell blebs (which are intact membrane vesicles)
- No inflammatory response
- Cellular blebs and remains are phagocytised by adjacent cells and macrophages

Table 1.1 Contrasting morphological features of necrotic and apoptotic cell death

Necrosis	Apoptosis
Swelling of the cell	Cellular shrinkage
Ruptured plasma membrane	Intact plasma membrane
Intact nucleus	Condensation of chromatin and mDNA damage
Nonspecific proteolysis	Specific coordinated proteolysis
Swelling of cell organelles	Normal size cell organelles
Occurs because no energy available	Energy is required

Molecular Biology of Apoptosis

Apoptosis is a highly regulated mechanism of cell death which helps in development process and getting rid of damaged cells. Most cells rely on a constant supply of survival signals without which they will undergo apoptosis. Neighbouring cells and the extracellular matrix provide these signals. Cancer, autoimmunity, and some viral illnesses are associated with inhibition of apoptosis and increased cell survival. Metastatic tumor cells circumvent the normal environmental cues for survival and can survive in foreign environments. The molecular basis of steps of apoptosis—death signals, genetic regulation, and activation of effectors—has been identified [23]. Apoptosis requires energy (ATP), and several Ca^{2+} – and Mg^{2+} dependent nuclease systems are activated, which specifically cleave nuclear DNA at the inter-histone residues. This involves the enzyme cysteine-containing aspartase-specific protease (CASPASE), which activates the caspase-activated DNAase (CAD)/inhibitor of CAD (ICAD) system. Apoptotic signals affect mitochondrial permeability, resulting in reduction in the membrane potential and mitochondrial swelling. The apoptotic trigger cytochrome c is released from mitochondria into cytosol [24].

Bcl-2, p53, and the Proapoptotic Gene Bax

Several proteins including members of the Bcl-2 family regulate mitochondrial permeability. Bcl-2 (24 kd) is associated with the internal membrane of the mitochondria and the nucleus. Bcl-2 suppresses apoptosis by directly preventing mitochondrial permeability and by interacting with other proteins [25]. The other gene that has been studied extensively is the tumor suppressor gene *p53*. It has an important role in cell cycle regulation and acts as a transcription factor that controls other gene products. Normal wild-type *p53* limits cell proliferation after DNA damage by arresting the cell cycle or activating apoptosis [25]. Also, *p53* has a complex role in chemosensitivity; it can increase apoptosis or arrest growth, thereby increasing drug resistance [26]. Drugs like taxanes and vinca alkaloids induce apoptosis independent of *p53*, as they do not damage DNA [26]. The proapoptotic gene *bax* has also been extensively investigated. In contrast to Bcl-2, *bax* is a promoter of apoptosis. Different pathways are discussed later.

Molecular Genetics

Genetic information is stored in the form of double-stranded deoxyribonucleic acid (DNA). Each strand of DNA is made up of a deoxyribose-phosphate backbone and a series of *purine* [adenine (A) and guanine (G)] and *pyrimidine* [thymine (T) and cytosine (C)] bases of the nucleic acid. For practical purposes, the length of DNA is generally measured in numbers of base pairs (bp). The monomeric unit in DNA

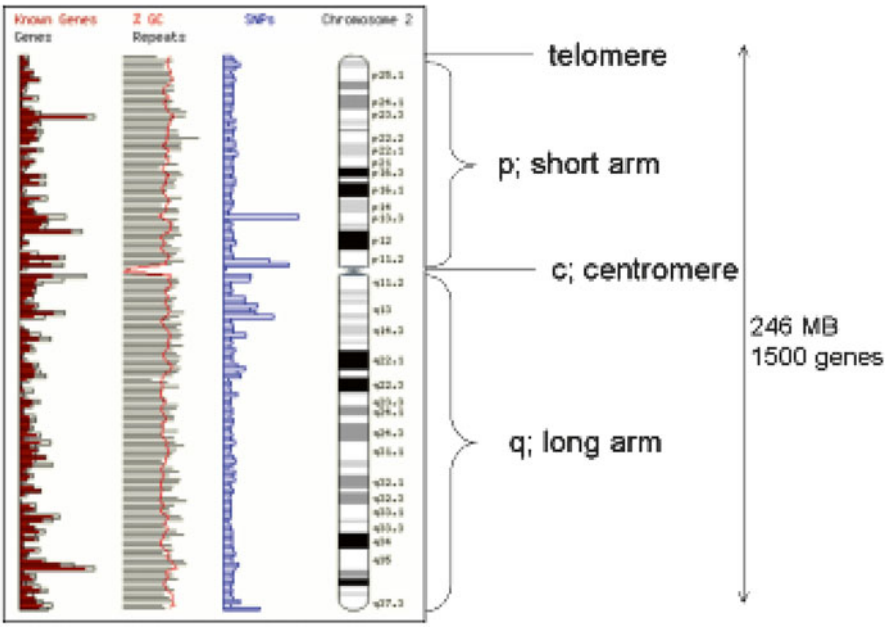

Fig. 1.2 Chromosome structure (ch7) showing the position of the centromere telomeres, and short (*p*) and long arms (*q*). A G-banding pattern is shown and how this maps to known sites of genes and genetic markers such as single nucleotide polymorphisms (SNPs) and the CG rich island, which are characteristic of gene control elements

(and in RNA) is the nucleotide, which is a base joined to a sugar-phosphate unit. The two strands of DNA are held together by hydrogen bonds between the bases. There are only four possible pairs of nucleotides: TA, AT, GC, and CG. The two strands twist to form a double helix with major and minor grooves, and the large stretches of helical DNA are coiled around histone proteins to form nucleosomes and are further condensed into the chromosomes that are seen at metaphase.

Human Chromosomes

The nucleus of each diploid cell contains 3×10^9 bp of DNA (Fig. 1.2). Chromosomes are massive structures containing one linear molecule of DNA that is wound around histone proteins, which are further wound to make up the structure of the chromosome itself. Diploid human cells have 46 chromosomes, 23 inherited from each parent; 22 pairs of autosomes, and two sex chromosomes (XX female and XY male). The chromosomes can be classified according to their size and shape, the largest being chromosome 1. The constriction in the chromosome is the *centromere*, which may be in the middle of the chromosome (metacentric) or at one extreme end (acrocentric). The centromere divides the chromosome into a short arm (*p* arm) and

a long arm (*q* arm). In addition, chromosomes can be stained when they are in the metaphase stage of the cell cycle and are very condensed. The stain gives a different pattern of light and dark bands that is diagnostic for each chromosome. Each band is given a number, and gene mapping techniques allow genes to be positioned within a band within an arm of a chromosome. During cell division, *mitosis*, each chromosome divides into two so that each daughter nucleus has the same number of chromosomes as its parent cell. During gametogenesis, however, the number of chromosomes is halved by *meiosis*.

Telomeres and Immortality

The ends of eukaryotic chromosomes, *telomeres*, do not contain genes but rather many repeats of a guanine-rich hexameric sequence TTAGGG. Telomeres are specialized DNA structures that protect the ends of chromosome from fusion and recombination events [27]. *Telomerase* is a ribonucleoprotein that is necessary to repair the telomeric losses. Replication of linear chromosomes starts at coding sites (origins of replication) within the main body of chromosomes and not at the two extreme ends. The extreme ends are therefore susceptible to single-stranded DNA degradation back to double-stranded DNA. As a consequence of multiple rounds of replication, the telomeres shorten, leading to chromosomal instability and ultimately cell death. Stem cells have longer telomeres than their terminally differentiated daughters. However, germ cells replicate without shortening of their telomeres because of telomerase. Most somatic cells (unlike germ and embryonic cells) switch off the activity of telomerase after birth and die as a result of apoptosis [28]. Many cancer cells, however, reactivate telomerase, contributing to their immortality. Conversely, cells from patients with progeria (premature ageing syndrome) have extremely short telomeres. Telomerase activity is detected in nearly all cancer cells [29]. Likewise, prostate cancer but not normal prostate or benign prostatic hyperplasia (BPH) tissue, expresses telomerase activity [30]. Inhibition of telomerase with DNA-damaging chemotherapy drugs seems a possibility in prostate cancer [31]. Telomerase from exfoliated transitional cell carcinoma cells has been used as a urinary marker in bladder cancer [32].

The Mitochondrial Chromosome

The mitochondrial chromosome is a circular DNA (mtDNA) molecule (16.5 kb), and every base pair makes up part of the coding sequence. These genes principally encode proteins or RNA molecules involved in mitochondrial function. These proteins are components of the mitochondrial respiratory chain involved in oxidative phosphorylation (OXPHOS) producing ATP. The mtDNA mutations are generated during OXPHOS through pathways involving *reactive oxygen species* (ROS), and unlike the nucleus these mutations may accumulate in mitochondria because they lack protective

histones [33]. There are many reasons to believe that the biology of mitochondria could drive tumorigenesis: (1) mitochondria generate ROS, which in high concentrations are highly mitogenic to the nuclear and mitochondrial genomes; (2) mitochondria have a key role in effecting apoptosis; and (3) mitochondria accumulate in high density in some malignant tumors (renal cell carcinoma) as tumor cells have lesser dependence on mitochondria for their oxidative phosphorylation [34]. The mutations of mtDNA have been demonstrated in renal cell, prostate, and bladder cancers.

Genes

A gene is a portion of DNA that contains the codes for a polypeptide sequence. Three adjacent nucleotides (a codon) code for a particular amino acid, such as AGA for arginine, and TTC for phenylalanine. There are only 20 common amino acids, but 64 possible codon combinations that make up the genetic code. This means that more than one triplet encodes for some amino acids; other codons are used as signals for initiating or terminating polypeptide-chain synthesis. Genes consist of lengths of DNA that contain sufficient nucleotide triplets to code for the appropriate number of amino acids in the polypeptide chains of a particular protein. In bacteria the coding sequences are continuous, but in higher organisms these coding sequences (exons) are interrupted by intervening sequences that are noncoding (introns) at various positions. Some genes code for RNA molecules, which will not be further translated into proteins. These code for functional ribosomal RNA (rRNA) and transfer RNA (tRNA), which play vital roles in polypeptide synthesis.

Transcription and Translation

The conversion of genetic information to polypeptides and proteins relies on the transcription of sequences of bases in DNA to mRNA molecules; mRNAs are found mainly in the nucleolus and the cytoplasm, and are polymers of nucleotides containing a ribose phosphate unit attached to a base (Fig. 1.3). RNA is a single-stranded molecule but it can hybridize with a complementary sequence of single-stranded DNA (ssDNA). Genetic information is carried from the nucleus to the cytoplasm by mRNA, which in turn acts as a template for protein synthesis. Each base in the mRNA molecule is lined up opposite to the corresponding base in the DNA: C to G, G to C, U to A, and A to T. A gene is always read in the 5′-3′orientation and at 5′ promoter sites, which specifically bind the enzyme.

RNA polymerase and so indicate where transcription is to commence. Eukaryotic genes have two AT-rich promoter sites. The first, the TATA box, is located about 25 bp upstream of (or before) the transcription start site, while the second, the CAAT box, is 75 bp upstream of the start site.

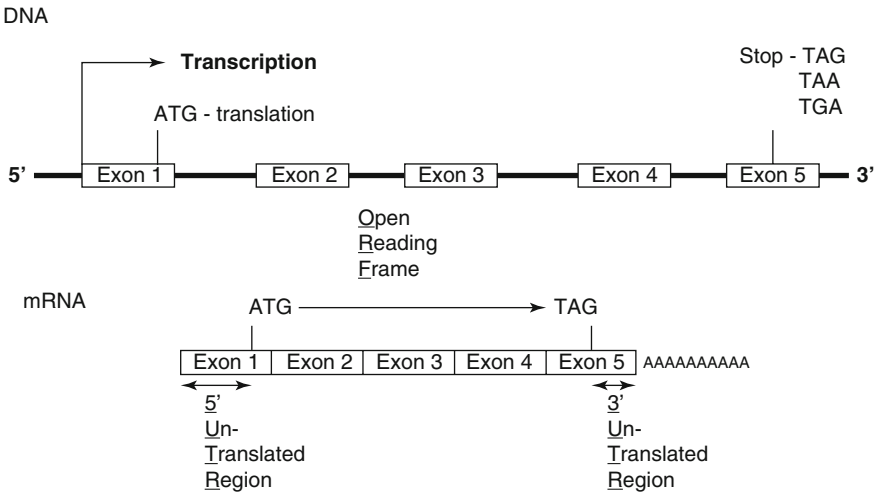

Fig. 1.3 The intronic and exonic structure of a gene coded on chromosomal DNA and the structural correspondence as a processed mRNA

The initial or primary mRNA is a complete copy of one strand of DNA and therefore contains both introns and exons. While still in the nucleus, the mRNA undergoes posttranscriptional modification whereby the 5′and 3′ ends are protected by the addition of an inverted guanidine nucleotide (CAP) and a chain of adenine nucleotides (Poly A), respectively. In higher organisms, the primary transcript mRNA is further processed inside the nucleus, whereby the introns are spliced out. Splicing is achieved by small nuclear RNA in association with specific proteins. Furthermore, alternative splicing is possible whereby an entire exon can be omitted. Thus more than one protein can be coded from the same gene. The processed mRNA then migrates out of the nucleus into the cytoplasm. Polysomes (groups of ribosomes) become attached to the mRNA. Translation begins when the triplet AUG (methionine) is encountered. All proteins start with methionine, but this is often lost as the leading sequence of amino acids of the native peptides is removed during protein folding and posttranslational modification into a mature protein. Similarly the Poly A tail is not translated and is preceded by a stop codon, UAA, UAG, or UGA. The mRNA align on the endoplasmic reticulum and the ribosomal subunit synthesis the polypeptide chain in to the lumen of the ER.

The Control of Gene Expression

Gene expression can be controlled at many points in the steps between the translation of DNA to proteins (Fig. 1.4). Proteins and RNA molecules are in a constant state of turnover; as soon as they are produced, processes for their destruction are at work. For many genes transcriptional control is the most important point of

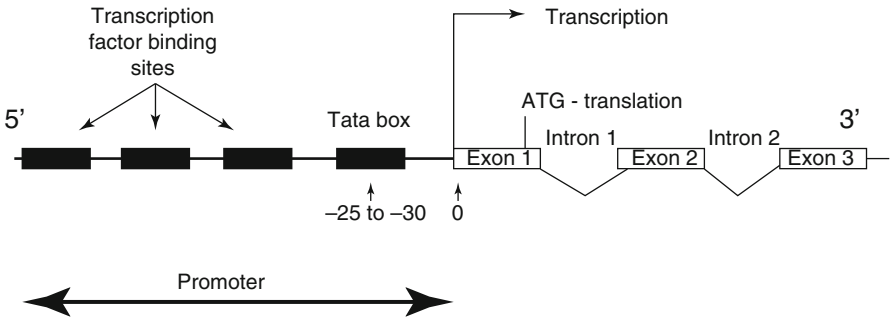

Fig. 1.4 Diagrammatic representation of the location of DNA binding sequence, which constitute the promoter recognition and assembly site in relationship to the site of gene transcription

regulation. Deleterious, even oncogenic, changes to a cell's biology may arise through no fault in the expression of a particular gene. Apparent overexpression may be due to non-breakdown of mRNA or protein product.

Transcriptional Control

Gene transcription (DNA to mRNA) is not a spontaneous event and is possible only as a result of the interaction of a number of DNA-binding proteins with genomic DNA. Regulation of a gene's expression must first start with the opening up of the double helix of DNA in the correct region of the chromosome. To do this, a class of protein molecules that recognize the outside of the DNA helix have evolved.

These DNA-binding proteins preferentially interact with the major groove of the DNA double helix. The base-pair composition of the DNA sequence can change the geometry of a DNA helix to facilitate the fi t of a DNA-binding protein with its target region: CG-rich areas form the Z-structure DNA helix; sequences such as AAAANNN cause a slight bend, and if this is repeated every 10 nucleotides it produces pronounced curves. DNA-binding proteins that recognize these distorted helices result either in the opening up of the helix so that the gene may be transcribed, or in the prevention of the helix being opened.

Structural Classes of DNA-Binding Proteins

The regulation of gene expression is controlled by DNA binding proteins. There are four basic classes of DNA-binding protein, classified according to their structural motifs: helix-turn-helix, zinc finger, helix-loop-helix, and leucine zipper.

Transcription Factors

The *promoter* is a modular arrangement of different elements that act as a binding site for RNA polymerase II and the initiation of transcription. The initiation of transcription involves a large complex of multimeric proteins [RNA polymerase (I or II)] plus the general transcription factors (GTFs). The GTFs can activate transcription of any gene that has a GTF recognition sequence such as the TATA box. The TATA box is a promoter element that is always located 25 to 30 base pairs from the start of transcription and serves to anchor RNA polymerase II.

Operators are proteins that bind to DNA sequences in the spatial areas where the large complex of proteins of the GTFs such RNA polymerase II complex assemble. Their mere presence stoichiometrically inhibits or enhances promoter protein assembly.

Enhancers are elements that can be at the 5′or the 3′ end of genes and can vary in distance from the coding sequence itself. Enhancers are not obligatory for the initiation of transcription but alter its efficiency in such a way as to lead to the upregulation of genes. Looping of the DNA helix allows distantly located enhancers to interact with the promoter site.

Transcription factors are proteins that bind to sequence specific regions of DNA at the 5′ end of genes called response elements to regulate gene expression. These elements can form a part of the promoters or enhancers. They can be divided into basal transcription factors, which are involved in the constitutive activation of so-called housekeeping genes, and inducible transcription factors, which are involved in the temporal and spatial expression of genes that underlie tissue phenotype and developmental regulation.

Insulators are DNA sequence elements which are the answer for the problem of enhancers inappropriately binding to and activating the promoter of some other gene in the same region of the chromosome as the target gene. Insulator binding regions of DNA (as few as 42 base pairs may do the trick) located between the enhancer(s) and promoter or silencer(s) and promoter of adjacent genes or clusters of adjacent genes. The function of the insulator protein is to prevent a gene from being influenced by the activation (or repression) of its neighbors.

The enhancer for the promoter of the gene for the delta chain of the gamma/delta T-cell receptor for antigen (TCR) is located close to the promoter for the alpha chain of the alpha/beta TCR (on chromosome 14 in humans). A T cell must choose between one or the other. There is an insulator between the alpha gene promoter and the delta gene promoter that ensures that activation of one does not spread over to the other.

All insulators discovered so far in vertebrates work only when bound by a protein designated CTCF (“CCCTC binding factor”; named for a nucleotide sequence found in all insulators). CTCF has 11 zinc fingers.

Genetic Disorders in Genitourinary Cancer

Normal cell growth and survival require genomic stability. One of the hallmarks of all neoplasms is genetic instability [35]. Gross chromosomal rearrangements (GCRs) such

as translocations, deletions of a chromosome arm, interstitial deletions, inversions, and gene amplification have been consistently reported in different cancers [36]. Genomic instability in cells leads to the activation of proto-oncogenes or inactivation of tumor suppressor genes leading to transformation and development of cancer phenotypes (see below). Knowledge of the mechanism by which genome stability is maintained is crucial for the development of therapeutic applications in cancer management

Definitions of Chromosomal Disorders

Aneuploidy refers to the state of an abnormal number of chromosomes (differing from the normal diploid number). Abnormalities may occur in either the number or the structure of the chromosomes.

Abnormal Chromosome Numbers

Nondisjunction

If a chromosome or chromatids fail to separate either in meiosis or mitosis, one daughter cell would receive two copies of that chromosome and other cells receive no copies of the chromosome. Nondisjunction during meiosis can lead to an ovum or sperm having either [1] an extra chromosome (trisomic), resulting in three instead of two copies of the chromosome [e.g., trisomy 7 bladder and ureteral tumors [36, 37]]; or [2] no chromosome (monosomic), resulting in one instead of two copies of the chromosome. Full autosomal monosomies are extremely rare and deleterious. Sex chromosome trisomies (e.g., Klinefelter's syndrome, XXY) are relatively common. The sex-chromosome monosomy in which the individual has an X chromosome only and no second X or Y chromosome is known as Turner's syndrome. Occasionally, nondysjunction can occur during mitosis shortly after two gametes have fused. It will then result in the formation of two cell lines, each with a different chromosome complement. This occurs more often with the sex chromosome, and results in a *mosaic* individual. Rarely the entire chromosome set may be present in more than two copies, so the individual may be triploid rather than diploid and have a chromosome number of 69. Triploidy and tetraploidy (four sets) are nonviable.

Abnormal Chromosome Structures

Abnormal constitution of chromosomes can lead to the disruption to the DNA and gene sequences, giving rise to genetic diseases. *Deletions* of a portion of a chromosome may give rise to a disease syndrome if two copies of the genes in the deleted region are necessary, and the individual will not be normal with the one copy

remaining on the nondeleted homologous chromosome. For example, Wilms' tumor is characterized by deletion of part of the short arm of chromosome11.

Duplications occur when a portion of the chromosome is present on the chromosome in two copies, in that there is an extra set of chromosomes present.

Inversions involve an end-to-end reversal of a segment within a chromosome; e.g. abcdefgh becomes abcfedgh. *Translocations* occur when two chromosome regions join together, when they would not normally. Chromosome translocations in somatic cells may be associated with tumorigenesis.

Mitochondrial Chromosome Disorders

Most mitochondrial diseases are myopathies and neuropathies with a maternal pattern of inheritance. Other abnormalities include retinal degeneration, diabetes mellitus, and hearing loss.

Analysis of Chromosome Disorders

The analysis of gross chromosomal disorders has traditionally involved the culture of isolated cells in the presence of toxins such as colchicine. It arrests the cell cycle in mitosis, and with appropriate staining, the chromosomes with their characteristic banding can be identified and any abnormalities detected. New molecular biology techniques, such as yeast artificial chromosome (YAC)-cloned probes, have made it simpler and cover large genetic regions of individual chromosomes. These probes can be labelled with fluorescently tagged nucleotides and used in in situ hybridization of the nucleus of isolated tissue from patients, as in fluorescent in-situ hybridization (FISH). These tagged probes allow rapid and relatively unskilled identification of metaphase chromosomes, and allow the identification of chromosomes dispersed within the nucleus. Furthermore, tagging two chromosome regions with different fluorescent tags allows easy identification of chromosomal translocations.

Gene Defects

Mutations

Although DNA replication is a very accurate process, occasionally mistakes occur to produce changes or mutations. These changes can also occur due to other factors such as radiation, ultraviolet light, or chemicals. Mutations in gene sequences or in the sequences that regulate gene expression (transcription and translation) may alter the amino acid sequence in the protein encoded by that gene. In some cases protein

function will be maintained; in other cases it will change or cease, perhaps producing a clinical disorder.

Point mutation involves the substitution of one nucleotide for another, thereby changing the codon in a coding sequence. For example, the triplet AAA, which codes for lysine, may be mutated to AGA, which codes for arginine. Whether a substitution produces a clinical disorder depends on whether it changes a critical part of the protein molecule produced. Fortunately, many substitutions have no effect on the function or stability of the proteins produced, as several codons code for the same amino acid.

Insertion or *deletion* of one or more bases is a more serious change, as it results in the alteration of the rest of the following sequence to give a frame-shift mutation. For example, if the original code was TAA GGA GAG TTT and an extra nucleotide (A) is inserted, the sequence becomes TAA AGG AGA GTT T. Alternatively, if the third nucleotide (A) is deleted, the sequence becomes TAGGAG AGT TT. In both cases, different amino acids are incorporated into the polypeptide chain. This type of change is seen in some forms of thalassemia. Insertions and deletions can involve many hundreds of base pairs of DNA. For example, some large deletions in the dystrophin gene remove coding sequences, which results in Duchenne muscular dystrophy.

Splicing Mutations

If the DNA sequences that direct the splicing of introns from mRNA are mutated, then abnormal splicing may occur. In this case the processed mRNA, which is translated into protein by the ribosomes, may carry intron sequences, thus altering which amino acids are incorporated into the polypeptide chain.

Termination Mutations

Normal polypeptide chain termination occurs when the ribosomes processing the mRNA reach one of the chain termination or stop codons (see above). Mutations involving these codons result in either late or premature termination. For example, haemoglobin constant spring is a haemoglobin variant where, instead of the stop sequence, a single base change allows the insertion of an extra amino acid.

Single-Gene Disease

Monogenetic disorders involving single genes can be inherited as dominant, recessive, or sex-linked characteristics. Inheritance occurs according to simple mendelian laws, making predictions of disease in offspring and therefore genetic counselling more straightforward.

Autosomal Dominant Disorders

Autosomal dominant disorders (incidence, 7 per 1,000 live births) occur when one of the two copies has a mutation and the protein produced by the normal form of the gene is unable to compensate. In this case a heterozygous individual will manifest the disease. The offspring of heterozygotes have a 50 % chance of inheriting the chromosome carrying the disease allele, and therefore also of having the disease (as in polycystic kidney disease).

These disorders have great variability in their manifestation and severity. Incomplete penetrance may occur if patients have a dominant disorder that does not manifest itself clinically. This gives the appearance of the gene having skipped a generation. New cases in a previously unaffected family may be a result of a new mutation. If it is a mutation, the risk of a further affected child is negligible. *Li-Fraumeni syndrome* (LFS) is an autosomal dominant disorder associated with cancer predisposition syndrome. Affected individuals have a *p53* mutation and have a predisposition to a number of malignancies including soft tissue sarcoma, breast cancer, leukemia, adrenocortical tumors, melanoma, and colon cancer [38]. Similarly, *hereditary non-polyposis colorectal carcinoma* (HNPCC) is an autosomal dominant predisposition to develop colorectal, endometrial, ovarian, urinary tract, stomach, small bowel, and biliary tract carcinomas, as well as brain tumors (Lynch syndrome I and II) [39].

Autosomal Recessive Disorders

These disorders manifest themselves only when an individual is homozygous for the disease allele. In this case the parents are generally unaffected, healthy carriers (heterozygous for the disease allele). There is usually no family history, although the defective gene is passed from generation to generation. The offspring of an affected person will have healthy heterozygotes unless the other parent is also a carrier. If both parents are carriers, the offspring have a one in four chance of being homozygous and affected, a one in two chance of being a carrier, and a one in four chance of being genetically normal. Consanguinity increases the risk. The clinical features of autosomal recessive disorders are usually severe; patients often present in the first few years of life and have a high mortality. Many inborn errors of metabolism are recessive diseases.

Sex-Linked Disorders

Genes carried on the X chromosome are said to be X-linked, and can be dominant or recessive in the same way as autosomal genes. As females have two X chromosomes, they will be unaffected carriers of X-linked recessive diseases. However, since males have just one X chromosome, any deleterious mutation in an X-linked gene will manifest itself because no second copy of the gene is present.

Imprinting

It is known that normal humans need a diploid number of chromosomes—46. In some way the chromosomes are imprinted so that the maternal and paternal contributions are different. The expression of a gene depends on the parent who passed on the gene. Imprinting is relevant to human genetic disease because different phenotypes may result, depending on whether the mutant chromosome is maternally or paternally inherited. It has been suggested that *DNA methylation* may be the epigenetic marking for imprinting phenomenon in mammals [40]. DNA methylation is involved in the activation of tumor suppressor and other genes in prostate, renal, and bladder cancer. Loss of imprinting may be a primary event in Wilms' and testicular tumors [41].

Complex Traits: Multifactorial and Polygenic Inheritance

Characteristics resulting from a combination of genetic and environmental factors are said to be multifactorial; those involving multiple genes can also be said to be polygenic. Measurements of most biological traits (e.g., height) show a variation between individuals in a population. This variability is due to variation in genetic factors and environmental factors. Environmental factors may play a part in determining some characteristics, such as weight, while other characteristics such as height may be largely genetically determined. This genetic component is thought to be due to the additive effects of a number of alleles at a number of loci, many of which can be individually identified using molecular biological techniques [42].

Cancer Cell Biology and Genetics

Cancer cells are a clonal population of cells in which the accumulation of mutations in multiple genes has resulted in escape from the normally strictly regulated mechanisms that control growth and differentiation of somatic cells. The malignant phenotype acquired by cancer cells has the following properties [43]:

1. Loss of growth control
2. Resistance to apoptosis
3. Ability to create new blood supply (angiogenesis)
4. Infiltration into the surrounding tissues
5. Metastasis: ability to colonize and survive in an ectopic environment

The process of oncogenesis can be thought of as a stepwise process, with mutations in particular genes being required for progression from one phase to another, that is, from transformed cell to metastatic cell; these gene mutations are rate-limiting. Rarely, if ever, is a single event responsible for conversion of a normal cell

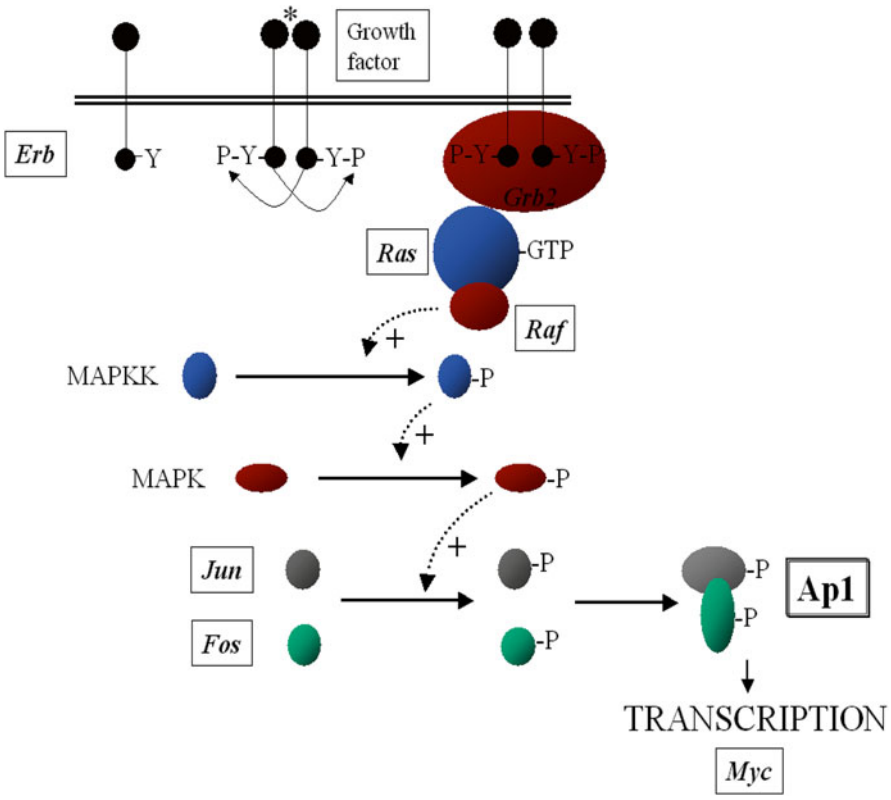

Fig. 1.5 Diagrammatic illustrations of proto-oncogene positions within the growth factor receptor signal transduction pathway. *GTP* guanosine triphosphate, *MAPK* mitogen-activated protein kinase, *MAPKK* mitogen-activated protein kinase

to a malignant cell. Mutations may be a combination of inherited, spontaneous, and environmentally induced factors. *Oncogenes* are mutated genes that cause normal cell to grow out of control and become cancer cells.

Tumor suppressor genes slow down cell division, repair DNA, and induce apoptosis. Often several oncogenes may be found within the same receptor-signalling pathway (Fig. 1.5).

The study of mechanisms and genes that are responsible for the loss of regulation of the cell cycle control does not in itself explain invasion and metastasis. There are events arising from expression of proteases to digest tissue stroma, downregulation of certain cell adhesion molecules such as cadherins that anchor cells, and the expression of those cells that regulate cytoskeletal changes and cell migration, such as the integrins. Most important is the deregulation of apoptotic pathways, both intrinsic and extrinsic, which would signal a cell that has lodged in an inappropriate tissue to undergo altruistic apoptosis.

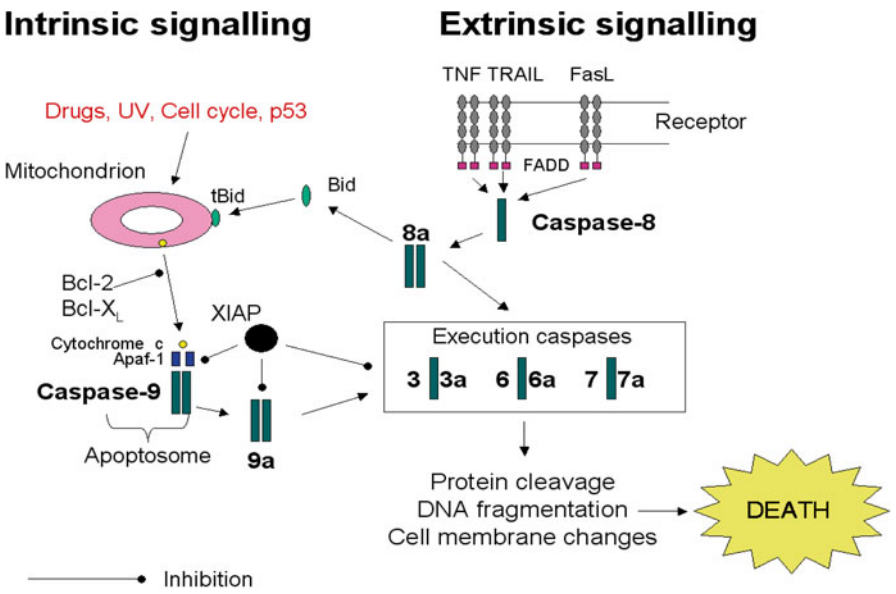

Fig. 1.6 Intrinsic and extrinsic apoptosis pathways and their linkage

Apoptosis

Apoptosis was mentioned earlier in this chapter (programmed cell death) (Fig. 1.6). It is triggered by a number of factors, such as ultraviolet rays, γ-radiation, chemotherapeutic drugs, and death receptors (DRs) [44]. In oncology it has become clear that chemotherapy and radiotherapy regimes work effectively if they can trigger the tumor cells' own apoptotic pathways. Failure to do so may result in resistant tumors.

Several factors initiate apoptosis, but in general there are two signaling pathways: the extrinsic apoptotic pathway triggered by death receptors on the cell surface, and the intrinsic pathway initiated at the mitochondrial level. Death receptors are all members of the tumor necrosis factor (TNF) receptor superfamily [TNF-related apoptotic inducing ligand receptor-1 family: TRAIL-R1 or D4, APO-2, and TRAIL-2; DR5, TRICK2 (TRAIL inducer of cell killing), and Fasligands (CD95) (APO-1/Fas)] [44].

Apoptotic Pathways Cysteine Proteases

Capsases are the regulators of apoptosis. They couple to proapoptotic signals, which once activated cleave and activate down effector capsases and subsequently TNF receptor (TNFR) and Fas ligands.

The extrinsic pathway is important in processes such as tissue remodelling and induction of immune self-tolerance. Activated receptors with internal death domain

complex multiple pro-caspase 8 molecules whose autocatalytic activity results in released of the initiator caspase 8. In turn, caspase 8 cleaves procaspases3 and caspase 3, in combination with the other effector caspases, and activates DNA cleavage, cell condensation, and fragmentation.

The intrinsic pathway centers on the release of mitochondrial cytochrome c. Cellular stress, such as growth factor withdrawal and p53 cell cycle arrest, induces the expression of the proapoptotic Bcl-2 family of proteins, Bax and Bak. Bax is normally localized in the cytosol or loosely associated with the outer mitochondrial membrane, whereas Bak is mostly localized in the outer mitochondrial membrane and remains inactive. Cytochrome C binds Apaf1, and forms a complex known as the apoptosome, which then activates an initiator caspase, in this case, caspase 9, which activates the effector caspase, caspase 3. Other proteins released from damaged mitochondria, Smac/DIABLO and Omi/HtrA2, counteract the effect of inhibitor of apoptosis proteins (IAPs), which normally bind and prevent activation of pro-caspase 3. Antiapoptotic Bcl-2protein, when incorporated as a member of the Bak/Bax pore complex, render the mitochondrial pore nonpermissive to release of cytochrome c and the anti-IAPs.

There is an amplification link between the extrinsic and intrinsic apoptotic pathways in that caspase 8 cleaves a Bcl-2 family member, tBid, which then aids formation of the Bcl-2/Bax/Bak pore complexes. If this complex is predominately formed from proapoptotic members of the Bcl-2 family of proteins, then apoptosome/caspase 9, along with mitochondrial anti-IAPs, amplifies the apoptotic activation of effector caspases 3. Conversely, overexpression of antiapoptoticBcl-2 will not only inhibit intrinsic but also dampen down extrinsic apoptotic signalling.

Cell Cycle Control Oncogenes and Tumor Suppressors

Regulation of the cell cycle is complex. Cells in the quiescent G0 phase (G, gap) of the cycle are stimulated by the receptor-mediated actions of growth factors [e.g., epithelial growth factor (EGF); platelet-derived growth factor (PDGF); insulin-like growth factor (IGF)] via intracellular second messengers. Stimuli are transmitted to the nucleus, where they activate transcription factors and lead to the initiation of DNA synthesis, followed by mitosis and cell division. Cell cycling is modified by the cyclin family of proteins that activate or deactivate proteins involved in DNA replication by phosphorylation (via kinases and phosphatase domains).

Thus from G0 the cell moves on to G1 (gap1) when the chromosomes are prepared for replication. This is followed by the synthetic (S) phase, when the 46 chromosomes are duplicated into chromatids, followed by another gap phase (G2), which eventually leads to mitosis (M). As shown in Fig. 1.6, mutations leading to deregulation of expression or function of any protein in the pathway from growth factor to target replication gene expression can be an oncogene (Table 1.2).

However, although multiple mutations may arise to give enhanced replication signalling, the cell cycle itself is regulated by two gatekeepers, which would normally

Table 1.2 Examples of oncogenes

Gene	Function of product
Sis	PDGF growth factor
ErbB/Neu	EGF receptor
	Truncated
Erb A	Thyroid hormone cytoplasmic receptor
Ras	G protein
Src	Membrane/cytoskeleton- associated tyrosine Kinase
Fes	Cytoplasmic tyrosine kinase
Raf	Serine/threonine protein kinase
Myc	Transcription factor nuclear proteins
Fos, Jun	

Table 1.3 Examples of tumour suppressor genes in urological cancers

Gene	Function of product	Hereditary tumours	Sporadic tumours
RB1	Transcription factor	Retinal and sarcoma	SCLC, breast, prostate, bladder, retinal and sarcoma
P53	Transcription factor	Li-Fraumeni syndrome - breast, osteosarcoma, leukaemia, soft-tissue sarcoma	50 % of all cancers
WT1	Transcription factor	Nephroblastoma (Wilms tumour)	Nephroblastoma
BRCA1 + 2	DNA repair	Prostate	Prostate
VHL	Stabilization of hypoxia inducible factor (HIF), Vascular endothelial growth factor (VEGF), transforming growth factor (TGFα and β)	Hemangioblastoma of the brain, spinal cord, retina; renal cysts and renal cell carcinoma; cystadenomas of epididymis, broad ligament, pancreas, liver and pheochromocytoma	Renal

SCLC small-cell lung cancer

halt the aberrant signal. Tumor suppressor gene products are intimately involved in control of the cell cycle (Table 1.3).

Progression through the cell cycle is controlled by many molecular gateways, which are opened or blocked by the cyclin group of proteins that are specifically expressed at various stages of the cycle. The RB and p53 proteins control the cell cycle and interact specifically within many cyclin proteins. The latter are affected by INK 4A acting on p16 proteins. The general principle is that being held at one of these gateways will ultimately lead to programmed cell death. p53 is a DNA-binding protein that induces the expression of other genes and is a major player in the induction of cell death. Its own expression is induced by broken DNA. The induction of *p53* gene transcription by damage initially causes the expression of DNA repair enzymes. If DNA repair is too slow or cannot be effected, then other proteins that are induced by *p53* will effect programmed cell death (Fig. 1.7).

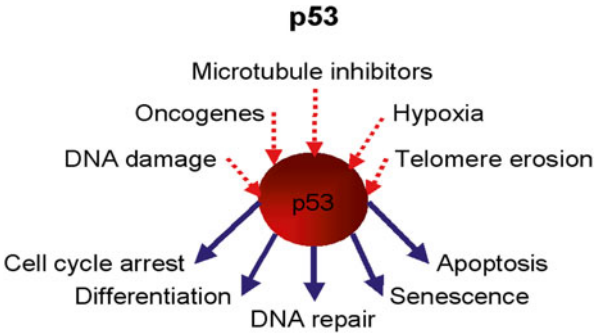

Fig. 1.7 Cellular events that induce tumour suppress gene p53 expression (*blue arrows*) and the cellular consequences of p53 activation (*red arrows*)

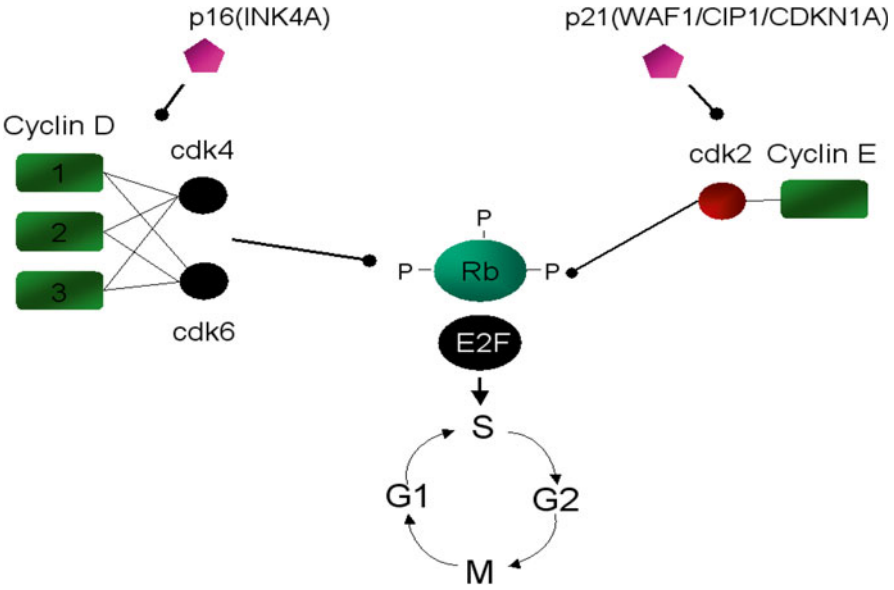

Fig. 1.8 Tumour suppressor RB protein 'gate keeper' role in preventing cell cycle progression from G1-S phase until progressive phosphorylation by cyclin molecules renders RB unable to bind the cycle specific E2F transcription factor

One gateway event that has been largely elucidated is that between the G1 and the S phase of the cell cycle. The transcription factor dimer complex E2FDP1 causes progression from the G1 to the S phase. However, the RB protein binds to the E2F transcription factor, preventing its induction of DNA synthesis. Other, cyclin D-related molecules inactivate the RB protein, thus allowing DNA synthesis to proceed. This period of rapid DNA synthesis is susceptible to mutation events and will propagate a preexisting DNA mistake. Damaged DNA induced *p53* expression rapidly results in the expression of a variety of closely related (and possibly tissue-specifi c) proteins, WAF-1/p21, p16, and p27. These inhibit the inactivation of *RB* by cyclin D-related molecules. As a result, *RB*, the normal gate that stops the cell cycle, binds to the E2F-DP1 transcription factor complex, halting S phase DNA synthesis. If the DNA damage is not repaired, apoptosis ensues (Fig. 1.8).

Table 1.4 Factors involved in tumour angiogenesis

Pro-angiogenic factors	Antiangiogenic Factors
Activators of Endothelial cell proliferation and migration: Vascular Endothelial Growth Factor, Fibroblast Growth Factor (FGF); Platelet-derived Growth Factor (PDGF); Epidermal Growth Factor (EGF)	Endogeneous Regulator
	Laminin: Binds with Endostatin
	Endostatin: Inhibitor of endothelial cell proliferation and migration
	Tumostatin: Induction of apoptosis of endothelial cells
Chemokines	BM components: perlecan, laminin and collagen
MMP mediated degradation	Genes upregulated by p53: Thrombospondin-1 (TSP1) and Matrix metalloproteinase 2 (MMP2)
Cyclo-oxygenase 2	

Viral Inactivation of Tumor Suppressors

The suppression of normal tumor suppressor gene function can be achieved by disabling the normal protein once it has been transcribed, rather than by mutating the gene. Viruses have developed their own genes, which produce proteins to do precisely this. The main targets of these proteins are *RB* and *p53*, to which they bind and thus disable. The best understood are the adenovirus E1A and human papillomavirus (HPV) E7 gene products, which bind *RB*, while the adenovirus E1B and HPV E6 gene products bind *p53*. The simian virus 40(SV40) large T antigen binds both *RB* and *p53*.

Hereditary Predisposition to Cancer

Some cancers have a clear hereditary nature, although a more subtle genetic predisposition, for example in affecting relative gene product function, will undoubtedly be present in a much higher percentage of patients. The majority are due to inheritance of tumor suppresser gene mutations. This is not surprising in view of the crucial role in development and differentiation of proto-oncogenes.

Approximately 5–10 % of all prostate cancer seems to be due to autosomal dominant cancer and cancer susceptibility genes [45]. Inherited oncogenes would be expected to be lethal, although two are recognized: multiple endocrine neoplasia type II (MEN-II) and hereditary papillary renal cancer. Only one hit is required to lose the function of the tumor suppressor gene if there is already a hereditary mutation on the other allele. Compared to patients with sporadic tumors, those with inherited predisposition to cancer tend to develop tumors at an earlier age and more commonly bilaterally or multifocal, and often with a more restricted tissue origin (Table 1.4).

Genomic Imprinting and Cancer

Genomic imprinting is the epigenetic marking of a gene, based on parental origin that results in monoallelic expression. This phenomenon differs from the classical sequence-based qualitative changes in that gene expression and effective gene

dosage are controlled by epigenetic dysregulation of parental alleles of an imprinted gene. Imprinting dysregulation may contribute to tumorigenesis either by activating a transcriptionally repressed allele, resulting in gene activation, or by inactivating an expressed allele of an imprinted tumor suppressor gene, leading to loss of function. Evidence implicating this process in tumorigenesis is based on the fi n ding of selective parental loss of heterozygosity (LOH) at certain imprinted domains in several pediatric tumors. The p57 KIP2 protein is a cell cycle inhibitor of several G1 cyclin complexes and is a negative regulator of cell proliferation. The p57KIP2 is located on 11p15.5, a region implicated in Beckwith-Wiedemann syndrome, which is characterized by childhood tumors including Wilms' tumor, rhabdosarcoma, and adrenal carcinoma, which display a specific loss of maternal 11p15 alleles, suggesting that genomic imprinting plays an important part [46].

Microsatellite Instability

Microsatellites are short (50–300 bp) sequences composed of tandemly repeated segments of DNA two to five nucleotides in length (dinucleotide/trinucleotide/ tetranucleotide repeats). Often used as markers for linkage analysis because of high variability in repeat number between individuals, these regions are inherently unstable and susceptible to mutations during DNA synthesis. Somatic microsatellite instability (MSI) has been detected in a number of cancers including bladder and upper urinary tract tumors. It has been assessed as a predictor of survival in patients with invasive upper urinary tract transitional cell carcinoma [47]. Detecting MSI involves comparing the length of microsatellite alleles amplified from tumor DNA with the corresponding allele in normal tissue from the same individual.

Tumor Angiogenesis

Once a nest of cancer cells reaches 1–2 mm in diameter, it must develop a blood supply in order to survive and grow larger, as diffusion is no longer adequate to supply the cells with oxygen and nutrients. As with all tissues, solid tumor cancer cells secrete substances that promote the formation of new blood vessels, a process called angiogenesis. The factors that favour and inhibit angiogenesis are summarized in Table 1.4 [48, 49].

Angiogenic Switch

Due to rapid growth and increased cell mass, there is oxygen and nutrient deprivation that leads to promotion of neovascularization by tumor cells by inducing the expression of angiogenic cytokines such as the vascular endothelial growth factor

(VEGF), which is a potent and unique angiogenic protein that induces endothelial cell (EC) proliferation, EC migration, and vascular permeability, and acts as a crucial survival factor for endothelial cells [50].

Oncogenes and Angiogenesis

The recruitment process of host blood vessels to the tumor site is triggered by the very same set of genetic alterations (activated oncogenes and inactivated tumor suppressor genes, inhibition of apoptosis, and aberrant mitogenesis) [51]. For example, mutant *ras* expression is associated with increased production of VEGF and increases the bioavailability of metalloproteinases [52].

Angiogenesis and Urological Cancers

Several therapeutic vaccine preparations are under development to produce a range of host immune (humoral, cellular) against proangiogenic factors and their receptors in tumors.

Renal Cell Carcinoma

Many angiogenic factors have been found to have increased expression in renal cell carcinoma. Increased expression of VEGF and VEGF mRNA is seen [53]. *VHL* mutation in relation to angiogenesis has already been discussed. The antiangiogenesis therapy of RCC is discussed in the chapter on renal cancer.

Bladder Cancer

Microvessel density is an independent prognostic indicator for muscle invasive TCC [54]. High serum levels of VEGF indicate metastatic disease [55], and high urinary levels correlate with tumor recurrence [56]. The therapeutic applications are discussed in Chap. 16.

Prostate Cancer

Vascular endothelial growth factor expression is low in the normal prostate but increased in cancer, and shows a positive association with MVD, tumor stage, Gleason grade, and disease-specific survival [57].

Testicular Cancer

Increased VEGF expression is seen in germ cell tumors. There is evidence to suggest that VEGF expression is involved in tumor development, angiogenesis and metastasis [58].

Cancer Biomarkers

In clinical chemistry an antigen or protein, which is secreted by the tumour itself or by the surrounding tissues in response to the tumour and can be determined in the serum samples of the patient is a cancer biomarker (formerly called tumour marker). Biomarkers could be sometimes measured in other samples such as cerebrospinal fluid, urine and tissues.

They are used in screening programs and clinical practice to:

1. Confirm DIAGNOSIS of malignancy
2. Indicate severity and hence PROGNOSIS
3. Provide post treatment information to MONITOR therapy and follow up

Scenarios for the use of biomarker-based diagnostics for cancer include risk assessment, noninvasive screening for early-stage disease, detection and localization, disease stratification and prognosis, response to therapy and, for those in remission, screening for disease recurrence [59].

Several decades ago the criteria of an "Ideal Tumour Marker" was established, they should be:

1. Tumour specific and common to tumour type
2. Absent from healthy individuals or benign disease
3. Easily detected at the early stage of tumour development
4. Directly proportional to tumour mass
5. Levels parallel response to therapy
6. it should be cost-effective
7. Predict recurrences before they become clinically detectable.

However in practice *tumour markers* never fulfilled these criteria (and hence the name was changed to *cancer biomarker*) and such markers are:

- Rarely tumour or type specific, even rarer is 100 % expression.
- Most cancer associated proteins and molecules are expressed regardless of tumour status. A low level is often found in benign conditions which will be intermediate between that found in healthy controls and that of those with early – late stage malignant disease.
- Most cancers only produce high levels of any given tumour marker in advanced stage and there is considerable variation between patients.
- Although tumour marker levels will parallel response to therapy this is an individual patient issue and there is often a lag response that may be preceded by 'tumour marker flare' whereby large amounts of the marker are released due to cancer cell death.

No tumour/ cancer bio-marker matches all these criteria but the nearest is hCG when used as a marker of gestational trophoblastic disease.

Clinical chemistry cancer markers can be defined by their biochemical nature: Organic and inorganic compounds & metabolites; peptide hormones, monoclonal defined cancer antigens and oncofetal antigens. There is a tendency for the ectopic expression of proteins to be associated with highly malignant tumours.

Organic and Inorganic Compounds and Metabolites

These markers are highly specific, often urinary and define well differentiated slow growing tumours. In the main they aid diagnosis following clinical observations. A good example is phaeochromocytoma, an adrenal gland tumour 1:10 of which are cancerous. Given the nature of the tissue, adrenal medullary cells, a clinical consequence of the expanded cell population is elevated production of adrenal hormones (adrenaline/ noradrenaline). If the tumour arose in the adrenal cortex rather than the medulla then it would be increased cortisol. Although the adrenaline has potent vasodilatory and flight or fight effects, biochemically it is rapidly degraded. Thus, to detect such increased secretion urinary catecholamines (breakdown products of the adrenalin) are measured.

It should be noted that the relationship to elevated metabolites and steroids are not always direct. For example Carcinoid tumours (neuroendocrine tumours found in small intestine or appendix – often benign) release ACTH which induces adrenal cortisol cells to produce and elevate serum cortisol levels.

Peptide Hormones

These markers when elevated are usually specific serum or urine based measurements and usually define well differentiated slow growing tumours. Again primary diagnosis is largely from clinical features. However, non-bioactive forms and fragments of the peptide hormone tend to define aggressive poorly differentiated tumours. For example elevated parathyroid hormone (PTH), its related peptide (PTH-RP), and luteinising hormone (LH), growth hormone (GH) and adrenocorticotrophic hormone (ACTH) are diagnostic of parathyroid and pituitary tumours respectively. Hypothalamic tumours require additional clinical investigation, but post chemotherapy or surgery, monitoring of levels is indicative of response to the therapy.

Monoclonal Defined Cancer Antigens

They are the result of raising antibodies (monoclonal and polyclonal) against human tumour cells and extracts thereof, immunized in mice, sheep rabbits etc. As such the molecules' are defined by the antibody that detects them e.g. CEA (Carcinoembryonic

Table 1.5 Examples of major monoclonal antibody defined cancer antigens in clinical use

Antibody defined cancer marker	Clinical significance/characteristics
CEA	Define Colorectal Cancers
	But also breast, lung, GI tract and liver
	Normal levels <5 mg/L
	Elevated in pregnancy, smokers, respiratory disorders.
	Not reliable for diagnosis but some prognostic value in colon cancers and in monitoring
	Post treatment levels fall $T^1/_2$ of 2–3 days.
CA125	Ovarian Cancer 85–90 %
	But also adenocarcinomas of breast, lung and G-I tract
	Also elevated in other gynaecological conditions
	Large Screening study completed – not proven effective policy for asymptomatic screening
	Not reliable for diagnosis but some prognostic value in ovarian cancers and in monitoring
	Post surgical levels fall $T^1/_2$ of 5 days
CA15.3	Breast Cancer – up to 35 % of early disease
	Also in Lung, GI tract, reproductive system cancers
	> 25kU/L indicates disease but not really diagnostic
	Not really prognostic
	Levels often indicate mass rather than malignancy
	5× cut off indicates metastatic disease
	Drop in levels post treatment indicate good response and elevations over
	25 % indicate recurrent disease
PSA	Prostate cancer (Prostatic Carcinoma)
	Also BPH (benign prostatic hypertrophy) & Prostatitis
	Normal <50 year 2.5 μg/L >50<70 year 4 μg/L
	No use in screening or diagnosis alone
	Some use in prognosis
	Good in monitoring
	$T^1/_2$ of 2.2 days to undetectable levels after radical prostatectomy

Antigen), CA125 (Cancer Antigen 125), CA15.3 (Cancer Antigen 15), PSA (Prostate Specific Antigen) etc. Characterisation has revealed all to be normal proteins inappropriately expressed as a result of oncogenesis. These do tend to be interesting functional molecules almost exclusively large molecular weight glycoproteins (Table 1.5).

Thus the reality of this category of *Tumour marker*s is that:

- None are tumour specific but more commonly associated with a particular cancer.
- Low levels are found in normal individuals, higher during pregnancy and occasionally during menses. Often expressed by more than one cancer.
- Found in serum, urine or tissue

- Can be detected at all stages of tumour development but usually correlate with advancing disease stage.
- They are generally not particularly diagnostic of very early stage disease.
- They are prognostic and used for monitoring disease.

Oncofetal Antigens

These are peptide hormones and proteins specifically expressed by the placental-fetal unit e.g. PLAP (Placental Alkaline Phosphatase), AFP (alphafetoprotein), β-hCG (human Chorionic Gonadotropin). They can be measured in serum or urine and when ectopically expressed by cancers tend to define poorly differentiated fast growing/malignant tumours and diagnosis is more reliant on the levels of these marker s. Indeed, β-hCG is diagnostic of gestational trophoblastic disease (GTD), particular forms of testicular germ cell tumours and some non trophoblastic tumours (Table 1.6). Additional clinical investigation is required, but monitoring of levels post chemotherapy or surgery is extremely useful in detecting response and recurrent disease prior to other clinical symptoms or imaging measures.

Table 1.6 Oncofetal antigens in clinical use

Oncofetal antigen	Clinical significance/characteristics
PLAP	Elevated in trophoblastic and Non trophoblastic dedifferentiated tumours. Particularly associated with seminomatous germ cell tumours of the testis and the female ovarian equivalent – dysgerminomas.
	Seminomas 90 % PLAP positive
	Dysgerminomas 75 % PLAP positive
AFP	Elevated in non trophoblastic, germ cell and trophoblastic dedifferentiated tumours:
	Non Trophoblastic/germ tumours
	Hepatocellular carcinoma
	Yolk sac tumours
	Diagnostic
	Prognostic
	High Levels the more extensive the tumour burden
	Monitor
	Levels Correspond to therapy
	Persistent or resurgent levels = resistance/recurrence
	Testicular Germ Cell Tumours
	Diagnostic of Non-Seminomatous type that contain yolk sac elements
	Prognostic
	In combination with hCG
	Monitor
	Levels correspond with therapy
	Persistent levels = resistance/recurrence

(continued)

Table 1.6 (continued)

Oncofetal antigen	Clinical significance/characteristics
hCG	Elevated in trophoblastic, germ cell and non trophoblastic dedifferentiated tumours.
	Testicular germ cell Tumours
	Diagnostic
	Seminoma (a radiosensitive tumour) – hCG positive 8 % (AFP 0 %)
	Non-Seminoma (a radioresistant tumour) – hCG positive 50 % (AFP 66 %)
	Prognostic
	Non Seminoma
	hCG > 10,000 mIU/mL = 53 % 3 year survival
	hCG < 1,000 mIU/mL = 85 % 3 year survival
	Seminoma
	80–97 % overall survival
	Monitor
	Levels Correspond to therapy
	Persistent or resurgent levels = resistance/recurrence
	Gestational Trophoblastic Disease (GTD)
	Including Hydatidiform Mole
	Partial Molar Pregnancy
	Placental Site Tumour
	Choriocarcinoma
	β-hCG for this disease is virtually an ideal tumour marker:
	Diagnostic – In young women it is generally diagnostic of GTD if not from any other source (e.g. pregnancy) and all GTD will produce hCG.
	A CSF : Serum ratio of greater than 1:60 is indicative of brain metastasis
	Prognostic – The higher the levels the high the tumour burden
	High pre-treatment levels = poor prognosis
	Monitor
	Levels Correspond to therapy
	Persistent or resurgent levels = resistance/recurrence

In monitoring GTD response to chemotherapy β-hCG has proven invaluable, as all GTD's express β- hCG and at high levels patients are monitored for response to therapy almost daily until in remission defined as β-hCG not detected for three consecutive weeks. They are then monitored by β- hCG serum assay every 2 weeks for 6 months then monthly for 5 years. Levels of β-hCG determine when and how chemotherapy is administered and in the absence of clinically apparent disease, persistently elevated serum β-hCG reflects the existence of micro tumours that if untreated will progress clinically.

Important Techniques in Molecular Cell Biology

Monoclonal Antibodies

Myeloma is a malignancy of transformed B-cell lineage that secretes a specific antibody. This fact is used to produce specific antibodies directed toward an antigen of choice. A laboratory animal is injected with the antigen of choice against which it mounts an immune response. B cells are then harvested from the spleen. The cells are fused en masse to a specialized myeloma cell line that no longer produces its own antibody. The resulting fused cells, or *hybridomas*, are immortal and produce antibodies specified by the lymphocytes of the immunized animal. These cells can be screened to select for the antibody of interest, which can then be produced in limitless amounts. Modification of the mouse antibody is then required for the recognition of the Fc (effector) region of the antibody to initiate human defense mechanisms and to avoid an immune response against the antibody shortening its half-life. Attachment of a human Fc fragment to the mouse Fab fragment to create a chimeric antibody is called humanization.

Southern Hybridization

DNA, which has first been digested with restriction endonucleases (e.g., Eco-R1), can be separated by virtue of the differential mobility of fragments of varying size in an electrical field. This is done in an agarose gel. The gel is then placed on a nylon transfer membrane, and the DNA is absorbed onto it by capillary action; this is the process of Southern blotting. (Northern and Western blotting refer to essentially the same process but using mRNA and protein, respectively, rather than DNA.) The nylon membrane can then be incubated with a short strand of DNA (the probe) that has been radiolabeled with 32p. If the DNA on the membrane contains sequences homologous to the probe, then Watson-Crick base pairing will occur and the probe will stick to the membrane. This can be visualized by exposing the membrane to a standard radiographic fi lm. Thus a probe for a given region of the genome can be used to investigate the DNA of patients to determine the presence or absence of a given mutation if that mutation creates or destroys a restriction enzyme recognition site, thereby altering the size of a band on the exposed film.

Polymerase Chain Reaction

Polymerase chain reaction (PCR) has led to a revolution in molecular biology. Two unique oligonucleotide sequences on either side of the target sequence,known as *primers*, are mixed together with a DNA template, a thermostable DNA

polymerase (*taq polymerase*), and purine and pyrimidine bases attached to sugars. In the initial stage of the reaction, the DNA template is heated to 90 °C to make it single stranded (denature), and then as the reaction cools the primers will *anneal* to the template if the appropriate, complementary, sequence is present. Then the reaction is heated to 72 °C for the DNA polymerase to synthesize new DNA between the two primer sequences. This process is then repeated on multiple occasions, up to about 30 or so cycles, amplifying the target sequence exponentially. Each cycle takes only a few minutes. The crucial feature of PCR is that to detect a given sequence of DNA it needs to be present only in one copy (i.e., one molecule of DNA); this makes it extremely powerful. The sensitivity of the technique is dictated by the amount of amplification and thus the number of cycles performed. The specificity relies on the uniqueness of the oligonucleotide sequence of the primers (if the primers bind at multiple sites, then multiple DNA sequences will be amplified).

Refinements of PCR include the following:

Multiplex PCR, in which where multiple pairs of primers are used to amplify several target areas of DNA in parallel Nested PCR, which improves the specificity of the reaction by including a second pair of primers just within the target sequence defined by the first set of primers. Reverse transcription (RT)-PCR which uses reverse transcriptase to form cDNA from mRNA, which can then be used for the standard PCR reaction. Real-time RT-PCR, which is a quantitative RT-PCR whereby relative levels of mRNA are determined by monitoring the simultaneous amplifi cation of the cDNA of a target gene against that of a housekeeping gene mRNA.

Expression Microarrays/Gene Chips

This is a methodology developed to examine the relative abundance of mRNA for thousands of gene present in cells/tissue of different types or conditions, for example, to examine the changes in gene expression from normal colonic tissue to that of malignant colonic polyps. The basic technology is the ability to immobilize sequence of DNA complementary to specific genes or different regions of known genes, onto a solid surface in precise microdot arrays. Total mRNA is extracted from one tissue and labelled with fluorescent tag Cy3-green and the mRNA from the second tissue with fluorescent tag Cy5-red. The two fluorescent- tagged total mRNA samples are mixed in a 1 : 1 ratio and washed over the DNA gene chips. The mRNA for specific genes will bind to their complementary microdot and can be detected by laser-induced excitation of the fluorescent tag, and the position and light wavelength and intensity recorded by a scanning confocal microscope. The relative intensity of Cy5-red : Cy3-green is a reliable measure of the relative abundance of specific mRNAs in each sample. Yellow results from equal binding of both fluorescent-tagged mRNAs. If no hybridization occurs on a dot, then the area is black. The power of the system is that many thousands of genes can be screened not only for their expression but also for their relative expression in normal and

diseased tissue. A considerable amount of computing power and analysis is required to interpret the thousands of dots on a microarray chip.

Proteomics and Genomics

A more direct route to understanding genetic and somatic disease is by studying the protein expression characteristics of normal and diseased cells—the proteome. This method relies on the separation of proteins expressed by a given tissue by molecular size and charge on a simple two-dimensional display and is achieved by using two-dimensional (2D) gel electrophoresis. The pattern of dots corresponds to the different proteins expressed. With the improvement in technology the patterns are reproducible and can be stored as electronic images. Non-, over-, and under expression of a given protein can be detected by a corresponding change on the proteome 2D electrophoresis. Furthermore, post-translational modifications of the protein show up as a change in either size or charge on the proteome picture. To positively identify the altered protein and the posttranslational modification it may contain, these protein spots are eluted and subjected to modern mass spectrometry techniques such as matrix-assisted laser desorption/ionization (MALDI) and electrospray ionization (ESI) time of flight (TOF), which not only give the precise mass of the protein, up to ~500,000Da, but also can sequence its amino-acid, phosphorylation and glycosylation structure, which cannot be detected by genome analysis. There is increasing interest in the proteomic and genomic study of urological cancers (prostate, bladder, and kidney) and their markers, which will help in early detection of the disease, to predict prognosis and response to therapy [60–62].

Metabolomics

In the postgenomic era, computing power, statistical software, separation science, and modern mass spectrometry have facilitated the analysis of complex mixtures as a complete entity and not merely the fluctuation in concentration of one analyte within it. To realize this potential, the metabolic pathways and networks can be traced by the flow of atoms through metabolites (isotopomeranalysis) [63]. Metabolomics is the study of the repertoire of nonproteinaceous, endogenously synthesized small molecules present in an organism. Such small molecules include well-known compounds like glucose, cholesterol, ATP, and lipid signalling molecules. These molecules are the ultimate product of cellular metabolism, and the metabolome refers to the catalogue of those molecules in a specific organism, for example, the human metabolome. In terms of clinical biochemistry, the analysis of the pattern of change of such molecules in urine samples of individuals with and without a particular disease and those treated with specific drugs represents a change in the metabolome. It is very likely that, in the future, medicine-regulating authorities will require metabolomic studieson all new drugs.

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Chapter 2
Experimental Urological Oncology: Cellular, Molecular, and Animal

Prabhakar Rajan and Hing Yip Leung

Experimental Models in Cancer

Cellular In Vitro Models

In vitro cell culture allows cultivation of human- and animal-origin cells for prolonged periods of time. Cancer cell lines, harvested *ex vivo* from primary or metastatic sites, maintain some of the phenotypic characteristics of the tumour of origin. Cells can be immortalized inadvertently by exposure to environmental carcinogens or by repeated passage, transfection with viral or human oncogenes, and chemical or radiation exposure. Immortalized cancer cell lines constitute an easily-accessible and -usable bank of *in vitro* models to investigate cancer cell biology and explore the potential efficacy of anti-cancer agents. Establishing cell lines from early or premalignant disease, such as direct primary cell culture, is technically demanding as these cells have a limited lifespan. Immortalised cell lines are vulnerable to significant inter-species and inter-cell-type contamination over time. Therefore, prior knowledge of their origin and genetic abnormalities is required to allow an informed choice of cell line(s) in experiments and interpretation of results.

P. Rajan, MA, MBBChir, PhD, FRCS(Urol.)
Institue of Cancer Science, University of Glasgow,
Glasgow, Strathclyde, UK

H.Y. Leung, MBChB, PhD, FRCS(Urol.) (✉)
Department of Urology, Beatson Institute for Cancer Research,
Institute for Cancer Sciences, University of Glasgow,
Glasgow, Strathclyde, UK
e-mail: h.leung@beatson.gla.ac.uk

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2-D Culture: (Reviewed in [1])

Typically, cells are grown in monolayer on flat polystyrene or glass dishes in two dimensions (2-D culture) in growth medium at an appropriate temperature and gas mixture (typically, 37 °C, 5 % CO_2 for mammalian cells) in an incubator. Growth medium can vary in pH, glucose concentration, nutrients, and growth factors (often derived from calf serum). Adherent cells can be genetically manipulated, treated with drugs, and observed using microscopy. A major criticism of 2-D culture is the assumption that accurate physiology is reproduced in a cell monolayer. Molecular and cellular responses differ significantly from the organ or tissue of origin due to a lack of extracellular matrix (ECM), which mediates cell-cell and cell-matrix communication *in vivo*.

3-D "Organotypic" Culture: (Reviewed in [2])

Three dimensional (3-D culture) is more physiological allowing cells to grow and respond to environmental cues within an "organotypic" structure resembling ECM (based on collagen, elastin, and other ECM proteins). 3-D spatial cell-cell and cell-matrix interactions emulate *in vivo* cell growth and response to drug therapies. Spheroid culture is the simplest 3-D culture technique and does not require an ECM scaffold. By single culture or co-culture of more than one cell line (e.g. hanging-drop, rotating culture, and concave plate methods), 3-D cell spheroids can be generated to model solid tumour growth. A number of biocompatible synthetic and naturally-derived scaffolds with specific surface chemical properties can be used to model the ECM environment, and examine *in vitro* cancer cell biology. Long-term maintenance of large biological cellular structures requires bioreactors, which continuously supply nutrients/oxygen and remove waste products/metabolites. Although, co-culture models facilitate the study of interactions between different cell types (e.g. epithelial-fibroblast interactions), these models lack additional cellular and humoral factors *in vivo*.

Animal In Vivo Models

Complex interactions between adjacent non-cancer cells (e.g stromal, endothelial and immune cells), blood vessels, and biological micro-environment (e.g. endocrine and paracrine pathways) play an important role in cancer progression. Hence, *in vitro* cell culture will never fully model the disease spectrum. The use of animal models has revolutionized *in vivo* cancer investigation and allows the evaluation of interactions between transformed cells (due to oncogenic mutations) and their non-cancer counterparts; termed cell and non-cell autonomous compartments, respectively. The laboratory mouse (*Mus musculus*) is one of the best cancer models, owing to its small size, propensity to breed in captivity, lifespan of ~3 years,

entirely-sequenced genome, and similarities to humans in terms of genetics and physiology [3]. Tumours can be monitored in real-time by ultrasonography and *in vivo* imaging using tagged reporters. These models may be used for pre-clinical studies of chemopreventative, anticancer, and immunotherapeutic agents.

Xenograft Models

Tumour tissue or immortalised human cell lines from one species can be ectopically (in another tissue or organ) or orthotopically (in organ of origin) transplanted into another species (usually an immune-deficient mouse). Common ectopic sites include subcutaneous flank, mouse tail vein, and renal capsule. Although xenografts allow rapid and facile assessment of *in vivo* tumour dynamics, these models have several shortcomings: For example, cell lines ectopically-transplanted in immune-compromised hosts tend to grow more rapidly than human cancers, yielding inaccurate modelling of response to anti-cancer agents. Orthotopic transplantation is thought to be more physiological and enhances the chances of metastatic spread. However, ectopically- or orthotopically-transplanted tumours are not genetically heterogeneous (due to clonal expansion or over-representation of a particular cell type) and lack normal architecture or microenvironment observed with autochthonous tumours (reviewed in [3, 4]).

Environmentally-Induced Models

Cancers can be induced in animal models, typically mice, by a variety of environmental carcinogens including radiation, chemicals, and pathogens. Tumour development is highly-reproducible, so these models can be used to screen potential carcinogens and chemo-preventative agents. However, these animals exhibit variable tumour susceptibility (dependent on the genetic background/strain) and latency, and do not always develop the full range of pathological tumour subtypes.

Genetically-Engineered Models: (Reviewed in [3])

Genetically-engineered models allow the spontaneous development of cancer in an immune-competent host, which accurately mimics the molecular, pathological and phenotypic features of human disease. Cancer can be caused by an accumulation of genetic insults over time, and these models allow individual analysis of oncogenic pathways. By integrating (or crossing) different genetically-engineered models, the combinatorial effects of multiple genetic defects can be studied *in vivo*. These models may also be used to test novel therapies specifically targeted to molecular pathways of interest, representative of genetic changes in human disease.

Syngeneic Models

Cell lines derived from or embryonic tissue is isolated from a particular species is genetically manipulated, and subsequently transplanted ectopically or orthotopically into a genetically identical and immune-competent adult host. Advantages of this model include the genetically-identical backgrounds of graft and host, and an intact immune system required for anticancer immunotherapy experiments.

Transgenic Models

Transgenic animals, usually mice, express oncogenes or dominant-negative tumour suppressor genes (transgenes) under the control of promoter and enhancer elements that drive gene expression in the tissue of interest following random integration into the genome. Specific gene expression within cells constituting the tissue of interest subsequently drives a particular phenotype. By incorporation specific genetic elements (operons) into the transgenic system, transgene expression can be reversibly switched on and off using exogenous ligands (e.g. tetracycline/doxycycline or tamoxifen). The use of synthetic promoters/enhancers and random integration into the genome can result in incomplete penetrance and phenotypic effects that are unrepresentative of endogenous gene. Transgenic animals are typically created by the following methods:

Non-Homologous Recombination

Using pronuclear microinjection, a gene of interest is microinjected directly into the male pronucleus within an oocyte after fertilisation and integrates at random into the genome. The oocyte is transferred to pseudo-pregnant host female. Germline transmission and subsequent inbreeding of heterozygote progeny is necessary for the subsequent generations to be fully transgenic.

Homologous Recombination

The gene of interest is introduced into embryonic stem (ES) cells, and undergoes homologous recombination and random integration into the genome. ES cells expressing the transgene are selected, microinjected into a blastocyst inner cell mass and transferred to a pseudo-pregnant host female, which bear chimeric progeny. Chimeras are bred with wild type animals to yield a heterozygote (containing one transgenic allele), and inbred to generate homozygotes.

Retroviral Transduction

ES cells or early embryos are transduced with the gene of interest using retroviruses, resulting in random integration into the genome. ES cells expressing the transgene are microinjected into a blastocyst and transferred to a pseudo-pregnant host female, which bears chimeric progeny. Chimeras are bred as above to create homozygotes.

Gene-Targeted Models

Gene disruptions, replacements, or duplications are introduced into ES cells via homologous recombination between the endogenous (target) gene and exogenous (targeting) DNA, which possesses high sequence homology. ES cells are then microinjected into a blastocyst and transferred to a pseudopregnant host female, which then bear chimeric progeny. Chimeras are bred as above to establish homozygotes. Where a gene is disrupted or deleted, it is called a knockout; and where it there is new or duplicated gene, it is called a knockin. Where germline biallelic disruption causes embryonic lethality, site-specific recombinase enzymes under the control of tissue-specific promoters can be use to target an organ of interest. Further temporal control can be provided using exogenous ligands (tamoxifen) to regulate expression of Cre-recombinase.

Urological Cancer-Specific Models

Prostate Cancer

The unique biological features of adenocarcinoma of the prostate (prostate cancer) pose challenges to pre-clinical modelling of the disease. Prostate cancer is initially slow-growing, multifocal, responsive to chemical/physical castration, subsequently castration resistant, and has a propensity for bony metastasis. The use of animal models in prostate cancer is significantly limited by the fact that this disease is extremely rare in other species, even non-human primates. Therefore, most studies have relied on human-derived and mouse models. Presently, a number of different models are in use [5]; however none representative of prostatic intraepithelial neoplasia (PIN) or metastasis are derived from humans.

Cellular In Vitro Models: (Reviewed in [6, 7])

The "classical" prostate cancer cell lines are: LNCaP, obtained from the supraclavicular lymph node metastasis of 50-year old Caucasian; DU-145, derived from a moderately-differentiated brain metastasis of 60-year old Caucasian; and PC-3, derived from a bony metastasis of 60-year old Caucasian. These cells lines have dominated the scientific literature, but are not representative of the full disease spectrum. Hence, a large number of new lines and clonal derivatives of the original lines have been developed by a variety of methods including chemical mutagenesis, castration of host animals bearing xenograft tumours, and viral transformation. For example, the LNCaP-AI clonal derivate of the androgen-dependent LNCaP cell line is able to grow in androgen-depleted conditions following repeated passages in steroid-depleted medium.

Animal In Vivo Models

Xenografts

The successful *in vivo* propagation of cell lines derived from primary tumours and metastases led to the development of a number of ectopic xenograft models including the CWR, MDA Pca, LuCaP and LAPC series (reviewed in [8]). The major successes in serially transplantable ectopic xenografts were the Case Western (CWR) series, established from primary human cell lines in Nude mice with sustained-release testosterone pellets (CWR 21, 31, 91, 22). CWR22 regresses after androgen withdrawal, but can become resistant to androgen ablation from castration (CWR22R). Immortalised xenograft-derived cell lines have also been established (e.g. 22Rv1). More recently, orthotopic transplantation of human prostate cancer cell lines has gained popularity, but is reliant on modern imaging techniques for tumour monitoring.

Mouse Models: (Reviewed in [9]*)*

Despite significant anatomical differences between the human and mouse prostate, the mouse remains the best and most widely-used pre-clinical prostate cancer model.

Syngeneic Model

The mouse prostate reconstitution (MPR) model is a syngeneic ectopic allograft model where the fetal urogenital sinus is differentiated into a mature prostate following grafting under the renal capsule of an adult isogeneic male host. *Ras* and *myc* oncogenes are introduced by retrovirus-mediated transduction into the mesenchymal and epithelial compartments of the syngraft prior to transplantation.

Transgenic Models

The first effective transgenic mouse model (TRAMP) was driven by a simian virus 40 (SV40) viral transgene under regulatory control of a prostate-specific promoter. Mice bearing this transgene develop high-grade prostatic intraepithelial neoplasia (HGPIN) that progresses to adenocarcinoma and metastasis. More recent models have overcome the issues associated with viral transgenes (pleiotropic effects, neuroendocrine differentiation), and have used a variety of endogenous-promoters and transgenes to induce malignant transformation.

Gene-Targeted Models

Using a gene-targeted model (Cre-LoxP recombination system), prostate-conditional loss of the *Pten* (phosphatase and tensin homolog) tumour suppressor gene has been shown to drive invasive carcinoma and metastasis [10]. This technology has been used to study the effect of other oncogenes and tumour suppressor genes in the murine prostate.

Dunning Rat Model: [11]

The R-3327 tumour is a well-differentiated, slow-growing, non-metastatic adenocarcinoma which developed spontaneously in a rat and was subsequently transplanted into a syngeneic rat host. A number of sub-lines have been established with different distinct phenotypes, useful for studying androgen ablation and castration resistance, and lymph node metastasis.

Canine Model

Canines are the only species in which benign prostatic hyperplasia, HGPIN, and prostate cancer are frequently seen. Prostate cancer spontaneously develops and can metastasise to bone. However, tumours do not express a functional androgen receptor, and are therefore androgen-independent. Tumours only develops in elderly animals, and hence maintenance costs preclude the widespread use of this animal.

Bladder Cancer: *(Reviewed in* [12]*)*

Urothelial cell carcinoma represents ~90 % of bladder cancers in the western world, and is unique amongst non-cutaneous epithelial cancers due to two molecular pathways of tumourigenesis yielding distinct disease phenotypes. Superficial bladder cancers frequently harbour mutations in *HRAS* and *FGFR3* genes, and invasive tumours arising from carcinoma *in situ* (CIS) or *de novo* often contain mutations within *TP53* and *RB*. Available experimental models reflect these genotypes.

Cellular In Vitro Models

Primary *in vitro* culture of bladder cancer cells is technically-difficult, and immortalised cancer cells may not be representative of the tumour of origin due to difference in morphology, growth characteristics and phenotype. The *ras* oncogenes were originally identified in the T24 human differentiated cell line derived from a recurrent bladder tumour, which also contains mutant *TP53*. Examples of cell lines used to study superficial cancers include RT4 (wild type *TP53*) and RT112. Cell lines used to study invasive disease include EJ28, and 253 J, which is derived from an orthotopic metastatic model.

Animal In Vivo Models

Spontaneously development of bladder cancer in mammals is a rare phenomenon, and therefore a number of techniques have been employed to drive carcinogenesis:

Environmentally-Induced Models: (Reviewed in [13])

Chemical carcinogens can be introduced into the bladder to induce spontaneous bladder cancer in immune-competent hosts. These include *N*-methyl-*N*-nitrosurea (MNU), *N*-[4–(5-nitro-2-furyl)-2-thiazolyl]-formamide (FANFT) and *N*-butyl-*N*-(4-hydroxybuthyl) nitrosamine (BBN). Direct application of carcinogens to the bladder induces urothelium-specific tumours high rates of success. The tumour grade, presence of CIS and other pathological features, disease progression and degree of invasion correlates with the type of carcinogen, dose, and host genetic background. Tumourigenicity is enhanced synergistically when carcinogens are delivered over several fractions. However, tumour induction can take 8–14 months and carcinogens are hazardous to the user.

Allograft and Xenograft Models: (Reviewed in [14])

Orthotopic transplantation of T24 and other human cell line xenografts into the murine bladder can be performed to study superficial and invasive bladder cancer. Xenografts have a variable tumour implantation and formation rate, which may affect the reliability and reproducibility of experiments. Intravesical immunotherapy can be tested in syngeneic orthografts of MB49 and MBT-2 cell lines in immune-competent hosts (derived from 7,12-dimethylbenzanthracene- and FANFT-transformed murine bladders, respectively).

Genetically-Engineered Models: (Reviewed in [13])

Typically, genetically-engineered models using a combination of spatial- and temporally-regulated transgenic and gene-targeted approaches in the murine bladder. A transgenic approach using the viral transgene SV40 under regulatory control of the uroplakin promoter yields CIS and highly-invasive murine bladder tumours through inactivation of *TP53* and *RB*. Mutant *HRAS* targeted to the bladder with the uroplakin promoter results in superficial papillary lesions in the murine bladder, and coupled with bladder-specific expression of dominant-negative *TP53* accelerates *HRAS*-driven invasive tumourigenesis. An example using conditional gene-targeted (Cre-LoxP recombination system) knockouts of *TP53* and *PTEN* tumour suppressor genes in the murine bladder yield tumours and metastases. The mTOR (mammalian target of rapamycin) pathway is up-regulated in these tumours, which regress following treatment with the mTOR inhibitor rapamycin.

Renal Cancer

Renal cell carcinoma represents ~85 % of all renal cancers, and most sporadic cases possess clear cell histology (followed by papillary, chromophobe, oncocytoma, and collecting duct carcinoma, respectively). Molecular research has focused on

hereditary syndromes that predispose to the disease, and are associated with somatic mutations (within *VHL*, *c-Met*, *BHD*, *FH*, *TSC1*, and *TSC2* genes), some of which are also present in some cases of sporadic tumours.

Cellular In Vitro Models

There are a number of human cell line models of renal cancer. Examples include the *VHL* positive RCC-1 and SN12C, and *VHL*-negative 786–0. The RENCA model, derived from a pleomorphic granular cell-type adenocarcinoma, which arose spontaneously in the kidney of Balb/c athymic mouse, is one of the most commonly studied models of renal cell carcinoma (reviewed in [15]).

Animal In Vivo Models: (Reviewed in [15])

Studies of renal cancer pathogenesis have been limited by the paucity of animal models that accurately represent the tumourigenesis and disease progression in humans.

Environmentally-Induced Models

A number of carcinogens are able to induce spontaneous renal cell carcinoma development but with poor transformation rates. However, a single dose of streptozocin injected into the tail vein of a CBA/H/T6J mouse has been shown to yield a high incidence of spontaneous renal cell carcinomas, which subsequently metastasizes in females [16].

Allograft and Xenograft Models

Human renal cell carcinoma cells can be ectopically implanted into immune-compromised mice and develop tumours, which only infrequently metastasize [17]. Subcutaneously implantation of RENCA cells in a syngeneic host (BALB/c mouse) results in highly vascular tumours, with spontaneous metastases develop to abdominal lymph nodes, lungs, liver, and spleen (reviewed in [15]). Orthotopic implantation of streptozotocin-transformed murine renal cancer cells in a syngeneic host results in hypervascular tumour formation and spontaneous lung metastases [18].

Genetically-Engineered Models

Genetic disruption of the most commonly-mutated genes in sporadic human renal cancers has failed to yield renal tumours in murine models. Conditional inactivation of *VHL* and *PTEN* tumour suppressor genes in the mouse kidney elicits cyst formation but not cancer [19]. Murine models harbouring genetic mutations associated

with familial renal cancer syndromes are associated with high neonatal mortality, long latency to tumour development, and lack of tissue-specific gene-targeting. Hereditary renal cell carcinoma develops in Eker rats heterozygous for an insertional germline mutation in the tuberous sclerosis *TSC2* tumor suppressor gene [20]. A germline mutation has been identified in the Birt-Hogg-Dube (BHD) gene of the Nihon rat, which is also predisposed to renal carcinoma, and may provide insight into human BHD syndrome [21].

Wistar-Lewis Model

Renal adenocarcinoma spontaneously develops in the Wistar-Lewis rat and predictably metastasizes to the lung. The histopathological features of the tumour mirror the clear cell histological subtype in humans [22].

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Chapter 3
Genetics and Genito-Urinary Cancer

Mark R. Morris and Eamonn R. Maher

Basic Principles

Cancer results from the accumulation of genomic alterations (mutation). Most cancers arise from random somatic (acquired) mutations (though germline (inherited) mutations are present in some tumours (see section on kidney cancer)). These mutations persist, and further genetic alterations occur, through a process of natural selection or **clonal evolution**. As a clone of cells acquire mutations that provide increased proliferative and survival potential they outgrow other cells with less "advantageous" mutations [1] (Fig. 3.1).

Within the tumour cell population it is common to find cancer stem cells [2], cells that have many of the traits of normal stem cells and have the capacity to seed new tumours [3]. To date it is not clear how these cancer stem cells originate; however they play a significant role in the pathogenesis of many cancers and may be the primary cause of disease recurrences following radio- and chemo-therapy [4].

M.R. Morris, PhD, BSc (✉)
Department of Biology, Chemistry and Forensic Science,
University of Wolverhampton, City Campus South, Wulfruna Street,
Wolverhampton WV1 ILY, UK
e-mail: morrismr@wlv.ac.uk

E.R. Maher, BSc, MD, FRCP, FMedSci
Department of Medical Genetics, University of Cambridge,
Cambridge, UK

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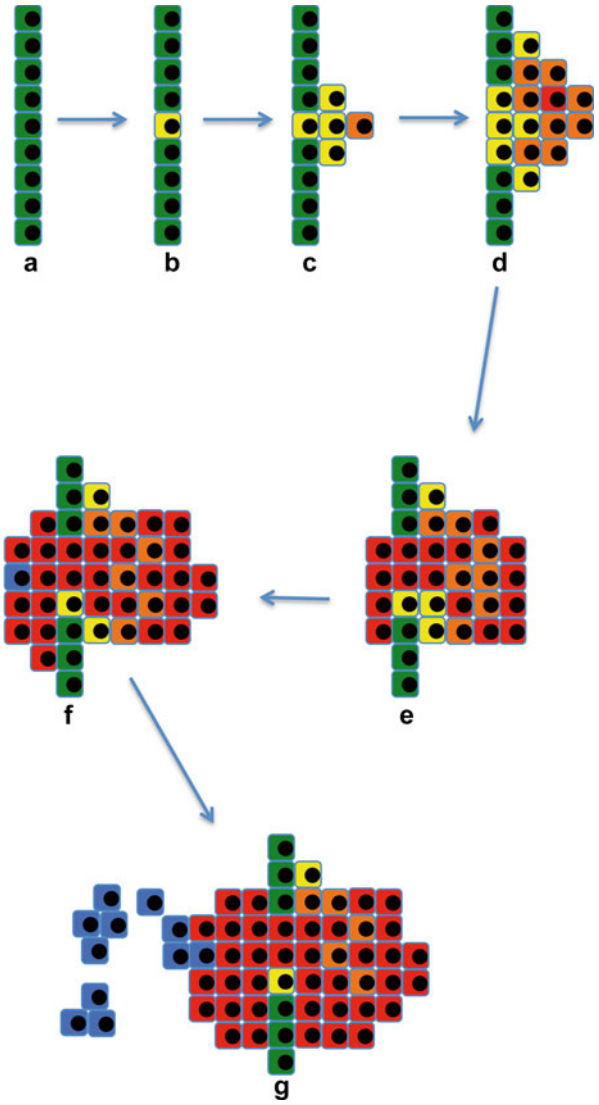

Fig. 3.1 Clonal evolution drives tumor progression. (**a**) Healthy epithelium. (**b**) The first oncogenic mutation occurs in a single epithelium cell (*Yellow* cell) resulting in the growth of a genetically homogeneous benign lesion. (**c**) A second mutation occurs in one of the cells in the benign lesion (*orange* cell) conferring a further growth advantage. (**d**) Increased numbers of rapidly dividing cells increases the likelihood of further mutations (*red* cell) which leads to (**e**) the growth of a more malignant and invasive clone within the primary tumor. (**f**) A further mutation in a cell within the malignant subclone causes further transformation and (**g**) the capacity for distant metastasis

Regulators of Tumour Development: Tumour Suppressor Genes and Oncogenes

Genomic alterations that drive tumour growth alter the activity of genes that express proteins responsible for the tight regulation of the cellular pathways involved in DNA replication, growth, differentiation, motility and cell survival (see below in "Molecular genetics"). Genes that express proteins that negatively regulate these processes are termed tumour suppressor genes and genes that positively regulate these processes are termed proto-oncogenes.

Tumour suppressor genes are commonly de-activated during tumour development and inactivation can occur by a variety of mechanisms including mutation, gross chromosomal deletion or epigenetic mechanisms such as promoter methylation.

Proto-oncogenes are normal genes that are necessary for normal cell survival. However mutations may occur that result in these genes being abnormally activated (e.g. mutations may cause activation in the absence of normal stimulatory signals) or expressed (e.g. chromosomal amplification may result in overexpression). Proto-oncogenes that are erroneously activated are termed **oncogenes**.

A number of key tumour suppressor genes, particularly those involved in the regulation of cell cycle control and DNA replication are commonly dysregulated in cancers. However, the frequency of specific gene disruption in tumours arising from different tissue types varies markedly. This holds true for tumours of the urological organs, most notably the frequent loss of the *Von Hippel-Lindau tumour suppressor gene* (*VHL*) in renal cancers and activating mutation of the proto-oncogene *Fibroblast Growth Factor Receptor* in Bladder cancers (see below on "Molecular genetics").

The Requirements of Tumour Growth: The Hallmarks of Cancer

For cells to persist and proliferate with an increasingly malignant phenotype they must acquire a number of specialized traits that enable them to escape normal cellular control and the growth constraints of their local microenvironment. In their seminal review, cancer biologists Douglas Hanahan and Robert Weinberg [5, 6] identified six key requirements for cancer evolution, these were termed the hallmarks of cancer. The six hallmarks that differentiate tumour cells from the non-malignant cells from which they have originated are common to all cancers, including those of the urological system. However the specific processes and pathways that facilitate the development of the hallmarks vary markedly between specific tumour types. The Hallmarks of cancer, as first outlined by Hanahan and Weinberg [5, 6], are outlined in Table 3.1.

1. **Tumour cells must become self sufficient in growth signals**. The vast majority of cells in any tissue do not frequently divide; they remain in a replicatively resting state termed quiescence. This is, in part, maintained by a tight control of growth factor molecules (GFs) in the tissue microenvironment. Cancer cells lose the requirement for microenvironment derived GFs through two principal mechanisms;

1. Tumour cells must become self sufficient in growth signals
2. Tumour cells must evade growth suppression
3. Tumour cells must evade programmed cell death; Apoptosis
4. Tumour cells are Immortal
5. Tumour cells induce angiogenesis
6. Tumour cells are invasive

Table 3.1 The hallmarks of cancer [5, 6]

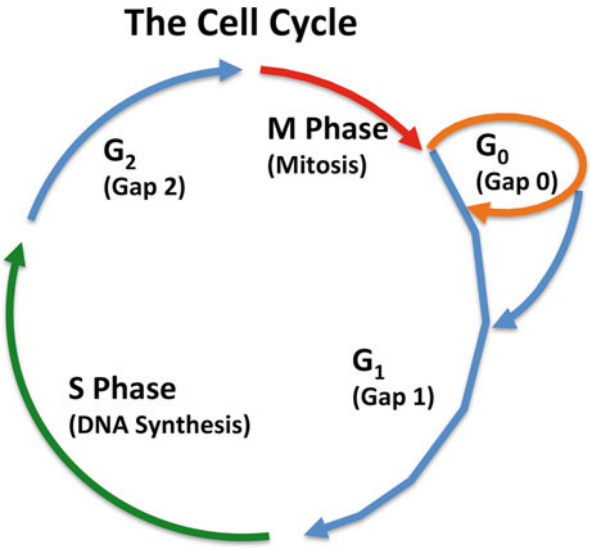

Fig. 3.2 The cell cycle. Differentiated cell in a tissue generally do not replicate, they are quiescent (Gap 0). G_0 is maintained by a delicate balance of anti and pro-proliferative signals. Transition from G_1 to S-phase is regulated by a complex network of proteins frequently dysregulated in tumour formation. The ultimate signal for a cell to enter S-phase is the Cyclin-dependent kinase mediated inactivation (by phosphorylation) of the retinoblastoma protein (pRB). Once a cell has entered S-phase it is committed to replicate its DNA. Following DNA replication a second checkpoint is reached (G_2) where mechanisms ensure that DNA damage has not occurred either by repairing lesions or committing the cell to apoptosis. Release from G_2 is followed by mitosis

they can acquire the capacity to produce their own GFs (autocrine growth factor stimulation) or/and they acquire mutations that results in cell signaling pathways down-stream of GF stimulation to be permanently switched on [7].

2. **Tumour cells must evade growth suppression**. Cell division is tightly regulated. This highly orchestrated process is known as the cell cycle (Fig. 3.2). The initial "decision" to divide occurs at the G1/S phase. Quiescent cells do not proceed through G1 to S phase due to the presence of anti-proliferative signaling molecules secreted by surrounding cells. In common with GFs, these molecules bind trans-membrane receptors that signal to intracellular molecules ensuring the cell does not divide. G1 transition is negatively regulated by a network of tumour suppressor genes and is ultimately controlled by the archetypal tumour suppressor; pRb and its relatives p107 and p130 [8, 9]. Genes involved in the negative regulation of G1/S phase transition are amongst the most frequently mutated in tumours and are common to many cancer types [10] (see section on "Molecular genetics" below).
3. **Tumour cells must evade programmed cell death**; **Apoptosis**. Cancer cells, under the influence of increased mitotic signaling and loss of cell cycle control replicate at an increase rate relative to normal cells. This dysregulated signaling and associated hyperproliferation result in physiological stresses that can trigger signaling

pathways that ultimately result in cell death, termed apoptosis. A finely balanced network of pro- and anti- apoptotic proteins determines the fate of cells. Apoptosis is triggered when pro-apoptotic signals outweigh anti-apoptotic signals. A common stress in cancer cells is increased DNA damage, which occurs as a result of hyperproliferation or exposure to mutagens. Elevated levels of DNA damage results in the accumulation of the canonical tumour suppressor p53 [10]. p53 is a transcription factor responsible for elevating the transcription of >100 target genes that direct a variety of cellular responses to stress including pro-apoptotic genes. Inactivation of p53 is the most common genetic defect in tumours; more than half of all tumours have loss of function mutations in p53 [11]. In addition to loss of apoptotic control, inactivation of p53 has wide-ranging pro-oncogenic effects. In tumours that retain wtp53, programmed cell death can be evaded by an imbalance of down-stream pro and anti-apoptotic signaling proteins through genomic alterations.

4. **Tumour cells are Immortal**: As discussed above, cells found within a tissue do not generally divide uncontrollably. However, once removed from the constraints of their surrounding microenvironment, either through oncogenic alterations *in situ* or experimentally removing cells from their constraining microenvironment and growing them *in vitro* (in tissue culture), cells can grow at a steady rate. However, this growth is not indefinite – there are two well defined barriers to continued cell growth. The first of these barriers is cellular senescence. Senescent cells stop dividing and in tissue culture become enlarged. Although senescent cells no longer have the potential to replicate they are still alive. Ultimately, many of the same intercellular pathways that regulate growth inhibition and aspects of apoptotic control are activated to induce senescence. Through the acquisition of mutations in these pathways senescence can be evaded [12]. Cells that escape senescence continue to divide until a second growth barrier is reached; this barrier, termed crisis, is the result of continued cell replication and is associated with increasing numbers of these cells dying. *In vitro*, crisis usually results in no viable cells remaining. However, very rarely a cell escapes crisis and become immortal, possessing limitless replicative potential [13].
   With every cell division chromosomes become shorter by 50–200 bp, this is a consequence of DNA polymerase not completely replicating the 3' ends of DNA during division [14]. To ensure that important genetic information is not lost and chromosome end-to end-fusion does not occur, the ends of chromosomes are capped with the repetitive sequence TTAGGG, termed the telomere. Telomeres have an average length of 10–12 kb. Telomere shortening acts a clock measuring cellular replicative age and when a specific telomeric length is reached (4–6 kb) signalling pathways leading to senescence are induced [14]. If senescence is not induced cells may proceed to crisis. For a cell to escape crisis it must be able to maintain telomere length. This is achieved in >90 % of all tumours by the expression of telomerase; an enzyme, generally not expressed in somatic cells, responsible for adding telomere repeat sequences to the end of chromosomes. Expression of telomerase alone is sufficient to immortalize cultured cells [15].
5. **Tumour cells induce angiogenesis**: All cells within a given tissue require oxygen and nutrients provided by nearby capillaries. This requirement is such that all

cells reside within 100 μM of a capillary. As a tumour forms many of its component cells will find themselves outside of the zone where oxygen and nutrients can readily diffuse, this low level of oxygen (hypoxia) and nutrients is a natural barrier to large tumour formation. To circumvent hypoxia-induced cell death many tumours secrete angiogenic factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) (See "Kidney cancer" below), these factors encourage capillaries to sprout and proliferate towards the tumour [16]. Over-expression of angiogenic factors alone is not sufficient for angiogenesis as many anti-angiogenic factors exist, these are often down regulated in the tumour itself and tumours express high levels of proteinases that degrade anti-angiogenic factors [17]. In combination this results in an imbalance of pro and anti-angiogenic factors that can result in the formation of well vasculated tumours.

6. **Malignant tumours invade the surrounding tissue and metastasis to distant organs**: The vast majority of cancer deaths are caused by secondary tumours (metastases) that derive from primary tumour cells invading their local microenvironment followed by entry into the local blood and lymphatic system (intravasation) and eventual invasion into distant organs (extravasation). Once the parenchyma of a new organ has been invaded these micrometastases must acquire the necessary traits to survive and proliferate within the confines of the new microenvironment [18]. This multi-step process requires multiple adaptions and although many of the details are not fully elucidated, it is known that invasive tumour cells have altered expression of cadherins (which determine the adherence of cells to one another) and often overexpress matrix-degrading enzymes. Expression of E-cadherin is required for the correct formation of epithelial tissue sheets and maintaining cell contact induced quiescence [19], and loss of E-cadherin expression is found in many cancers. Conversely, other cadherins, such as N-cadherin, that are involved in cell migration during embryogenesis are often expressed at high levels in aggressively invasive tumour cells [20]. The capacity of a tumour to invade and colonise a particular distant organ is, to some degree dependent upon the site of origin. The most common sites of metastasis for Bladder, Prostate, kidney and testicular cancers are local lymph nodes, bone, lung and liver [21].

Molecular Genetics

Common Molecular Components of Cancers

All tumours have a number of common pathways that are dysregulated, many of these pathways regulate cell cycle progression which is controlled by a number of checkpoints that ensure cells commit to divide only when the appropriate signals are received and once a cell commits to divide it's DNA is replicated with high fidelity and chromosomal separation occurs correctly prior to cytokinesis [8]. Quiescent cell do not enter the DNA synthesis phase (S phase) of the cell cycle while the canonical tumour suppressor gene product Retinoblastoma protein (pRB) is activated. pRB is a nuclear phosphoprotein that binds to, and inhibits the activity of, the E2F family of transcription factors. Following

inactivation of pRB, E2F transcription factors are released and mediate the transactivation of target genes that facilitate the transition from G0/G1 to S phase. These targets include Cyclins, Cyclin dependent kinases, E2F family members themselves, DNA polymerases, DNA repair genes. Also, to ensure control of growth is maintained negative regulators are targeted, these include pRB, p53, p21 and BRCA1 [11]. Loss of functional pRB is common to a number of tumours, particularly retinoblastoma (it was first identified in patients with germline RB1 gene mutations who developed bilateral retinoblastoma), osteosarcoma, lung, melanoma and bladder cancers [22]. The *RB1* gene has been found to be mutated in 32 % of sporadic bladder cancers [23]. The presence of *RB1* mutations in other urological cancers is low; 7 % of prostate tumours have mutations and less than 1 % of kidney or testicular cancers have *RB1* mutations [23].

Loss of cell cycle control is a key requirement for tumour progression and the RB pathway can be considered a central hub of control that is regulated by many tumour suppressors and proto-oncogenes. These controlling proteins themselves often have multiple functions whereby dysregulation results in a contribution to the development of multiple cancer hallmarks.

Following appropriate mitogenic signalling Cyclins D and E and their associated dependent kinases (cyclin dependent kinase 4, 6 and 2) phosphorylate pRB resulting in its inactivation [11]. The cyclins and their dependent kinases are proto-oncogenes frequently found to be over-expressed or constitutively activated through genomic alterations or dysregulation of upstream regulators of their expression. In kidney cancer Cyclin D1 is frequently over-expressed due to loss of the tumour suppressor pVHL, which influences many cancer-related pathways and networks. The activity of Cyclin/CDKs is a negatively regulated by a family of proteins called CDK Inhibitors. These include $p16^{INK4a}$, $p15^{INK4b}$, $p18^{INK4c}$ and $p19^{INK4d}$ that inhibit the D type cyclin dependent kinases 4 and 6 and the CIP/KIP family, whose members ($p21^{CIP1/WAF1}$, $p27^{KIP1}$, $p57^{KIP2}$) inhibit the activity of all CDKs, these proteins are commonly under-expressed or lost in multiple tumour types [24]. Loss of $p16^{INK4a}$ is a common, early event in the evolution of bladder cancers [25]. Following DNA damage, or other physiological stresses, p53 is activated by phosphorylation resulting in the up-regulation of cell cycle inhibitory genes such as $p21^{CIP1/WAF1}$ or pro-apoptotic genes such as *PUMA* and *BAX* [26]. p53 is the most commonly dysregulated gene in tumours, it may be lost by deletion or epigenetic dysregulation or by point mutation, including dominant negative mutations that cause p53 to form inactive tetramers [27].

Genetics of Genito-Urinary Cancers

Kidney Cancer

The most common type of kidney cancer is Renal Cell Carcinoma (RCC). RCC is derived from proximal tubular epithelial cells. The majority of RCC (~75 %) are classified as clear cell (conventional), the next most common type are papillary tumours (~15 %) [28].

Unlike many other tumours, in RCC the tumour suppressor genes *TP53* and *RB1* are infrequently deactivated by direct mutation (*TP53* is mutated in 11 % and RB1 in <1 % of all kidney cancers, while *CDKN2A*-p16 is mutated in 10 %) [23]. The low frequency of mutation in these key tumour suppressors indicate a significant difference in the pathogenesis of RCC compared to many other neoplasms. Deletion of the short arm of chromosome 3 is the most common genetic aberration in RCC occurring in up to 90 % of clear cell RCC. However 3p loss is not associated with papillary RCC [29].

VHL

The *VHL* gene was identified by studying patients with the Von Hippel-Lindau disease, familial kidney cancer syndrome, which is caused by germline *VHL* gene mutations [30]. The *VHL* gene maps to the short arm of chromosome 3 (3p25.3) and the most frequent genetic event in the evolution of clear cell RCC is the Inactivation of *VHL*. The VHL protein binds to elongin B, elongin C and cullin 2 to form a ubiquitin ligase complex [31] that facilitates the ubiquitination of target proteins leading to their proteosomal degradation. The best studied of these targets are the Hypoxia Inducible Factors HIF1-α and HIF2-α subunits (form herein referred to as HIF-α) that in combination with HIF-β form the Hypoxia Inducible Factor HIF, a transcription factor [32]. Under normal oxygen conditions (normoxia) HIF-α is targeted for VHL-directed ubiquitination by the hydroxylation of a crucial proline residue by the enzyme HIF Prolyl Hydroxylase (PHD) [33]. Hence, in the presence of functioning (wild-type) VHL, and under normoxic conditions, HIF is rapidly degraded. However loss of both copies (alleles) of *VHL* results in the accumulation of HIF under normoxic conditions and elevated levels of its target genes [32].

The Target genes of HIF are regulatory units of several key pathways that can contribute to cancer hallmarks, notably **angiogenesis** by the upregulation of: Vascular Endothelial Growth Factor (VEGF), Platelet Derived Growth Factor β (PDGFβ), Transforming Growth Factor β (TGFβ) and Connective Tissue Growth Factor (CTGF), **Invasion and metastasis** by the up-regulation of: Stromal cell derived Factor (SDF) CXC chemokine receptor 4 (CXCR4), Matrix Metallopeptidase 1 (MMP1) and c-MET, **Proliferation and Survival** by the up regulation of: Cyclin D1 and Transforming Growth factor α (TGF α). **Cell metabolism** is also up regulated by HIF dependent increased expression of genes involved in glucose uptake and metabolism: Hexokinase 2 (HK2) and pyruvate dehydrogenase kinase (PDK1) and genes involved in acid/base regulation: Carbonic dehydrogenase 9 (CA IX) and Carbonic dehydrogenase 12 (CAXII) [34]. Clear cell RCC is a highly angiogenic tumour type, resulting from the dysregulation of multiple positive regulators of angiogenesis following the loss of a single tumour suppressor gene (*VHL*). In addition to regulating HIF1 levels, VHL has multiple HIF-independent functions but it is unclear how they may contribute to RCC. Although Loss of VHL is extremely common in clear cell RCC it is not sufficient alone for tumorigenesis to occur, further oncogenic events are required.

PBRM1

In 2011, following a screen of clear cell RCC by whole exome sequencing truncating mutations were found in the *PBRM1* gene which maps to chromosome 3p21 and encodes BAF 180 (Polybromo 1) a component of the pBAF SWI/SNFB chromatin re-modelling complex [35]. Chromatin re-modelling associated with pBAF SWI/SNFB is implicated in replication, transcription, **DNA repair** and control of **proliferation** and **differentiation**. *PBRM1* truncating mutations were found in 41 % of clear cell RCC, Many of these tumours had also lost functional VHL. Three other genes involved in histone modification have been identified as mutated (at a lower frequency than *PBRM1*), these are *SETD2* or *JARID1C* and *UTX* [36] suggesting that, in addition to VHL related gene dysregulation, modifying gene expression by an epigenetic mechanism plays a principal role in the formation of many renal tumours.

c-MET

c-MET is a cell surface transmembrane receptor for hepatocyte growth factor (HGF). Activated c-MET signals, via RAS and PI3K, to the Mitogen-Activated Protein Kinase (MAPK) cascade resulting in **proliferation** and (upon sustained activation) **Invasion** [37]. Activating mutations of the tyrosine kinase domain of c-MET have been found in 13 % of sporadic papillary RCC [38]. Moreover, amplifications of the region of chromosome 7 where the cMET gene lies and chromosome 7 trisomy are common in papillary RCC [39]. Up-regulation of cMET can result in receptor auto-activation that, as with activating mutations, negates the requirement for HGF. PTEN, a negative regulator of the MET-PI3K pathway has been found to be mutated in approximately 3 % of RCC (COSMIC) and Hepatocyte growth factor activator Inhibitor 2 (HAI-2) which prevents activation of c-MET by HGF is frequently down regulated or silenced by epigenetic mechanisms [40]. Activating mutations of the RAS family of proto-oncogenes is rare in RCC.

RASSF1

RASSF1 encodes a protein that regulates cell cycle at the G1/S phase and G2/M phase transitions and also induce apoptosis, it is frequently epigenetically inactivated in RCC by promoter hypermethylation [41].

Bladder Cancer

The vast majority of Bladder cancers (90 %) arise from the urothelial cells that line the bladder (Urothelial carcinoma; UCa or Transitional Cell Carcinoma; TCC). These cancers are traditionally classified by their histopathology and are either

non-muscle invasive bladder cancer (NMIBC) or muscle invasive bladder cancer (MIBC) bladder cancer that grow into the muscle layer of the bladder. The remaining 10 % of tumours are either squamous cell, derived from the bladder lining cells (8 %) or adenocarcinoma, derived from the mucous producing cells (1–2 %) [42].

Loss of the short arm of chromosome 9 (9p) is common to both nonmuscle and muscle invasive bladder cancers. The tumour suppressor *CDKN2A* (*p16/ARF*) is present in this region. Chromosome deletion, point mutation and promoter methylation resulting in complete loss of p16/ARF activity is common [43, 44]. Other Tumour suppressor genes present on 9p include the interferon-α (*INF-α*) gene, the product of which is involved in apoptotic control [45], and *Tuberous Sclerosis 1* (*TSC1*) the product of which is involved in the regulation of multiple processes including cellular growth [46].

Loss of Chromosome 9p is an early event in bladder cancer that results in the proliferation of a pre-neoplastic clone that is phenotypically similar to normal urothelium. The proliferation of a large number of phenotypically 'normal' cells with an increased neoplastic potential is known as a field effect because there is a large number of cells (the field) from which additional genomic alterations may occur in a single cell for tumorigenic clonal expansion to occur [47].

Two separate genetic mechanisms lead to the development of the two main phenotypic variants of bladder cancers, both arise from a pre-neoplastic field. 70–80 % of TCC are low-grade non-invasive papillary tumours, these commonly have activating mutations in the Fibroblast Growth Factor receptor 3 gene (*FRGF3*), this is the most commonly mutated gene in bladder cancers (45 %) [23]; over-expression of *FGFR3* is also common [48]. Fibroblast Growth Factor receptor 3 is a tyrosine kinase receptor that (in a similar manner to c-MET (see "Kidney cancer" below)), when activated, signals to the MAPK cascade via RAS and PI3K [49]. Activating mutations of the *RAS* proto-oncogene are also common (9 %;) [23] as are activating mutations of *PIK3CA* (20 %;) [23], the gene that encodes the catalytic subunit of PI3K.

Loss of p53 and/ or pRB activity in cells found within a pre-neoplastic field is associated with the development of Carcinoma *In Situ* (CIS) that frequently develops into high-grade invasive UCa. These highly invasive and metastatic tumours often overexpress the angiogenic factor VEGF, matrix metalloproteinases (MMPs) and have reduced expression of the epithelial cell adhesion molecule E-cadherin. Approximately 15 % of low-grade non-invasive papillary tumours progress to high-grade invasive tumours, this progression is associated with dysregulation of p53 and/or pRB and loss of chromosomes 8p, 11p and 13q which harbour the known tumour suppressor genes *SFRP1*, *WT1*, and *RB1* respectively [48]. As is common in RCC the tumour suppressor gene *RASSF1* is frequently silenced by promoter methylation in bladder cancer [50].

Prostate Cancer

Prostate cancer can be regarded as a multifocal disease as primary tumours often contain histologically and genetically distinct regions. However, the genomes of cells in advanced prostate cancer are similar indicating that these advanced

tumours have undergone clonal evolution. The majority of prostate tumours are adenocarcinomas derived from the epithelium. Prostatic Intraepithelial Neoplasia (PIN), which is characterized by luminal epithelial hyperplasia and a reduction of basal cells. PIN cells often have variation in the size and shape of their nuclei consistent with increased DNA content [51, 52].

Of the known Cancer-related genes, p53 is the most commonly mutated (19 %: COSMIC) in prostate cancer. The *MYC* oncogene is upregulated in many PIN lesions, However, this up-regulation is often not associated with chromosomal amplification (8q24). Genetic studies to identify inherited factors that predispose to prostate cancer found that genetic variants at chromosomal region 8q24 predisposed to prostate cancer by disturbing regulation of the *MYC* proto-oncogene [53]. The *MYC* containing 8q24 region is amplified in a significant sub-set of advanced metastatic prostate cancers [54]. Inactivation of the PTEN tumour suppressor gene (an inhibitor of the AKT/mTOR signalling pathway) is a common early event in prostate carcinogenesis [55] and inactivating mutations are also observed in 14 % of tumours (COSMIC). Less frequently the AKT/mTOR pathway is upregulated by activating mutations of *AKT* and *PI3K* (COSMIC). The RAS/RAF MAPK pathway is frequently upregulated through a paracrine mechanism in advanced prostate cancers [56] and less commonly via activating mutations of *RAS* (5 %: COSMIC) or *RAF* (4 %: COSMIC).

NKX3.1

NKX3.1 is a homeobox gene that codes for the homeodomain-containing transcription factor NKX3-1. NKX3-1 is predominantly expressed in the prostate and in an androgen dependent manner. *NKX3.1* is found within a 150 Mb region of Chromosome 8q21 that displays loss of heterozygosity (LOH, a marker of chromosomal alterations in cancer) in up to 85 % of high grade PIN lesions and adenocarcinomas, the frequency of LOH increases with increased grade of tumour [57]. Reduced expression of *NKX3.1* is associated with a reduced response to oxidative DNA damage [58]. It is thought that *NKX3.1* may act as a haploinsufficient tumour suppressor and that inactivation may be a key initiating event in the evolution of prostate cancer.

Androgen Receptor (AR)

AR is a member of the steroid hormone receptor family of ligand-activated nuclear transcription factors, its principal ligand is testosterone. AR plays a key role in normal prostate development and prostate cancer. Following androgen binding, AR is translocated to the nucleus where it acts as a transcription factor for a wide range of target genes via binding to hormone response elements in their promoters [59]. In relation to tumour formation, activation of AR positively regulates genes involved in cell proliferation and anti-apoptotic signaling [60].

Intact AR signaling is necessary for the development of prostate cancer; AR is present in primary and metastatic prostate cancers irrespective of tumour stage. Treatment for advanced prostate cancer is often surgical or chemical castration to reduce the level of testosterone signalling to AR. This treatment leads to rapid tumour apoptosis however relapse is common. In approximately 30 % of castration resistant tumours the AR gene copy number is amplified [61] a further 10–30 % acquire gain of function mutations that increase AR activity via different mechanisms including increased sensitivity to androgens, the capacity to respond to other hormones, auto-activation or increased protein stability [62]. In addition, metastatic tumours can express enzymes that synthesize androgens or convert other hormones into testosterone [63].

Testicular Cancer

Testicular cancer is the most frequent malignancy in men between 20 and 40 years of age [64]. Most tumors are of germ cell origin (Testicular Germ Cell Tumours: TGCT) composed of embryonic neoplastic germ cells. However, approximately 5–10 % are sex cord/stromal tumors (e.g., Leydig and Sertoli cell), or gonadoblastoma which contain germ cell and stromal elements [65]. Epidemiologic studies have suggested that gonadal hormone drive is a major factor in the development of germ cell tumors [66]. High frequency tumour suppressor gene mutations in TGCT are not obvious; the most frequently mutated genes are p53 (8 %: [23]) and KIT (9 %: [23]). Activating mutations of *KIT*, which encodes a tyrosine kinase receptor, are the most common point mutation in TGCT [67]. Upon binding its ligand Stem Cell Factor (SCF) KIT signaling via RAS/RAF to the MAPK cascade and PI3K to the mTOR pathway results in **increased proliferation** and **resistance to pro-apoptotic signals** [68]. In addition to this autocrine signaling, paracrine signaling is evident by increased levels of SCF in the microenvironment. Amplification of Chromosome 4p, containing KIT has been reported [69]. The Epidermal Growth Factor Receptor (EGFR) is overexpressed in >25 % of seminomas, this correlates to *EGFR* gene amplification. However EGFR overexpression has not been reported in teratomas [70]. EGFR2 (HER-2/neu) is also overexpressed (~13 %) in TGCT [71].

Invasive TGCTs commonly have amplifications of the short arm of Chromosome 12; to date relevant genes in this region have not yet been identified [72].

Hereditary and Genetic Aspects of Urological Cancers

Hereditary Renal Cell Carcinoma (RCC)

Von Hippel-Lindau Disease (VHL Disease) is an autosomal dominantly inherited neoplastic disorder. Affected individuals are at risk of developing renal cysts and clear cell RCC. Mutations in the *VHL* gene (see VHL gene above) have been identified in nearly all families with Von Hippel-Lindau Disease. VHL disease is also associated with retinal

and central nervous system haemangioblastomas, phaeochromocytomas, pancreatic islet tumours and endolymphatic sac tumours. The incident of *VHL* disease is approximately 1 in 36,000 [73]. Approximately 30–40 % of germline *VHL* mutations consist of deletions that remove one or more exons. The remaining mutations are either truncating or missense substitutions [74]. Truncating and exon deleting mutations or missense mutations that disrupt pVHL tertiary structure correlate with RCC and haemangioblastomas but not phaeochromocytomas. Whereas missense mutations that affect surface residues which results in some retention of function correlate with haemangioblastomas and phaeochromocytomas but a reduced risk of RCC. The pVHL mutations that do not disrupt HIF regulation correlate with phaeochromocytomas only, suggesting that HIF dysregulation is necessary for RCC development in VHL disease [75–77].

Hereditary Papillary RCC

Histopathologically, papillary RCC may be divided into two subtypes: type 1 tumors that are characterized by small basophilic cells with pale cytoplasm and inconspicuous nuclei are associated with activating mutations of the tyrosine kinase domain of the *c-MET* gene [78]; type 2 papillary RCC susceptibility may be associated with germline fumarate hydratase (*FH*) mutations [79]. Germline heterozygous *FH* mutations cause the Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) syndrome, Papillary type 2 tumours are rare in these patients; however, they are aggressive. Mechanistically, loss of FH results in an increase of fumarate, which inhibits the activity of Prolyl Hydroxylase Domain-containing proteins (PHD), which in turn are required for VHL dependent HIF degradation, resulting in the upregulation of HIF target genes.

Birt-Hogg-Dube Syndrome (BHD)

BHD is a dominantly inherited disorder characterized by cutaneous fibrofolliculomas, pulmonary cysts and chromophobe kidney tumours [80]. Germline mutations in the Folliculin gene (*FLCN*) have been identified in >90 % of families affected. The precise mechanism of FLCN activity is yet to be determined. However, it appears to regulate the mTOR pathway [81].

Familial RCC Associated with Succinate Dehydrogenase (SDH) Mutations

SDH proteins (SDHA, SDHB, SDHC and SDHD) are the enzymes that convert succinate to fumarate. Germline *SDHB* mutations are associated with a high risk of malignant phaeochromocytoma. Approximately 5 % of patients with inherited RCC will have a

SDHB mutation [82]. A variety of histological subtypes of RCC may be associated with *SDHB* mutations (and less frequently *SDHD*) and the lifetime risk of RCC in *SDHB* mutation carriers was estimated to be about 15 % [83]. In a similar manner to FH mutations loss of SDH activity may contribute to RCC development via stabilization of HIF.

Wilms' Tumour

Wilms' tumour is the most common solid tumor in childhood and affects approximately 1 in 10,000 children. The median age at diagnosis is 3–4 years [84]. Wilms' tumor is believed to arise from remnants of immature kidney. There is a high incidence of developmental abnormalities in children with Wilms' tumor e.g. about 5 % have genitourinary abnormalities. Approximately 1 % of children with Wilms' tumor have aniridia (the absence of the iris), compared with 1 in 50,000 of the general population and these children may also have other characteristic abnormalities associated with the WAGR syndrome (Wilms' tumor, aniridia, genitourinary abnormalities, mental Retardation) [85]. Most children with WAGR syndrome have cytogenetically visible chromosome 11 deletions involving band 11p13 and the association of aniridia and Wilms' tumour results from the contiguous deletion of the *WT1* (Wilms tumour 1) and PAX6 (aniridia) genes that are ~700 kb apart. WT1 is a DNA binding protein that activates or represses transcription dependent upon chromosomal context. Approximately 50 % of WAGR patients develop Wilms' tumours indicating the presence of other susceptibility genes [86].

Perlman Syndrome is a rare recessive overgrowth and cancer susceptibility syndrome with an associated increased risk of Wilms' tumour development [87]. Recently, causative mutations in the *DIS3L2* gene have been identified, DIS3L2 is an exonuclease that may regulate RNA levels controlling the expression of proteins key to the regulation of mitosis [88]. *DIS3L2* Mutations have also been found in sporadic Wilms' tumours.

Hereditary Bladder Cancer

There are no known Bladder cancer-specific hereditary diseases. However there is a familial aspect; first degree relatives of patients with bladder cancer have a two-fold increased risks of bladder cancer, a proportion of this risk can be accounted for by shared environmental factors; the most significant risk factor to developing bladder cancer is tobacco smoke [89]. Recent Genome wide association studies (GWAS) have identified a number of Simple Nucleotide Polymorphisms (SNPs) that, individually, have a low level of association with bladder cancer risk, indicating that susceptibility to the disease is a result of exposure to exogenous carcinogens and a large number of susceptibility genes with individual modest effects [25].

Hereditary Prostate Cancer

Men who have a first-degree relative with prostate cancer have a two-fold risk of developing prostate cancer, this increases to a five-fold risk if two first-degree relatives have prostate cancer. As with bladder cancer a large number of susceptibility alleles have been identified by GWAS [90, 91]. However, none have been found to occur with high frequency amongst families with a history of prostate cancer. Most notable are *BRCA2* mutations, approximately 2 % of men with early-onset prostate cancer (<55 years) had a germline *BRCA2* mutation [92]. A male *BRCA2* mutation carrier was estimated to have a 23-fold increased risk of developing prostate cancer by age 55 years and it also appears that male *BRCA2* carriers with prostate cancer have a poorer prognosis than similar non-carriers [93]. Recently germline mutations in the *HOXB13* gene were reported to increase prostate cancer risk at least 10-fold [94]. However germline *HOX13B* mutations appear to be uncommon.

Hereditary Testicular Cancer

Large families with a high incidence of testicular cancer have been described but are rare [95] and the majority of families are relative pairs, usually brothers, suggesting that susceptibility may be caused by genes with small or moderate effects. Sons and siblings of TGCT patients have a 4–6 fold or 8–10 fold increased risk of TGCT respectively. Twin studies have shown that risk is increased in monozygotic compared to dizygotic twins indicating that the genetic contribution in familial TGCT cases is greater than environmental factors [96]. Genome wide linkage analysis has indicated that susceptibility to TGCT is likely to be due to more than two genes. A 1.6 Mb Y chromosome deletion (designated gr/gr) that has been implicated in spermatogenic failure has been found in 3 % of TGCT cases with a familial history compared to 1.3 % of unaffected males indicating that this defect confers a two-fold increase of risk [97].

Recent GWAS have identified a number of loci that associate with increased risk of TGCT [98]. Perhaps most interesting amongst these is a region of chromosome 12q21 that contains the gene *KITLG* which encodes Stem Cell Factor, the ligand that activates KIT. A region of chromosome 5q21 that contains the gene *SPRY4* was also identified, SPRY4 is an inhibitor of the MAPK pathway that is activated by KIT signalling [99]. Furthermore, two SNPs were found within the region of chromosome 5p15 that contains the *TERT* gene that encodes telomerase, which is activated in germ cells and the majority of immortal tumour cells. These and a number of other associated regions are not sufficient to account for all cases of familial TGCT and further analysis is ongoing to identify other predisposition loci and genes.

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Chapter 4
Principles and Design Considerations of Clinical Trials

Bo Hu and Michael W. Kattan

Clinical trials are gold standard for evaluating any type of interventions used to screen, diagnose, prevent or treat urologic cancer. Herein we introduce the basic principles and design considerations of clinical trials. The discussion largely focuses on the various stages of clinical trials and design and implementation considerations in each stage. Possible sources of bias in clinical trials and methods of minimizing or eliminating this bias are also discussed.

Phases of a Clinical Trial

Modern clinical trials were introduced in 1950s [1], and they have become essential research tools evaluating medical interventions of diseases on human subjects. Clinical trials can be generally categorized into phases I-IV, which reflects the sequential process of the development of any therapies.

Phase I – Toxicity and Clinical Pharmacology

Once a new agent is tested in animal studies and is shown to have promise, a phase I clinical trial is carried out to evaluate its safety profile in human subjects. In most cancer trials, the subjects will be cancer patients, usually with advanced disease for which no established treatment has been effective. In other (non-cancer) settings,

B. Hu, PhD • M.W. Kattan, PhD (✉)
Department of Quantitative Health Sciences, Cleveland Clinic,
9500 Euclid Avenue, JJN3-01, Cleveland, OH 44195, USA
e-mail: kattanm@ccf.org

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phase I investigations will often include healthy volunteers [2]. Phase I trials in oncology have a primary purpose of finding the dose range that is safely tolerated in a patient population, which is referred to as the maximum tolerated dose (MTD). Secondary outcomes may include pharmacokinetics, pharmacodynamics, and any drug-related side effects. The number of patients recruited to a phase I trial is typically kept to a minimum (less than 80) to ensure that patients are not unnecessarily exposed to a drug that may be of little clinical use or that may have adverse side effects.

The design of a phase I trial generally follows a dose-escalation scheme that depends on the number of observed toxicity events (as predefined by the investigators). There are many different designs available, but a common scheme (3-plus-3 design) is as follows. Three patients are treated using the lowest dose of the agent under investigation. If more than one patient experiences unacceptable toxicity, the trial is terminated. If no unacceptable toxicities occur, the dosage is escalated to the next higher dose level and another group of three patients are treated at the higher dose level. If only one unacceptable toxicity occurs, three additional patients are entered at the current dose level. The dosage is escalated to the next higher level if none of these three patients experiences unacceptable toxicity; the current dose is declared the MTD if one patient experiences toxicity; accrual stops and the next lower dose is accepted as the MTD otherwise. Another popular design is the continual reassessment method (CRM), which estimates the dose–response relationship and consequently the MTD using a Bayesian modeling approach [3].

As a simple example, suppose a phase I clinical trial is used to investigate intravesical gemcitabine therapy in nonmuscle invasive bladder cancer. Toxicity of the gemcitabine dose is defined by any the Eastern Cooperative Oncology Group (ECOG) grade 3 or 4 hematologic toxicity or grade 3 or higher nonhematologic toxicity [4]. The study starts with an initial dose of 500 mg of gemcitabine in 100 mL 0.9 % w/v NaCl (0.9 % Sodium chloride-normal saline). Using increasing doses of 100 mg per escalation and the 3-plus-3 design scheme, the MTD of intravesical gemcitabine therapy is determined. Sometimes the MTD is not the dose taken forward to phase II, but could be the preceding dose that causes moderate and revisable toxicity in most patients [5].

Phase II – Safety, Feasibility and Efficacy

Phase II trials assess the safety, feasibility, and efficacy of the appropriate dose determined in phase I and its acceptable schedule. Patient response is measured after a predefined period of follow-up time. For instance, in the assessment of a cytotoxic agent to treat a tumor, the response can be classified as complete (no measurable tumor), partial (tumor has shrunk by some percentage), or stable (no sufficient shrinkage). Secondary outcomes that may also be investigated are the duration of the response, side effects of the agent, ease of administration to patients, and cost. Depending on the observed response rate, the drug is either accepted for further testing in large-scale phase III trials or it is concluded that the drug is not clinically effective in improving patient response.

A phase II trial design could be fixed, staged, or sequential in nature. Whatever the design though, a phase II trial has to be conducted prospectively. For a fixed design, a single cohort of patients is recruited, often with a sample size less than 200. This trial design was used to investigate the pain response in patients taking Tesmilifene plus Mitoxantrone for hormone refractory prostate cancer [6]. More commonly used designs are staged designs involving two or more patient cohorts. In staged designs, the response for the first cohort is assessed and, depending on the cohort's response rate, the trial is either terminated (due to strong evidence against or in favor of the efficacy of the drug) or continued to the next stage to evaluate the next cohort of patients. The Southwest Oncology Group 8811 is a trial that employs the two-stage design to study 5-fluorouracil and folinic acid in advanced breast cancer [7]. A detailed review of these designs is given in Gehan [8], Fleming [9] and Simon [10].

Multiple-stage designs are preferred over a fixed or single-stage design because the trial is terminated early if sufficient evidence exists partway through the trial that indicates that the treatment is ineffective in improving patient response. Early termination increases the speed with which trial results are reported, reduces the cost of the trial, and minimizes the number of patients who are given an ineffective treatment. However, multiple-stage designs are much harder to implement if the response to treatment takes a long period of time. In this case, the investigator must decide if accrual of patients should continue between stages.

The conventional phase II design has limitations [2]. The tumor response as a predictor of long-term efficacy might be questioned, particularly when the patients have advanced disease states and have been heavily treated. Another key problem is that patients in phase II trials are often highly selected, and such selection bias is not well understood.

To address these limitations and accelerate the drug testing process, alternative designs have been developed [11]. Phase I/II clinical trials have become increasingly popular where the first part of the trial establishes the safety of the agent and its MTD, and the second part of the trial assesses the safety and efficacy of the agent. This type of combined design was used to evaluate the safety and efficacy in the administration of dendritic cells and prostate-specific membrane antigen peptides in patients with advanced prostate cancer [12].

Phase III – Comparative

Once phases I and II have successfully demonstrated the safety and efficacy of a new treatment, phase III clinical trials are implemented to compare this new treatment to a control treatment. The control treatment may be the standard treatment that is currently being used to treat the disease, may involve the use of a placebo, or may involve no form of treatment at all. In most phase III trials, patients are randomly assigned to the treatment or control arm, leading to randomized clinical trials (RCTs). RCTs are the established gold standard for determining the value of any new treatment, and it is rare that a new treatment will be accepted without a

successful completion of a randomized phase III trial. In this phase of trials, patient response is typically measured by the time to disease recurrence or death.

Another type of design that is occasionally used in phase III trials is called the crossover design and is only used if the administration of treatments and response measurement are of short duration. In a two-period crossover design, patients are first randomly assigned to one of the two possible treatments. Patient response is then assessed after a certain time period. After a washout period where the effects of the first treatment are considered to be absent in the patient, he or she is then given the alternative treatment, and response is assessed again after the same length of time that was used for the first treatment. Such a paired design requires fewer patients than the parallel group design. However, a washout period is unethical in some trials due to a patient's need for treatment at all times. In addition, there might be a carryover effect where the first treatment affects the response of the second treatment.

The sample size of phase III trials depends on the trial design and may range from a few hundred to several thousand patients. In some cases, patients are recruited from several medical centers to ensure that sample size requirements are met within a reasonable time frame. Multicenter trials also provide heterogeneous populations so that the trial results can be generalized to a much broader population. However, more sophisticated analysis must be applied to account for the heterogeneity in patients, and a more organized and expensive effort is required for the planning and administration of the clinical trial.

An example of a phase III trial is a trial that was used to investigate the effect of finasteride on the development of prostate cancer in 18,882 men [13]. Patients were randomly assigned to receive finasteride (5 mg per day) or placebo for 7 years. In this study, the response was the time gap between drug administration and the development of prostate cancer.

While randomization is the cornerstone in comparing treatments, it could be infeasible in some situations due to logistics, budget or ethics. There are two options to form a non-randomized comparative control group, historical or concurrent controls. A historical group is a group of diseased patients who have been treated in the past using a standard treatment. Using historical controls leads to a wealth of bias. The standard of care may be much lower for historical controls, and the patient population may have appreciably changed over time. Using concurrent controls raises the concern of selection bias, since controls receive their treatment as a result of clinical judgment, and the factors determining that choice may not be quantifiable and recorded. Meanwhile patient characteristics could differ between patients receiving the new treatment and concurrent controls. Therefore the difficulties in interpreting the comparison results from a non-randomized trial are considerable [2].

Phase IV – Postmarking Surveillance

After the successful completion of phase III trials, the new treatment will likely achieve regulatory approval and will be made available to the public, but there could be relatively little knowledge about long-term effects of the new treatment. Phase

IV trials typically monitor uncommon adverse effects not seen in phase III trials. The sample size for a phase IV trial could be thousands, including only patients taking that treatment; randomized comparisons are not necessary. For cancer treatments, many phase III trials evaluate the treatment efficacy based on patient survival. Thus the long-term follow-up in a phase IV trial is an integral feature.

Design Issues

The design of any phase in a clinical trial requires careful thought and consideration. A properly designed clinical trial minimizes the amount of bias present in the study while providing ethical treatment to patients enrolled. This section discusses the important elements of designing a clinical trial, including study objectives, primary and secondary endpoints, patient selection, treatment choice, randomization, blinding, and sample size requirements.

Objectives and Endpoints

The planning of a clinical trial begins with a clear definition of the study objectives. These objectives should be defined by a precise explanation of the disease and the treatment(s) to be evaluated in the study. For instance, statements such as "compare treatment A with treatment B" are not sufficient. Proving the superiority of a new treatment over the control is the most common objective in clinical trials, but some trials aim to prove the equivalence or non-inferiority of the new treatment.

Endpoints are quantitative measurements implied or required by the objectives, which can be measured accurately and precisely in the trials. Clinical trials generally have a single primary endpoint and multiple secondary endpoints. "Hard" endpoints are always preferred, which are defined as clinical events that are well defined in the study protocol, definitively related with disease progression, and defined without subjectivity. Endpoints that are measured subjectively are referred to as "soft" endpoints, which are problematic in one way or another, often due to correlations among different outcomes and logical traps in complicated situations [14].

In cancer trials, the primary endpoint of interest is often the overall or cancer-specific survival rates following treatment. Secondary endpoints, such as the change in a patient's quality of life as measured through the use of previously validated questionnaires, are also of interest. If the endpoint of interest cannot be measured directly due to resource limitations or inability, surrogate endpoints are often used. For instance, D'Amico et al. [15] state that it is generally agreed upon that a patient with a history of prostate cancer having a Gleason score of 8 or prostate-specific antigen (PSA) level greater than 20 has a high risk of relapse. This could potentially be used as a surrogate endpoint to indicate recurrence of prostate cancer. However, the use of a surrogate endpoint depends heavily on the assumption that the surrogate endpoint is a good measure of the primary endpoint, which may not always hold.

Patient Selection and Treatment Choice

Careful selection of patients is critical to the success of any clinical trial. Patient selection is typically determined by inclusion and exclusion criteria. The inclusion criteria should ensure that the selected group of patients must be somewhat homogeneous so that the clinical trial results can be applied to a defined population. Meanwhile, considerations should be also given to desired generalizability of the trial results and timely enrollment of patients to meet sample size requirements.

Regarding the exclusion criteria, the following guidelines have been suggested [16]. A patient should be excluded in any of the following situations:

1. The treatment's known side effects may cause them harm.
2. A placebo is being used for comparison and a patient's disease state is severe enough to require some form of treatment at all times.
3. A patient is at a very low risk (or not at risk at all) of developing the primary outcome of interest.
4. A patient is taking an existing treatment(s) that may interfere with the new treatment or may affect his or her response to any treatments.
5. A patient's disease state will cause him or her to never respond to the new treatment.
6. A patient is unlikely to follow the trial protocol (may not follow treatment schedule, may move within the allotted follow-up time, etc.).
7. A patient does not consent to the clinical trial.

These criteria also depend on the phase of the clinical trial. In phase I and some phase II clinical trials, patients with advanced disease who are receiving no known effective treatment are often chosen. These patients are easier to recruit for these types of preliminary studies, although it is quite likely that they do not form a representative population to which the treatment will be applied in the future. This is not the case in phase III trials, which apply very stringent criteria to patient selection.

It is also very important to determine how and where to recruit patients. If patients volunteer or some type of financial incentive is used to recruit patients, differences between this population and the population that is not recruited must be carefully considered to ensure that the study population is not biased. It is also common for patients to be recruited from institutions that are highly skilled in conducting clinical trials. This type of recruitment also introduces bias because these patients may represent challenging cases that have been referred to these institutions due to their expertise in the research area.

The treatments involved in a clinical trial must be carefully considered. The investigator must have reason to believe that the new treatment has benefits (and comparably fewer risks) that are not seen in the control treatment. The administration of the treatments to the patients must also be determined; the method used to administer the drug, the dosage level, the frequency and duration, dose modifications in response to adverse events, interactions with other treatments, packaging, and distribution are just a few of the issues that must be reviewed. These issues

may differ for each phase of trials as well. For instance, in a phase I trial, it is common to use an initial dose LD10, which is one tenth of the dose that causes 10 % mortality in animals. Some phase III trials compare more than one treatment to the control treatment.

The control treatment in a phase III clinical trial should be also carefully selected. If there is no effective standard treatment that can be used for comparison, a placebo should be used in its place rather than the patient receiving no form of control treatment. This avoids the placebo effect, so called because if no treatment was given to patients, the psychological toll that this may have on a patient may result in a greater treatment effect than is actually present. However, the use of a placebo may be unethical in some circumstances because patients assigned to placebo may need some type of treatment for their disease. For example, it is unethical to give a patient a sham surgery as a control in surgical studies.

Randomization

Randomization is the cornerstone of clinical trials methodology [14], which ensures an unbiased treatment assignment to patients at the group level. There are no other allocation procedures that have this crucial property. Randomization reduces selection bias by preventing investigators from consciously or unconsciously assigning better prognosis patients to a treatment that they hope will be superior. Another benefit of randomization is that it balances both known and unknown factors that may affect the trial outcome between the treatment arms, leading to an unbiased comparison of the treatment arms.

Historically, randomization is associated with phase III trials. A more recent development is randomized phase II trials. These types of trials are used when several similar treatments must be compared in the same patient population. An example is a study that randomized 57 patients with recurrent or metastatic bladder cancer to either a cisplatin-containing regimen or a carboplatin-containing regimen [17]. In this case, the two regimens were compared using several toxicity measures (ototoxicity, gastrointestinal, nephrotoxicity, neurotoxicity) and response to treatment.

Various randomization schemes have been developed to allocate patients. A simple randomization scheme can be used where each patient is randomized to a trial arm with a probability of 0.5. Simple randomization does not guarantee balance in numbers during trial when the sample size is small. Block randomization is often used to fix this issue. The basic idea of block randomization is to divide potential patients into blocks, and within each block, patients are randomized until exactly half of the patients are randomized to one treatment. In some cases, some most important factors have to be balanced between treatment arms, which, however, could be compromised for moderate or small size trials. To prevent this, stratified randomization schemes are used where strata are constructed based on these important factors (stratification factors). For example, if a trial is to be stratified on gender (male vs. female) and family history of disease (presence vs. absence), patients will

be randomized within each of the four patient groups. In multi-center clinical trials, center is clearly a factor that needs to be stratified for randomization.

Adaptive randomization schemes have gained much popularity recently since they are generally more efficient and ethical [18]. The basic idea of adaptive randomization is to revise the probabilities of treatment assignment based on the information of previously randomized patients. For instance, the play-the-winner scheme [19] assigns a patient to the current best arm with a higher probability than the other arms. After a small cohort of new patients is randomized, the treatment arms are then reassessed and a new best arm might be identified. Adaptive randomization is difficult to implement since it requires dynamic updates and analyses of the trial data accumulated. Also, unlike the previous randomization schemes, the randomization codes based on an adaptive randomization scheme cannot be prepared before the study begins.

The time at which randomization occurs is also important. In general, the best time to randomize is the closest possible time to the start of the treatments. Regulatory agencies typically want all data reported on any patient who is randomized to an arm of the trial, regardless of whether or not the patient complied with the treatment protocol. If patients are immediately randomized to a treatment arm once they are enrolled into the clinical trial, there may be a large delay between time of enrollment and receiving treatment, during which the patient may decide to drop out of the study. Such a patient must still be followed throughout the trial, and any adverse events must be reported. On the one hand, this will not affect the per-protocol analysis of the data, which includes only patients who followed the treatment protocol. However, patients who dropout of the study will be included in an intent-to-treat (ITT) analysis; this includes all patients who were randomized to any arm of the study. Randomizing patients too early may bias the results of the ITT analysis.

Blinding

Blinding is another design consideration that is used to minimize the amount of bias in clinical trials. A single blinded trial is where either the physician or patient is unaware of the treatment assignment. A double-blinded trial is where both the physician and patient are blinded to the treatment assignment. The treatment assignment could be unblinded after the trial is closed and the data analysis is complete. For physicians, blinding ensures that all patients, regardless of their treatment, receive the same standard of care. Patients who know their treatment assignment may also inadvertently affect their response to treatment based on their own belief in the treatment under investigation.

There are also situations where blinding is not feasible even if considered necessary. For instance, surgeons cannot be blinded to the type of surgery performed on a patient. Blinding also may not be possible if there are complicated dose schedules, possible dose modifications, or obvious treatment side effects.

Interim Analysis and Early Stopping

Analysis of data during the conduct of a trial is called an interim analysis. Ethical concern is the primary reason for performing an interim analysis. An interim analysis may cause the trial to be stopped if there are significant results in favor of one arm over another (efficacy rule), or inadequate power to detect a clinically meaningful treatment effect if the trial continues (futility rule).

Stopping rules are typically decided from the statistical perspective under the framework of the so called group sequential design [20]. There are two elements that have to be determined at the start of a group sequential trial: (i) the total number of interim analyses (or groups) and (ii) the number of patients evaluated between successive analyses. Stopping boundaries are calculated at each interim analysis while maintaining an overall false discovery rate. If the interim analysis suggests strong evidence of crossing the stopping boundaries, the trial may be stopped early.

The results of the interim analysis should be kept confidential. An independent data monitoring committee (DMC) often takes the responsibility of interpreting the interim results and making decisions of stopping or continuing the trial in the light of other scientific knowledge. Investigators should be blinded with the interim results since they may change their outlook and future participation.

Sample Size and Power

Sample size considerations begin with the formulation of a clearly defined hypothesis that is to be tested in the clinical trial. In phase I clinical trials, sample size requirements are unnecessary because of the exploratory nature of the trial. In phase II and III clinical trials, sample size calculations are required to ensure that the sample size is large enough to provide adequate power to detect clinically meaningful response rates for a treatment (phase II) or differences in response rates between treatments (phase III). At the same time, the sample size must be small enough to meet budgetary constraints.

In any sample size calculation, the investigator must pre-specify acceptable probabilities of making incorrect decisions based on the trial results. For instance, suppose trial results indicate an effective treatment but in truth, the treatment does not have a clinically meaningful effect. This is called a type I error (or a false positive) and its probability is denoted by the Greek letter α. A type I error is undesirable because the ineffective treatment is further tested in other clinical trials, wasting time and money and possibly causing harm to patients. Thus α is typically set to .05 or lower. Another type of error is called a type II error (or a false negative) and its probability is denoted by the Greek letter β. In this case, trial results indicate an ineffective treatment even though the treatment truly has a clinically meaningful effect. Although this type of error is still of concern, it is typically larger than α and is set to .10 or .20. Power is the probability of not making a type II error, or $1-\beta$.

The remainder of this section focuses on basic sample size calculations for some commonly used outcomes.

A phase III trial attempts to detect clinically relevant differences between treatments. In general, there are three types of primary outcomes, continuous, dichotomous and survival, and each requires its own method of sample size calculation. Although other outcomes are certainly used (e.g., count outcome, ordinal outcome), only these types are considered in this section to simplify the discussion.

Dichotomous Outcome

A dichotomous outcome measures whether or not a particular event occurred in a patient. An example is cancer recurrence 6 months after drug administration. In a trial that has a dichotomous primary outcome, the general goal is to determine if the event rates differ between the arms.

Let p_t and p_c be the event rates in the control and treatment arms, respectively. Using this notation, the required sample size is calculated based on testing the hypothesis

$$\mathrm{H}_0 : p_C = p_t \text{ versus } \mathrm{H}_\mathrm{a} : p_C \neq p_t$$

such that the probability of a false positive is α and the power to detect the largest clinically relevant difference in event rates is $1-\beta$. Assuming that both the treatment and control arms consist of independent groups of patients, Pocock [21] suggests a Chi-squared test without continuity correction for testing the above hypothesis.

Based on this test, the required sample size for each arm is given by

$$N = \frac{\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2 \left[\, p_c\left(1-p_c\right) + p_t\left(1-p_t\right)\right]}{\left(p_t - p_c\right)^2},$$

where Z_q is the qth quantile of the standard normal distribution. Table 4.1 provides the most commonly used values of Z_q. Note that several other methods can be used to determine sample size in this situation, and the above formula is only presented as a general guideline.

Table 4.1 Commonly used values of Z_q for sample size calculations

	Type I error (α)			Type II error (β)	
	0.05	0.025	0.01	0.80	0.90
q	0.975	0.9875	0.995	0.80	0.90
Z_q	1.96	2.24	2.58	0.84	1.28

As an example, suppose it is known that the control treatment has a 30 % response rate and it is of clinical interest to detect a 20 % increase (or a 50 % response rate) in the new treatment with a 90 % power. The investigator would also like to ensure that the probability of a false positive is 5 %. Using the above formula, each arm of the study requires 121 patients.

Continuous Outcome

A continuous outcome takes a value that ranges between negative and positive infinity in theory. An example is the change in PSA level 3 months after drug administration in a prostate cancer trial. For continuous outcome, the goal is to determine if there is a difference in outcome means between the arms. To determine the number of patients in the trial, the investigator must first specify the expected means in the control and treatment arms, given by μ_c and μ_t respectively. The standard deviation of the outcome in the control group is denoted by σ. Using this notation, the required sample size is calculated based on testing the hypothesis

$$H_0 : \mu_C = \mu_t \quad \text{versus} \quad H_a : \mu_C \neq \mu_t$$

such that the probability of a false positive is α and the power to detect the largest clinically relevant difference in means is $1-\beta$. Assuming that both the treatment and control arms consist of independent groups of patients and the standard deviation of the outcome in the control arm is similar to that in the treatment arm, a two-sample *t*-test is often used to test the above hypothesis. Based on this test, the required sample size for each arm is given by

$$N = \frac{2\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2 \sigma^2}{\left(\mu_t - \mu_c\right)^2},$$

where Z_q is the qth quantile of the standard normal distribution. Note that this formula is suitable for a relatively large N, but may not apply for small sample sizes.

As an example, the outcome is the change of glomerular filtration rate (GFR) after 5 years in a kidney trial. Suppose that the change (decline) of GFR is 10 ml/min/1.73 m^2 in the control arm, with a standard deviation of 20. It is of clinical interest to detect a 5 ml/min/1.73 m^2 decline in the new treatment with 90 % power. The investigator would also like to ensure that the probability of a false positive is 5 %. Using the above formula, each arm of the study requires 337 patients.

Survival Outcomes

A survival outcome, or more generally a time-to-event outcome, measures the time to the occurrence of certain clinical events in patients from their enrollment into the trial. In most cancer clinical trials, the primary outcome is patient survival, that is, time to mortality, and the most common objective is to evaluate the effect of a new treatment on prolonging patient survival.

Survival outcomes are usually subject to censoring. For patients who are alive at the end of the trial or lost to follow-up during the trial course, their exact deceased times are unknown but larger than the last follow-up time. The analysis of survival outcomes in a clinical trial is typically to compare hazard rates or median survival times between treatment arms. Hazard is the risk of developing the event at an instant in time, and median survival time is the time at which half of the patients are event-free. These two parameters are equivalent when the survival curve follows an exponential shape. Furthermore, the hazard ratio between two treatment arms may be constant over time, leading to the so called proportional hazards. Thus, without loss of generality, we focus on the sample size calculation for comparing hazard rates.

Let λ_c and λ_t be the hazard rates in the control and treatment arms, respectively. Using this notation, the required sample size is calculated based on testing the hypothesis

$$\mathrm{H}_0 : \lambda_C = \lambda_t \quad \text{versus} \quad \mathrm{H}_\mathrm{a} : \lambda_C \neq \lambda_t$$

such that the probability of a false positive is α and the power to detect the largest clinically relevant difference in event rates is $1-\beta$. Assuming that both the treatment and control arms consist of independent groups of patients, the log-rank test is the

$$N = \frac{4\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2}{\left(P_t + P_c\right)\left(\log\dfrac{\lambda_t}{\lambda_c}\right)^2}$$

primary analytic tool for testing the above hypothesis. Based on this test, the required sample size for each arm is given by

$$N = \frac{4\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2}{\left(p_t + p_c\right)\left(\log\dfrac{\lambda_t}{\lambda_t}\right)^2},$$

where Z_q is the qth quantile of the standard normal distribution, and P_t and P_c are the proportions of deceased patients at the end of trial in the treatment and control arms,

respectively. There are alternative methods [22] that allow for incorporation of accrual information and trial duration into sample size calculation.

For example, consider a 5-year cancer trial, where the mortality rate at 5 years is assumed to be 50 % for the control arm, and a 10 % reduction in mortality is anticipated for the treatment arm. The investigators would also like to ensure a false positive probability of 5 % and a power of 90 %. Using the above formula, each arm of the study requires 501 patients.

Other Sample Size Considerations

Investigators must also provide accurate estimates of the rate of patient withdrawal from the study, the rate of lost to follow-up, the rate of protocol deviation and the accrual rate. These rates need to be incorporated into the final sample size consideration to ensure the successful recruitment of the trials. The monetary cost of the trial per patient must also be considered to ensure that budgetary constraints are met.

Conclusion

Clinical trials have significantly improved the treatment of patients with any disease. However, clinical trials are susceptible to many sources of bias, and results from a clinical trial can only be accepted by physicians and regulatory agencies alike if it is carefully designed and implemented. This discussion attempts to give a brief outline of the various issues that must be considered when designing a clinical trial. A more thorough discussion is given by Girling et al. [2], Pocock [21] and Piantadosi [23].

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Chapter 5
Non-Interventional Imaging in Genitourinary Cancer

Shirish G. Prabhudesai, Audrey E.T. Jacques, and Anju Sahdev

Urography

Intravenous Urogram (IVU) (Excretory Urography)

The intravenous urogram (IVU) is a plain film technique, which evaluates the entire renal tract. It consists of a series of plain x-rays of the renal tract followed by intravenous administration of water soluble, iodinated, contrast medium. The injected contrast media is taken up, concentrated and excreted by the kidneys into the ureters and bladder. As the contrast media is radio-opaque, a sequence of plain films taken at precise time points allows assessment of different parts of the renal tract. The contrast medium is excreted by the kidneys enabling visualisation of high-density contrast filled calyces, renal pelvis, ureters and bladder. Tumours, calculi and blood clots are demonstrated as filling defects (Figs. 5.1 and 5.2). The IVU forms part of the initial workup for patients with unexplained renal angle pain, suspected renal calculi, haematuria, renal obstruction and suspected congenital (inherited) abnormalities. With recent advances in CT and MRI technology, the future of the IVU is a subject of ongoing debate [1], although at present it still remains integral to the diagnosis and surveillance of urothelial malignancy.

S.G. Prabhudesai, MBBS, MS, MRCS (✉)
Department of Radiology, St Bartholomew's and
The Royal London Hospital, London, UK
e-mail: shirish.prabhudesai@bartsandthelondonnhs.uk

A.E.T. Jacques, MDDS, BSc, MRCP, FRCR
Department of Radiology, Guy's and St. Thomas Hospital, London, UK

A. Sahdev, MBBS, MRCP, FRCR
Department of Imaging King George V Block, St. Bartholomew's Hospital,
London, UK

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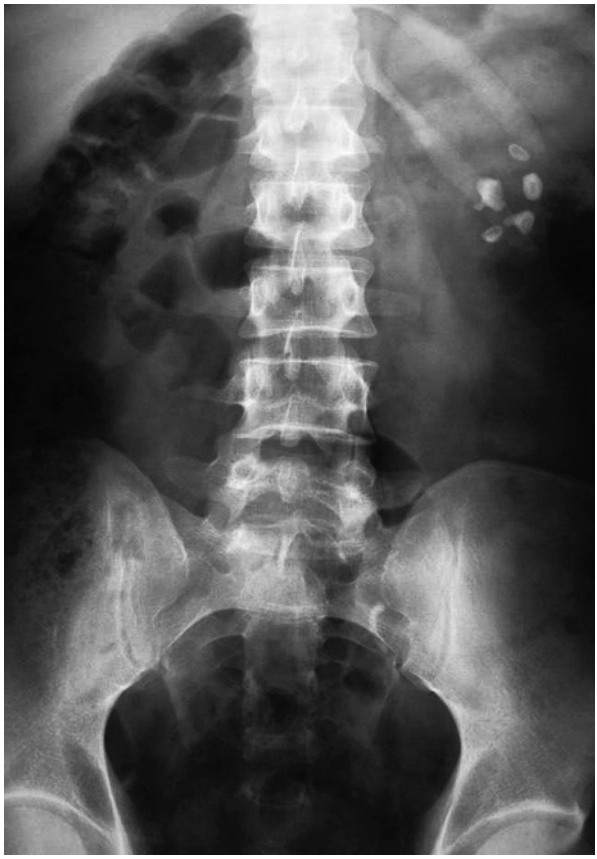


Fig. 5.1 IVU plain films showing stones. Plain full length film from an IVU series showing multiple calculi in the lower pole calyces of the left kidney. Calculi are best demonstrated prior to injection of intravenous contrast media, as the high density contrast can obscure small calculi

In an emergency setting, low dose unenhanced CT through the renal tract (CT KUB) has replaced IVU in patients with painful haematuria and suspected urinary lithiasis. CT IVU has 3 main applications: (1) evaluating the urinary tract in patients with suspected injury. CT IVU is particularly accurate in assessing severity of renal parenchymal and collecting system injury. Injury to the collecting system is seen as contrast extravasation from the intra-renal collecting system, pelvi-ureteric system and urinary bladder (2) confirming the presence of iatrogenic ureteric/bladder injuries following pelvic surgery. This may be seen either as obstruction of the collecting system in instances where the ureter is occluded or as contrast extravasation when the ureter is wholly or partially transected. (3) in patients with unexplained haematuria in the absence of urinary lithiasis-helps in demonstrating urothelial carcinoma that appear as filling defects either in the intra-renal collecting system, ureters or the urinary bladder.

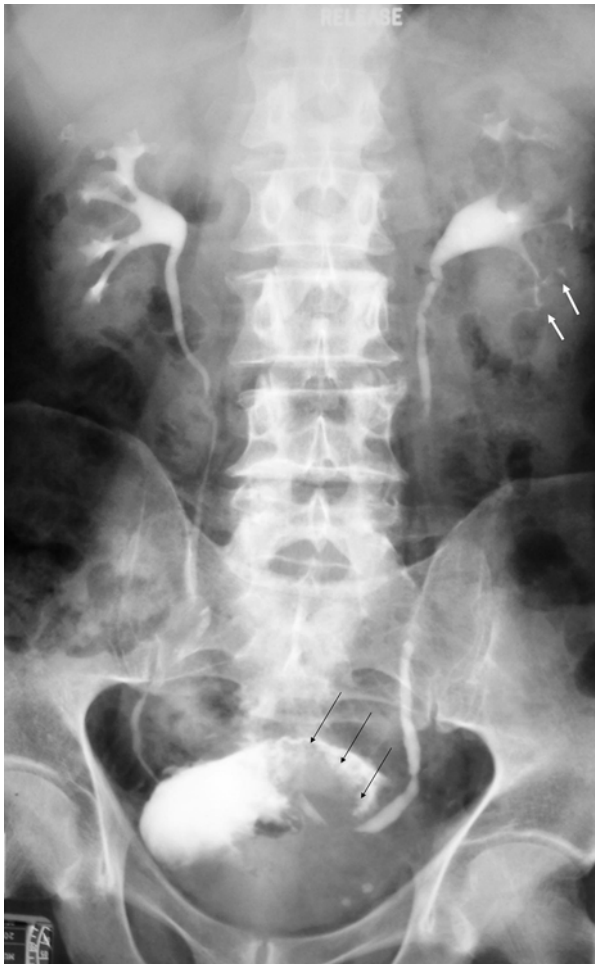


Fig. 5.2 IVU small subtle upper tract TCC lesion. Full length film from an IVU series demonstrating a large filling defect in the bladder, confirmed as a large TCC on cystoscopy (*black arrows*). Within the lower pole calyces there are small subtle filling defects (*white arrows*) which were suspected further foci of TCC. This was confirmed on the cystonephroureterectomy specimen

Patient Preparation for IVU and CT IVU

The patient is starved for at least 4 h prior to the study and is ambulant for 2 h, in order to reduce the amount of bowel gas overlying and obscuring the renal tract. The routine use of purgatives is no longer employed as it does not significantly improve diagnostic quality. Fluid restriction is no longer advocated as dehydration is associated with an increased risk of contrast medium nephrotoxicity. The patient is advised to empty their bladder prior to the examination. Diabetic patients on Metformin no longer need to stop medication but require close monitoring if their blood sugar either by the patient or general practitioner. Pregnant women are advised not to undergo an IVU unless potential benefits outweigh risks to the fetus.

Table 5.1 Cautious use of iodinated intravenous contrast medium (ICM)

1. History of previous allergic reaction to ICM: absolute contraindication to use of ICM excluding those with previous mild flushing or nausea
2. Asthmatics: prophylactic oral steroid cover given prior to the procedure according to local policy and guidelines
3. Those at risk of nephrotoxicity;
Renal impairment (can be given to patients with renal failure having regular dialysis when discussed with clinical team)
Known diabetic nephropathy and those on Metformin (follow local guidelines regarding the use of ICM in patients on Metformin)
Severely debilitated and dehydrated patients

Precautions and Contraindications

Patients with diabetes, multiple myeloma, sickle cell disease and infants are at increased risk of nephrotoxicity and good hydration prior to the examination is advised in these patients. Renal impairment is a relative contraindication for the use of iodinated contrast medium due the risk of precipitating severe renal failure. Poor renal function results in poor renal contrast uptake, concentration and excretion, thereby limiting visualisation of the collecting system. Those with mild renal impairment may be given iso-osmolar non-ionic iodinated contrast medium such as Iodixanol, which is less nephrotoxic than standard non-ionic iodinated contrast agents in this group [2]. Patients with a history of previous severe contrast medium reaction should be excluded (Table 5.1).

IVU Technique

An initial full-length film to include the renal area and bladder is taken to assess technical factors and identify renal calcification, which may become obscured on later contrast enhanced films. A standard adult dose of 50 ml of 350–370 g Iodine/ml (I/ml) or 100 ml of 300gI/ml contrast medium is administered intravenously. This can be altered for patients larger or smaller than the average sized 70 kg adult. A standard sequence of films is obtained at timed intervals, with variations tailored to the individual. The series includes; immediate, 5 and 10-min post contrast renal area films, 15-min full length and post-micturition films. The immediate post contrast film demonstrates renal parenchymal enhancement with contrast medium uptake in the proximal tubules and is termed the nephrographic phase. This enables renal size, position, contour and parenchymal integrity to be evaluated. Excretion of contrast medium into the calyceal system is seen from the 5-min film onwards. Collecting system opacification can be augmented with the use of abdominal compression and a variety of devices are available for this. Compression serves to impede ureteric emptying and enhance pelvicalyceal distension and is applied after the 5-min film if the pelvi-calyceal system is not obstructed. Compression is

contraindicated in patients with acute abdominal pain, recent surgery, a known abdominal aortic aneurysm or other large abdominal mass. Compression is released once adequate views of the upper tract have been achieved. This is followed by full-length film to demonstrate contrast medium within the lower ureters.

Diagnostic Value of the IVU

Deformity or calyceal compression or distortion of the renal contour seen on nephrographic phase images indicates a focal parenchymal mass. The nature of the focal mass cannot usually be determined further on IVU and the differential diagnosis includes a simple cyst, renal carcinoma or other benign lesions. In practice, ultrasound or CT are indicated for detection and characterisation of focal renal masses. In the investigation of haematuria, IVU images must be carefully examined for presence of any filling defect within the renal collecting system, ureters or bladder, which may indicate urothelial tumours. These are frequently small and may be seen as a broad based flat or polypoid filling defect arising from the wall. In some cases, slight irregularity of the wall may be the only indication of a tumour (Fig. 5.2). Large tumours may cause obstruction and dilatation of a single or group of calyces (Fig. 5.3). As urothelial carcinomas (UCa) arise on a background of dysplastic urothelium, bilateral or multiple synchronous or metachronous lesions may occur in up to 38 % [3, 4]. The IVU still has a role in excluding multifocal disease in patients with bladder cancer, and in the follow up and surveillance of treated patients.

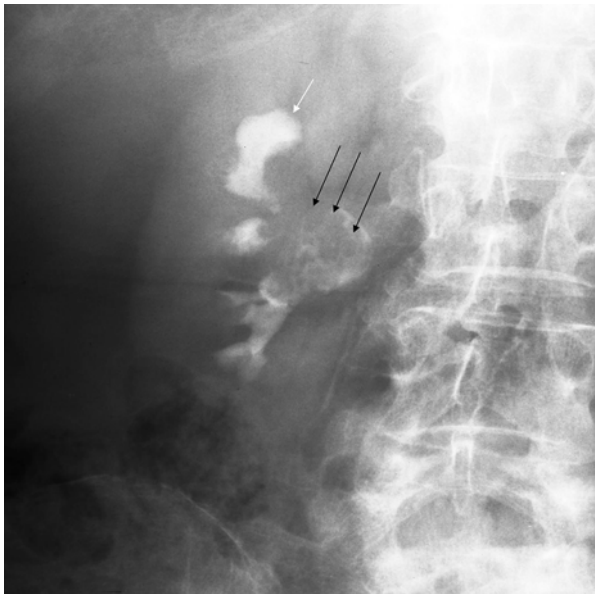


Fig. 5.3 IVU Large lesion with dilated and amputated calyx. A cross-renal image demonstrating a large renal pelvic TCC (*black arrows*). The lesion invades and obstructs the infundibulum of the upper pole calyx resulting in a dilated, obstructed and amputated upper pole calyx (*white arrow*)

Alternatives to the IVU

Multi-detector row CT (MDCT) has made a significant impact in all areas of radiology in recent years (see "Computed tomography" section). It enables the fast scanning of a large volume of the patient in a single breath-hold. Thin slices as narrow as 1.25 mm, of the patient can be reconstructed resulting in much improved spatial resolution. These images can be further reconstructed into sagittal and coronal planes. Images of contrast filled structures can be also reconstructed to produce CT angiographic images in 3 dimensional planes. CT has almost entirely replaced the IVU. Plain non-contrast CT KUB has replaced the IVU in the diagnosis and management of stone disease. In the work up of haematuria, when renal tract malignancy is suspected, CT IVU has an increasingly important role. Excretory phase CT can now be used to evaluate the calyces, renal pelvis and ureters and provide images akin to that of a standard IVU [5] (Fig. 5.4).

CT urography is performed with a combination of unenhanced, nephrographic phase and excretory phase imaging. As in standard IVUs, renal tract calcification is detected on unenhanced images and focal renal parenchymal lesions are detected

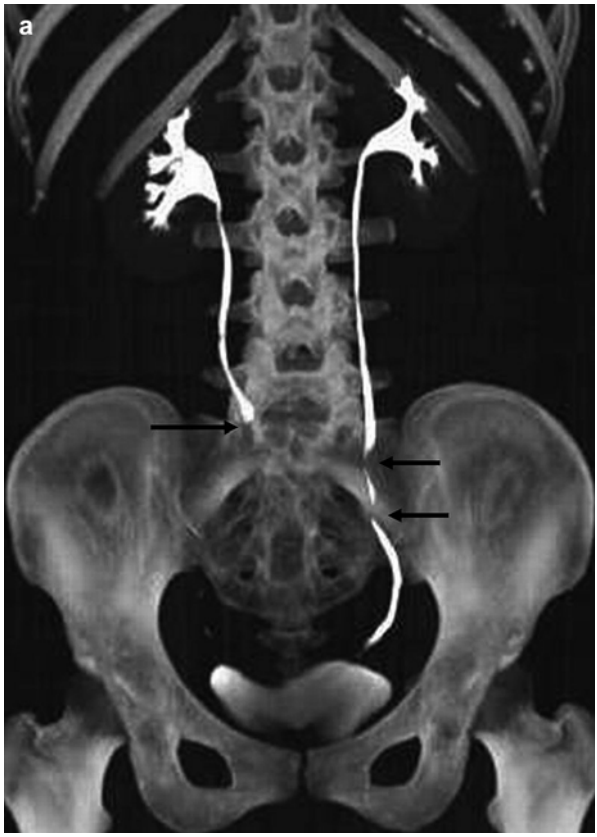
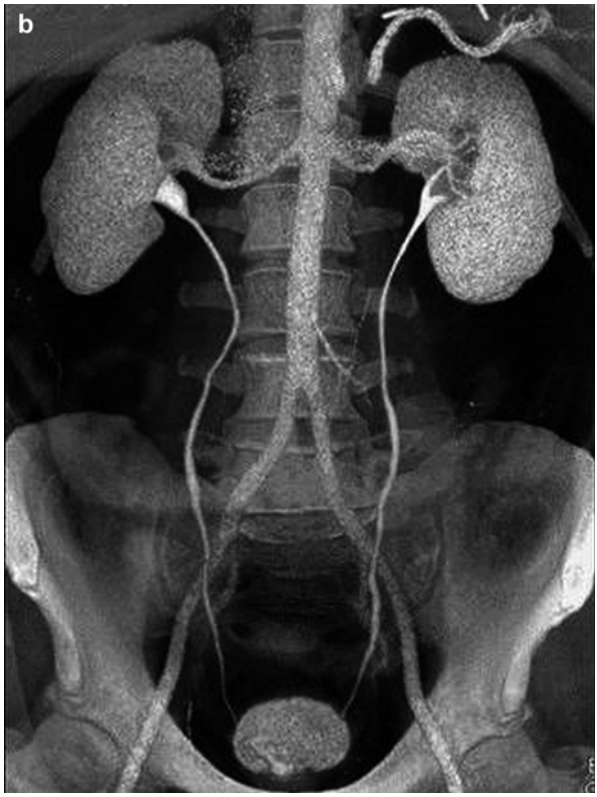


Fig. 5.4 Normal CT IVU. (**a**) A maximum intensity projection image from a CT IVU series demonstrating normal renal calyces, ureters and bladder. Peristalysis within both ureters can result in under distension, as seen in the distal right ureter or as linear areas of contrast interruption as seen in the left ureter (*arrows*). (**b**) Volume rendered 3D image from the same patient demonstrating the detail of the renal parenchyma overlying the calyces the whole length of the ureters and bladder

Fig. 5.4 (continued)



and characterised on corticomedullary (40-s) or nephrographic phase (90-s) imaging. Images obtained 10–15 min after intravenous contrast administration demonstrate contrast filled calyces, ureters and bladder (excretory phase) and are ideal for evaluating the urothelium and filling defects within the collecting systems. The advantage of this technique is that comprehensive evaluation of the renal tract can now be achieved during a single examination [6, 7]. The disadvantages of the technique include cost and time implications as well as radiation dose considerations. The estimated dose equivalent for the CT urogram is approximately 14.8 mSv +/– 3.1 (standard deviation) compared with about 1.5 mSv for a typical standard IVU [8]. However, recent studies using dual phase split bolus protocols, which obtain images in the nephrogenic and delayed phases simultaneously have shown approximately 65 % reduction in radiation exposure without associated reduction in the urinary tract opacification [9]. The guidelines published by the European Society of Urogenital Radiology (ESUR) in 2008 justified the use of CT urography as the first-line imaging investigation for patients with macroscopic haematuria at high-risk for urothelial cancers. They defined high risk as patients above 40 years, macroscopic haematuria, smoking history, history of current or previous GU malignancy and occupational exposure to urothelial carcinogens [10].

Magnetic Resonance (MR) Urography

MR Urography combines the advantage of CT urography in being able to investigate both the renal parenchyma and the urothelium in a single examination. MRI is safe for patients with iodinated contrast allergies or radiation exposure considerations where standard IVU or CT urography are contraindicated e.g. pregnancy. Both dilated and non-dilated renal collecting systems can be visualised using MR urography which is achieved by using either heavily T2-weighted (T2W) sequences or gadolinium-enhanced T1 weighted (T1W) sequences [11]. Heavily T2W MRI sequences generate high signal intensity from simple fluids such as urine, while suppressing signal intensity from surrounding tissues.

Thin section coronal images of the urine filled collecting system provide IVU like images. T2- weighted techniques are fast imaging techniques, which can be successfully applied to patients presenting with painful hydronephrosis of pregnancy in the detection of calculi. In this group of patients both standard and CT IVUs are contraindicated due to the radiation burden and necessary use of iodinated contrast media (Fig. 5.5). Gadolinium-enhanced MR urography relies on

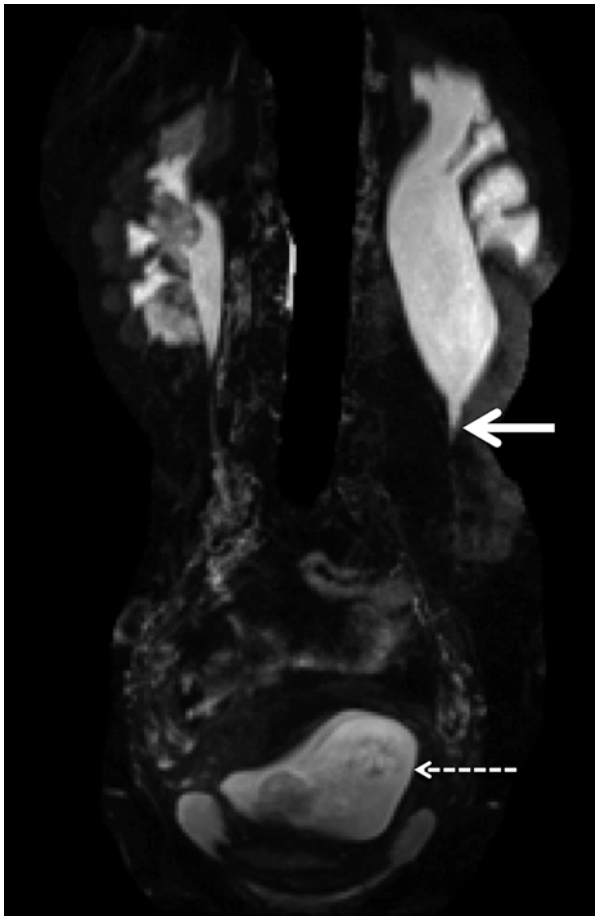


Fig. 5.5 Magnetic resonance urography. Coronal MRU in a pregnant woman presenting with left loin pain and hydronephrosis. The *solid arrow* demonstrates a typical PUJ obstruction as the cause of the hydronephrosis. The *dashed arrow* shows the early gravid uterus

contrast excretion in the same way as standard or CT urography to visualise the collecting system. Suboptimal collecting system opacification may limit this technique in the presence of markedly impaired renal function or high-grade urinary obstruction. While the presence and level of ureteric obstruction can be evaluated, the absence of signal from calculi makes them difficult to visualise with both MRI techniques.

Ultrasound

General Principles

Ultrasound imaging is based on the principle that when sound waves are directed into the body by a transducer placed on the skin surface, some will be reflected back to the body surface and detected by the same transducer. The transducer surface is made of material that has the unique property of expanding or contracting when a voltage is applied across it, known as the **piezoelectric effect**. When the transducer is in contact with skin and a voltage applied, the piezoelectric material expands and compresses an adjacent layer. This pressure induces a corresponding voltage to the next layer of the material, which also expands. The mechanical energy thus created by this wave of compression within the probe is transmitted to the skin surface and propagates through the patient. The propagation and reflection of sound wave through the patient is dependent on density and elasticity of the tissues (**acoustic impedance**). Reflected echoes returning from the patient to the probe induce a voltage which can be detected by the transducer and converted into a **grey scale image**. The reflection of sound waves is greatest where there is a large difference in acoustic impedance of two tissues. Thus soft tissue structures reflect more echoes than fluid and appear bright or echogenic. Fluid, which absorbs sound, appears dark, or **hypoechoic**. The time delay between the initiated and returning pulse to the probe is proportional to the distance the beam has travelled, and spatial information as to the position and depth of tissues are incorporated into the image composition. Constant pulses of sound waves are produced to generate fast real time images of moving body tissues, including flowing blood (**Doppler ultrasound**). Bone and air reflect sound and cannot be imaged, whereas fluid in simple cysts or bladder does not reflect sound waves, which pass through and are available for imaging deeper structures, a phenomenon termed acoustic enhancement. This is of use in the pelvis where the urine filled bladder is used as an acoustic window for visualising deeper pelvic organs such as the prostate gland and uterus.

Advantages

Ultrasound (US) is a non-invasive real time imaging method, does not use ionising radiation, and is well tolerated by patients. The examination does not require special preparation. It poses no real risk to patients making it ideal for repeated surveillance imaging without the radiation burden associated with CT.

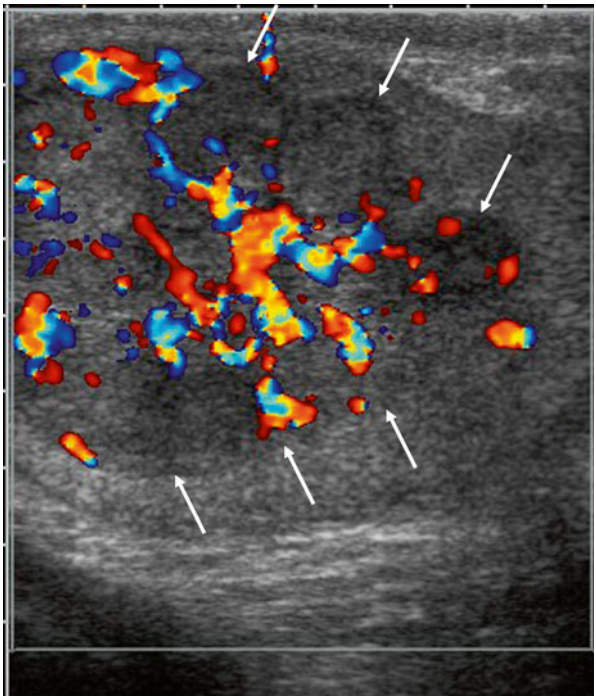


Fig. 5.6 Testicular non seminomatous germ cell tumour. Ultrasound image of a large heterogenous testicular mass (*white arrows*) replacing the whole testes with increased vascularity. Although the ultrasound features are non-specific, the combination of a focal mass and increased vascularity is high suggestive of a germ cell tumour

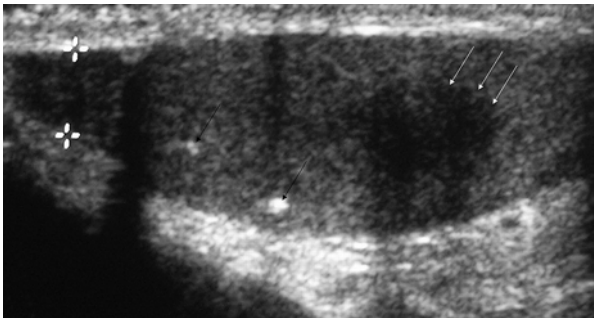


Fig. 5.7 Testicular seminoma. Ultrasound image demonstrating a small focal testicular lesion (*white arrow*) on a background of testicular microlithiasis (*black arrows*). The lesion is poorly vascular and well defined. The lesion was confirmed as a testicular seminoma

The ability to image flowing blood in real time is a major advantage of ultrasound, which can detect tumour extension into the renal vein and IVC in the case of renal and adrenal carcinomas. The demonstration of vascularity within a lesion can aid its characterisation (Figs. 5.6 and 5.7). The real time aspect of ultrasound is well suited to guide procedures such as fine needle aspiration, biopsy and drain insertions. The echogenic tip of a biopsy needle for example, can be easily demonstrated with ultrasound, providing a clearly visible route for safe insertion. Intraoperative ultrasound probes have also been designed which can be used to localise tumours during a radiofrequency ablation and partial nephrectomy.

Disadvantages

The success of US is very **operator-dependent** and images may not always be reproducible between different operators. Although a representative sample of reference images are usually saved onto hardcopy or digital archiving, images are generally best appreciated dynamically during the scan. Comparing a current study with saved hardcopy images from a previous study is not as accurate as it is with CT or MRI.

Patient factors such as body habitus may influence the quality of the images produced with greater attenuation of the ultrasound beam occurring in larger patients, resulting in poor visualisation of deeper structures. As the ultrasound beam is absorbed by air, the presence of prominent bowel gas in the abdomen or pelvis may limit visualisation of deeper organs.

Ultrasound in Genito-Urinary Cancers

There is a wide application of US in genitourinary cancers. Some of these indications are summarised in Table 5.2

Table 5.2 Role of ultrasound in urologic oncology

A. Kidney
1. Investigation of haematuria
2. Detection of incidental renal cell carcinoma
3. Characterisation of cystic renal lesions
4. Distinguish between adrenal and upper pole renal mass
5. Ultrasound guided intervention: Biopsy of renal masses Radiofrequency ablation of renal cell carcinoma Intra-operative ultrasound to aid nephron-sparing surgery
6. Tumour staging Perinephric and local invasion Venous invasion Characterisation of liver lesions
7. Follow up and surveillance eg. particularly testicular cancer
8. Assessment of suspected hydronephrosis in patients with pelvic malignancy
B. Bladder: Investigation of haematuria
C. Prostate: (Transrectal ultrasound; TRUS): TRUS guided biopsy in patients with raised PSA, TRUS guided insertion of fiducial markers for image guided radiotherapy radiotherapy (IGRT)
D. Testes: Investigation of palpable testicular mass Surveillance of normal testis after cancer treatment Assessment for suitability for partial orchidectomy

Ultrasound of the urinary tract forms part of the early screening of patients with haematuria, aimed at excluding renal cell carcinoma or tumours of the bladder and renal pelvis.

Renal Masses

Renal cell carcinomas (RCC) are typically very vascular solid lesions on US showing multiple collateral vessels or intra-tumoural arteriovenous shunting on Doppler ultrasonography. The widespread use of CT and ultrasound has contributed to the increased detection of incidental renal carcinomas in recent years. Thus more RCCs are being detected at an early, asymptomatic stage which has contributed to improved survival [12, 13]. Ultrasound is used to diagnose and characterise variety of renal lesions. Simple renal cysts are extremely common and when confidently diagnosed on ultrasound need no further follow up unless they become symptomatic. Ultrasound can be used to characterise complex cystic lesions and highlight those which have features suspicious for malignancy and warrant consideration for surgical excision. The features suggestive of malignancy include the presence of thick wall and septae, internal solid components, vascular flow within the lesion and associated retroperitoneal lymphadenopathy. Doppler ultrasound is highly sensitive for the detection of vascularity, the presence of which in soft tissue components of a cystic mass is suspicious for malignancy. Ultrasound can be used to characterise very small (<1.5 cm) indeterminate renal lesion detected on CT. These masses may represent either solid lesions which will have vascular flow or hyperdense cysts which are hypoechoeic on US and have no internal vascular flow.

The presence of bilateral or multifocal RCCs clearly has an impact on the choice of patient management and careful ultrasound examination of the remainder of the kidney and of the contralateral kidney should be made. This is particularly important in patients with von Hippel Lindau (VHL) syndrome where multiple renal cell carcinomas may exist, often on a background of multicystic kidneys (see Chap. 17). Complex features of any cysts should be carefully evaluated. Renal cell carcinomas arising in small, complex cysts (<1.5 cm) in these patients are typically slow growing and are often followed up for some time.

Ultrasound may be used in conjunction with CT or MRI although ultrasound is less accurate than CT or MRI in RCC staging and perinephric invasion is poorly demonstrated. It is helpful however in diagnosing tumour extension into the renal vein and IVC (Fig. 5.8) which can be diagnosed with up to 75 % sensitivity [14], or higher when clinically important IVC thrombus is considered [15]. Supradiaphragmatic extension is not well seen and if suspected, echocardiography should help to exclude tumour extension into the right atrium.

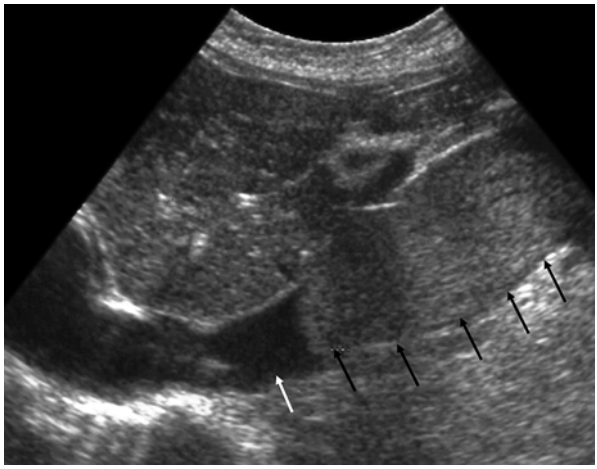


Fig. 5.8 Inferior vena cava thrombus on US. Longitudinal section of the abdominal IVC. The normal IVC is seen as a fluid filled tubular structure (*white arrow*) on ultrasound. A large tumour thrombus is seen as a hyperechoic lesion within the lumen expanding the IVC (*black arrows*). The thrombus is limited to the infra-diaphragmatic IVC with its superior extent clearly demonstrated on US

Urothelial Tumours

Ultrasound is supplemented by IVU in the work up of patients with haematuria. Alternatively for the detection of renal and urothelial lesions, a CT IVU would replace both studies. CT IVU has the added advantage of staging a detected malignancy. The renal pelvis, proximal ureter and bladder can usually be visualised with ultrasound. The ureter however, unless dilated, is not well visualised throughout its length. The bladder should be well filled for its optimal examination with ultrasound as focal areas of wall thickening, representing plaque lesions of urothelial carcinoma can be mimicked by a collapsed bladder wall.

In patients with haematuria, demonstration of an echogenic mass with vascular flow on ultrasound within the renal pelvis, proximal ureter or bladder suggests the presence of malignancy, commonly TCC. Visualisation of the upper tract collecting system is improved in the presence of obstruction where an echogenic mass may be seen outlined by hypoechoic urine. Differentiation of echogenic debris from tumour within the collecting system or bladder can be made by the detection of vascularity within tumours on Doppler scan. Doppler can therefore aid characterise of an extrinsic mass or collecting system filling defect demonstrated on IVU and US. US may demonstrate evidence of extension of tumour outside of the renal collecting system or bladder, but overall staging is achieved with a combination of cystoscopy, CT and MRI.

Adrenal Glands

Normal adult adrenal glands are not usually visualised with ultrasound given their small size and deep location. Incidental adrenal mass lesions may occasionally be detected with ultrasound. Ultrasound may be useful to interrogate a large suprarenal

mass seen on axial CT, to determine its origin, exclude invasion of the liver, kidney, tail of pancreas or IVC and renal vessels. CT and MRI are the investigations of choice for the characterisation of adrenal masses and staging of adrenal carcinoma. Large adrenal masses may be biopsied under US control but only after biochemical exclusion of pheochromocytoma.

Testis

Given its superficial location, the testis is well visualised with ultrasound making it the first line investigation of a patient with a palpable scrotal mass. Benign lesions of the epididymis such as simple cysts are common and when a lesion has been detected clinically, ultrasound is used to determine whether it lies within the testis or not. Benign solid lesions within the testis are extremely rare (dermoids and epidermoids), and all such lesions, in the absence of clinical features to suggest infection, are presumed to be malignant. testicular germ cell tumours are typically solid, heterogeneous masses which may be multiple, and are often highly vascular (Figs. 5.6, 5.9 and 5.10). Careful ultrasound examination of the contralateral testis is essential.

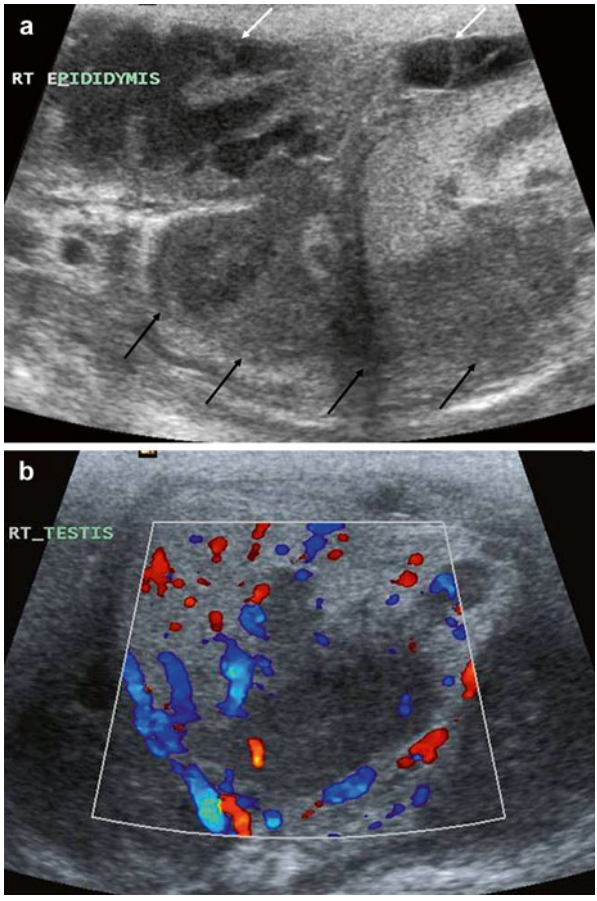


Fig. 5.9 Scrotal TB. (**a**) Longitudinal image of the epididymis which is thickened and hypoechoeic (*black arrows*) with extensive surrounding inflammatory change. There is loculated fibrinous free fluid in the scrotum (*white arrows*) indicating an inflammatory process. (**b**) Transverse image of the testes, demonstrating focal areas of hypoecoic change in the testes with an associated increase in vascularity of the whole testes. These features are highly indicative of an epididimo-orchitis

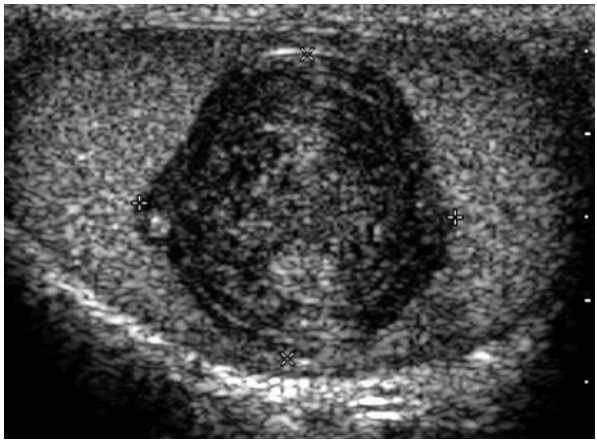


Fig. 5.10 histologically confirmed testicular epidermoid cyst.
A longitudinal image of the testes showing a well defined smooth mass with internal laminated rings. These echogenic rings are highly suggestive of an epidermoid cyst

If such a suspicious testicular tumour is detected with ultrasound urgent urology referral should be made. Staging of testicular tumours is primarily centred on the detection of retroperitoneal lymphadenopathy and excluding distant metastases to the lungs, bone or brain. CT is the imaging modality of choice for staging (see CT staging).

Prostate

Prostate ultrasound is indicated in patients with elevated prostatic specific antigen (PSA) in whom prostate carcinoma is suspected. Locally advanced tumours may be visualised on ultrasound within the bladder, and hydronephrosis due to outflow obstruction by a large or invasive tumour can also be diagnosed.

Endocavity ultrasound with a transrectal transducer (TRUS) places the beam in close proximity to the prostate gland. This is performed with the empty bladder. Anatomical detail of the prostate gland can be appreciated with clear delineation between the central and peripheral zones. Tumours are demonstrated as well defined hypoechoic nodules within the peripheral zone with increased vascularity on colour flow Doppler (Fig. 5.11). Carcinomas may also be ill defined and isoechoic or hyperechoeic to the normal prostate gland. Carcinomas in the central gland cannot be distinguished from benign adenomatous changes of the central zone. Ultrasound guided targeted and non-targeted biopsy of multiple sites of the peripheral zone is the main indication for TRUS, in those suspected of prostate carcinoma. Local staging is best achieved with MRI in those considered for radical treatment and with CT for advanced carcinomas to identify nodal disease and distant metastases. This is described in detail later..

Contrast Enhanced Ultrasound

In recent years intravascular contrast agents have been developed which when administered enhance both grey scale and Doppler ultrasound [16, 17]. The ultrasound contrast agents, which have been developed consist of small (<7 μm),

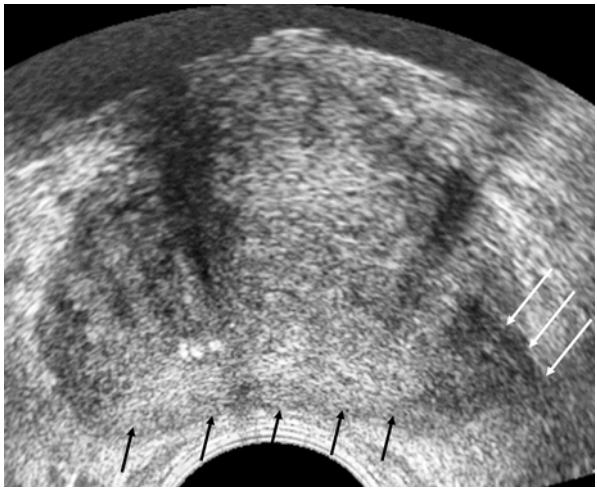


Fig. 5.11 Transrectal ultrasound of the prostate. Transverse section through the mid gland of the prostate. The peripheral gland is seen a homogenous hyperechoic area (*black arrows*). A focal carcinoma is noted within the left peripheral zone as a hypoechoeic area (*white arrows*). This extends beyond the prostatic margins into the peri-prostatic fat indicating extra-capsular disease

encapsulated microbubbles. They are small enough to pass through the pulmonary and capillary circulation and stable enough to withstand hydrostatic pressure within the vascular system and acoustic pressure from the ultrasound wave. When administered they remain in the vascular system. Specific properties of the microbubble capsule and gas within induce greater reflection of the acoustic wave, resulting in increased backscatter. This increases the echogenicity and enhances the grey scale or Doppler image. New ultrasound imaging parameters have been developed which increase the conspicuity of microbubble enhanced backscatter.

The images produced using US contrast agents are greatly enhanced compared to standard grey scale and Doppler imaging and may aid in the detection and characterisation of small isoechoic renal or prostatic malignacies.

Computed Tomography

General Principles

The production of an image by Computed Tomography (CT) is based on differential absorption of an x-ray beam by tissues within the body in the same way as conventional radiography. The amount of absorbed x-rays depends on tissue density, with dense tissue absorbing greater number of x-rays and thereby appearing whiter than less dense tissue which absorb fewer x-rays.

In CT the x-ray beam is collimated into a narrow beam, which passes through a thin slice of the patient. The attenuated x-ray beam, emerging from the patient, is absorbed by detectors, which are capable of differentiating very subtle differences in tissue density. CT therefore has a much greater contrast resolution than plain x-rays and eliminates problems of superimposition of overlying structures to

a much greater extent. The information collected by the detectors is converted into an arbitrary scale (Hounsfield units; HU) based on the attenuation of the x-ray beam by the tissues it has passed through, which varies with differing densities of body tissues. Bone or calcification are the most attenuating and are given a value of +1000HU while air, the least attenuating is given a value of −1000HU. The values are converted to a grey scale image and assigned a brightness level with the highest numbers white and the lowest numbers black. The range (window width) and mean value (window level) of density units is selected to optimise visualisation of different tissue densities of interest. Tissues of densities outside of the range selected will not be discernable and be either totally black or totally white. Standard settings can be selected to display lung, bone or soft tissue 'windows' as required.

Types of CT

Spiral CT

Newer generation scanners utilise a method of volume rather than slice by slice acquisition. A continuous fan x-ray beam, rotating around the patient, traces a spiral path as the patient is moved through the gantry of the machine. Data is continuously acquired through each 360° rotation. Thus a volume of tissue per rotation rather than a slice is imaged. The distance the patient is moved through one revolution of the tube is equal to the slice thickness. Decreased scan acquisition time is a significant advantage of this technique enabling imaging of a larger volume of the patient in a singe breath-hold. This eliminates problems with variation of respiration with each slice. Partial volume effects are also minimized.

Multi-detector CT (MDCT)

It is now possible to acquire data from more than slice thickness simultaneously using parallel banks of detectors. Spiral scanners are now available which are able to acquire up to 128 slice thicknesses in one tube rotation. Data is thus acquired much faster than with a single slice or spiral scanner.

Much thinner slices can be acquired resulting in greatly improved spatial resolution and reduced partial volume effects. In addition, post processing of the large volume of thin slices acquired enables 3 dimensional (3D) and multiplanar image reconstruction. 3D reconstruction applications include CT angiography, virtual endoscopy and CT 'fluoroscopy'. Multiplanar images enable the tumour and its relationship to surrounding structures to be delineated accurately. Combined with CT renal angiography it plays an important role in preoperative surgical planning for renal cell carcinoma, particularly when nephron-sparing surgery is being considered (Fig. 5.12).

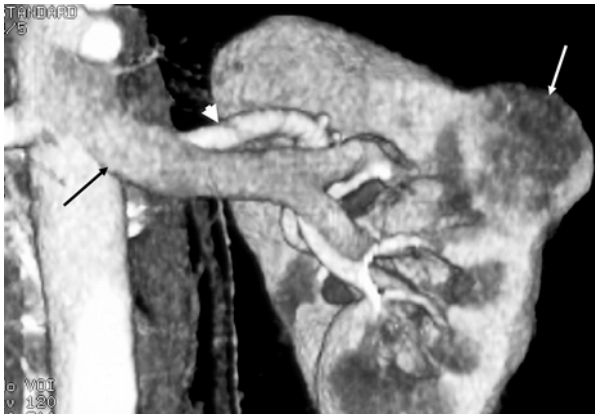


Fig. 5.12 3D volume rendered multi-detector CT reconstruction. A coronal 3D reconstruction of the left kidney showing a focal small renal carcinoma (*white arrow*). Its location in the kidney is well demonstrated along with its relation to the central renal vessels. The main renal artery is shown by the *black arrow* and the main renal vein by the *arrow head*. Both have a normal hilar configuration

Patient Preparation and Technique

Oral contrast medium or water is administered prior to the examination to optimise opacification of small and large bowel to allow better anatomical detail, particularly in the pelvis or retroperitoneum, where the presence of unopacified loops of bowel can be misinterpreted as soft tissue masses or lymph nodes. For bladder and prostate tumours a moderately full bladder is preferable.

For characterising space occupying lesions of the kidney or an adrenal gland, initial unenhanced scans are obtained through the renal or adrenal area at 5 mm slice thickness. The scan is obtained in a single breath-hold at either maximum inspiration or expiration. This allows visualisation of calcification within the lesion and enables the density of the lesion to be calculated. The scan is then repeated following administration of intravenous contrast medium unless contraindicated (see Table 5.1). 100 ml of non-ionic iodinated contrast medium (300–350 mg iodine/ml) is administered via a pump injector at a rate of 3–5 ml/ s. To optimise characterisation of liver, renal or adrenal lesions scans are obtained at variable times to maximise vascular enhancement. For renal lesions scans are obtained at 40 s and 90 s following contrast infusion. For adrenal lesions scans are obtained at 60 s and 15 min following contrast administration and for liver lesions, scans are acquired at 30 s, 70 s and delayed scans up to 15 min may be required.

In the kidney 40 and 90 s equate to corticomedullary and nephrographic phases of enhancement respectively. While the nephrographic phase is more sensitive for the detection and characterisation of small renal lesions, evaluation of the kidneys during both phases provides optimum information. Images obtained during the corticomedullary phase detect low grade enhancement in papillary carcinomas and allow for evaluation of the renal vein and identification of accessory renal arteries. Images obtained at 3–15 min post contrast administration demonstrate contrast within the pelvicalyceal system (excretory phase), and can be used to delineate tumour within the renal pelvis or ureter. In centrally located RCCs, the proximity of

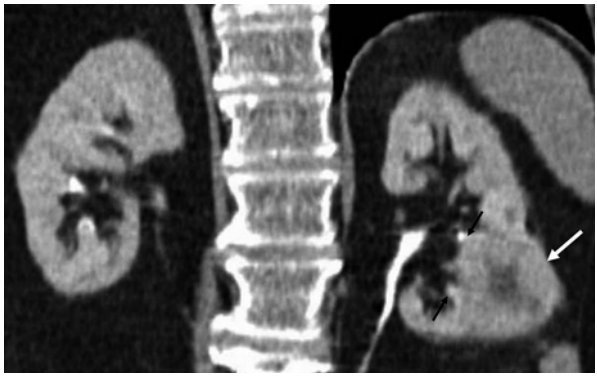


Fig. 5.13 Coronal multi-detector CT reconstruction. A CT IVU coronal reconstructed image. A left lower pole renal cell carcinoma is demonstrated (*white arrow*). The medial margins of the tumour extend up to the renal sinus and abuts the calyces (*black arrows*)

the lesion to the pelvi-calyceal system and the hilar vessels allows evaluation for the suitability for nephron sparing surgery (NSS) (Fig. 5.13).

For a full staging scan, axial 2–5 mm images are acquired through the whole abdomen from the level of the diaphragm to the pelvis. These are obtained with the 90 s scan when a renal protocol scan has been performed. Alternatively, scanning is timed to commence at approximately 60 s following contrast infusion so as to image the liver during maximum portal venous phase enhancement, the optimum time for the detection of most hepatic metastases. For tumours such as renal cell carcinoma and testicular carcinoma which have a propensity to metastases to the lung, images through the thorax are initially acquired at approximately 20–40 s after contrast infusion.

The Role of CT in Urologic Oncology

There are a myriad of uses for CT in urological cancer management. These are summarized in Table 5.3.

Lesion Detection and Diagnosis

CT does not usually form part of the initial diagnosis of bladder, prostate or testicular carcinomas although incidental detection of a soft tissue filling defect within the contrast filled renal collecting system or bladder may suggest the presence of a transitional cell carcinoma. Contrast enhancement of such a mass confirms the diagnosis and excludes the presence of debris or blood clot.

Occasionally testicular carcinoma might present as large retroperitoneal lymph nodal mass and in a young male patient the possibility of testicular germ cell tumour should be considered. CT has an established role in the detection and characterization of indeterminate renal and adrenal lesions.

Table 5.3 Role of CT in Genito-Urinary cancers

A. Kidney
1. Detection of incidental renal cell carcinomas
2. Characterisation of cystic renal mass lesions
3. Tumour staging Local: perinephric and organ invasion Nodal staging Venous invasion Distant metastases: lung, liver, bones, brain
4. 3D CT for surgical planning
5. Follow up and surveillance
B. Adrenal
1. Detection and characterisation of incidental adrenal mass lesions
2. Primary adrenal carcinoma staging: Local and Distant metastases: lungs, liver, bones
3. Planning surgical resection in large adrenal masses
C. Bladder
1. Tumour staging: Locally advanced disease; Nodal: Iliac and para-aortic lymph nodes Distant metastases: lung, brain, liver, bones
2. Radiotherapy planning
3. Post chemotherapy evaluation and surveillance
D. Prostate
1. Tumour staging: Locally advanced disease; Nodal: pelvic side wall and retroperitoneal
2. Rising PSA following radical therapy for nodal or bony metastases
3. Radiotherapy planning
E. Testis
1. Tumour staging, Nodal staging and Distant metastases: lungs, brain, liver and bones
2. Surveillance
3. Planning retroperitoneal lymph node dissection

Renal Space Occupying Lesions

RCCs are suspected on CT in the presence of a wholly or partially solid, enhancing and often heterogeneous parenchymal renal mass, frequently detected incidentally [12, 13, 18]. Cystic renal cell carcinomas are well recognised and need to be differentiated from complicated benign cysts such as simple cysts which have become infected or bled.

Bosniak Grading of Cystic Renal Lesions

A system of grading the appearances of cystic renal masses with CT, according to the presence of features associated with malignancy has been devised by Bosniak [19, 20], is summarized in Table 5.4. Simple cysts with no suspicious features are within **category I** and those with increasingly complex features are graded up to

Table 5.4 Bosniak classification of cystic renal lesions

Category	Description
I	Simple benign cyst with an imperceptible or hairline thin wall that does not contain septa, calcification or solid components. It measures as water density and does not enhance following contrast administration
II	Benign cyst that may contain a few hairline thin septa. Fine calcification may be present in the wall or septa. Uniformly high attenuation lesion of <3 cm that is sharply marginated and does not enhance
IIF	Cyst might contain more hairline thin septa. Minimal enhancement of septa or wall. May be minimal thickening of the wall/septa. Cyst might contain calcification that may be nodular and thick but does not enhance. Does not contain enhancing soft tissue elements. Non enhancing high attenuation lesions >3 cm
III	Indeterminate cystic masses that have thickened irregular wall or septa in which enhancement can be seen.
IV	Cystic lesions are likely malignant that contain enhancing soft tissue elements.

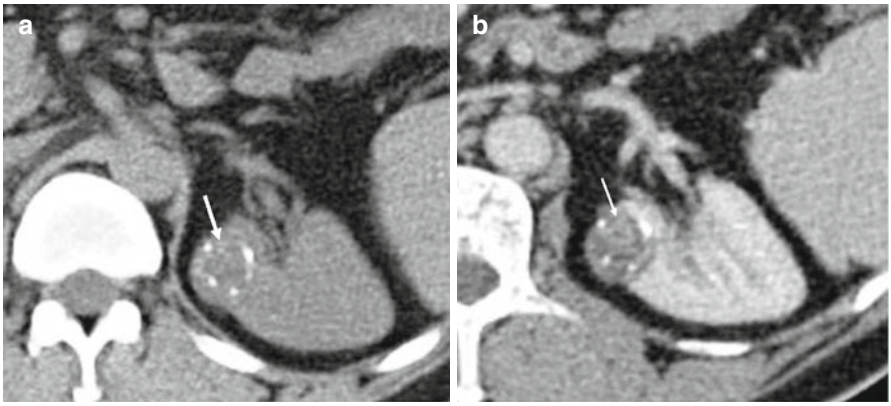


Fig. 5.14 Bosniak 3 renal cyst. (**a**) Pre contrast CT demonstrating a cortical lesion with dense amorphous calcification (*white arrow*). (**b**) Post contrast CT showing small areas of soft tissue enhancement (*white arrow*) within the lesion in keeping with a Bosniak 3 cyst. The lesion was confirmed as a clear cell renal cell carcinoma on histology

category IV, which are frankly malignant. Suspicious features include the presence of thick punctate calcification, wall or septal thickening and the presence of enhancing soft tissue components. **Category III and IV** lesions have malignant features and should be surgically removed (Figs. 5.14 and 5.15). In category III and IV, 60 % of the lesions are malignant and the main benign lesions are inflammatory and infective diseases. **Category II** lesions have some complex features such as fine, linear calcification, thin septa of are of increased density, but no enhancing soft tissue. These lesions do not need to be followed up. More recently category IIF has been introduced and includes benign complicated cysts which require follow up

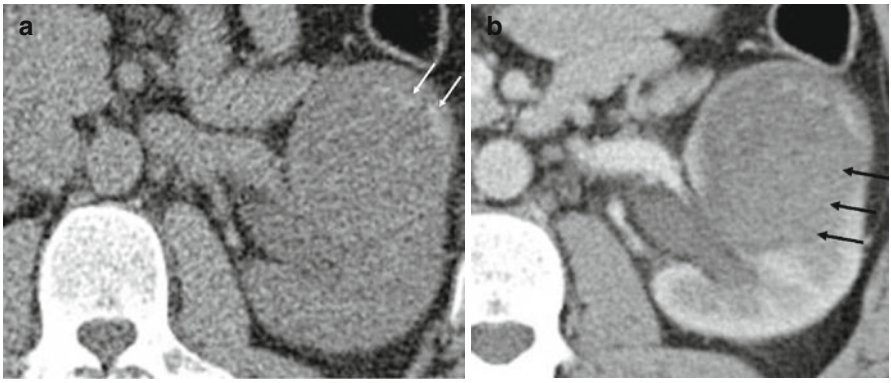


Fig. 5.15 Bosniak 4 renal cyst. (**a**) Pre contrast CT demonstrating a large left renal mass with irregular areas of calcification and low attenuation cystic background (*white arrow*). (**b**) Post contrast CT showing diffuse and homogenous enhancement centrally within the lesion (*arrows*). In view of the size and the enhancement, the lesion is consistent with a Bosniak 4 cyst. The lesion was a papillary carcinoma on histology

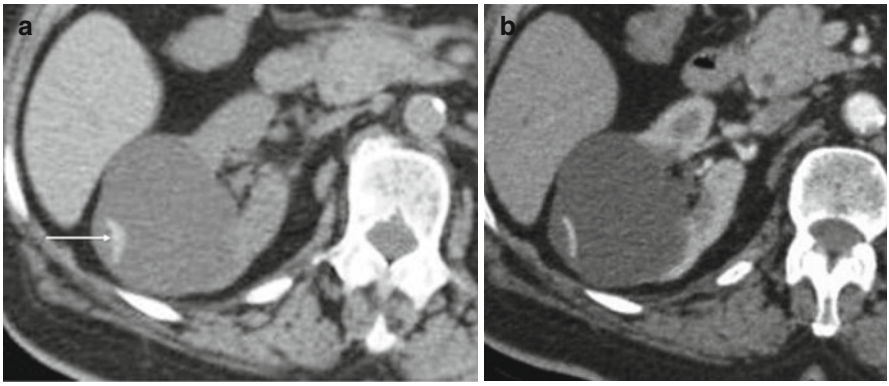


Fig. 5.16 Bosniak 2F renal cyst. (**a**) Pre contrast CT of a large right renal cyst with a focal area of thick calcification (greater than 2 mm) within a septum (*white arrow*). (**b**) Post contrast, no areas of enhancement are demonstrated in the cyst and no other complex features are seen in keeping with a Bosniak type 2F cyst

over time to confirm stability. Features in this group include those with numerous but thin septa, septal or wall enhancement but no soft tissue component, hyperdense category II lesions which are totally intrarenal or greater than 3 cm [21] also fall into this category (Fig. 5.16).

Adrenal Lesions

Adrenal mass lesions are detected incidentally in approximately 4–7 % of the population [22]. They are therefore not an infrequent incidental finding in patients with malignancy. The adrenal glands are also a site of haematogenous metastases from

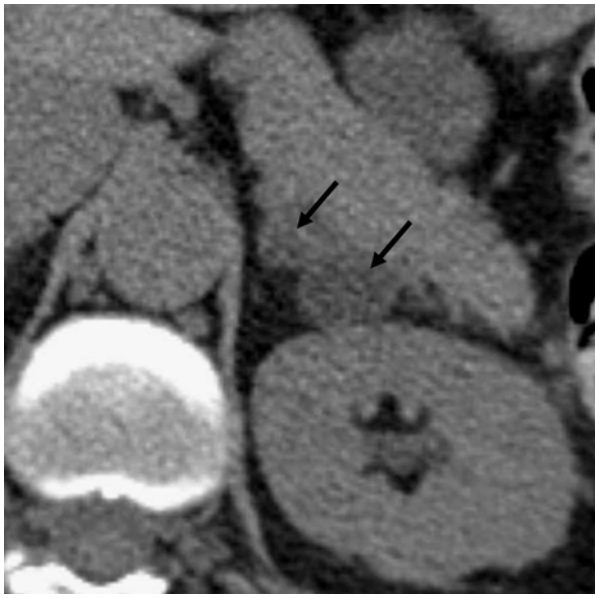


Fig. 5.17 CT lipid rich adrenal adenoma. Pre contrast CT showing two small homogenous adrenal masses (*black arrows*). Both have low attenuation on CT measuring -6HU and 2HU in keeping with lipid rich benign adenomas

other cancers. In a patient with cancer it is often critical to distinguish between an adenoma and metastases. Adenomas are typically smaller than metastases on unenhanced CT imaging. Metastases are more heterogeneous than adenomas and their margins are not well-defined. However, small metastases may be homogeneous and with well-defined margins. Lesions greater than 4 cm in maximum diameter are suspicious for malignancy, although adrenal metastasis in the absence of a known primary are exceedingly rare [23, 24]. However, 36–71 % of incidental adrenal masses found in known oncology patients are metastases [25–27]. Adrenal cortical carcinomas usually present as very large mass lesions, which may or may not be functioning. Non-functioning carcinomas present later with symptoms related to mass effect. These tumours are usually heterogeneous with areas of enhancement. The differential diagnosis of a large adrenal mass includes adrenal metastasis or phaeochromocytoma. Biochemical correlation will confirm the diagnosis in the latter.

The cornerstone of adrenal imaging is CT, performed before and after intravenous injection of contrast medium and acquired as 3–5 mm scans through the adrenal glands. Most adenomas contain an abundance of intracellular lipid and have relatively low density on unenhanced scans. An inverse relationship between percentage fat content and attenuation value on unenhanced CT has been shown [28], with lipid rich adenomas characterized by density measurement of 10HU or less (Fig. 5.17). When a pre-contrast upper threshold measurement of 10HU is taken for a homogenous adrenal mass, a sensitivity of 71 and 98 % specificity is obtained in the diagnosis of a benign adenoma [29]. However, a subset of adenomas cannot be diagnosed on the basis of their unenhanced CT attenuation as they lack intracellular fat. The diagnosis of both lipid poor and lipid rich adrenal adenomas can be made with a high degree of certainty on CT based on their contrast medium enhancement

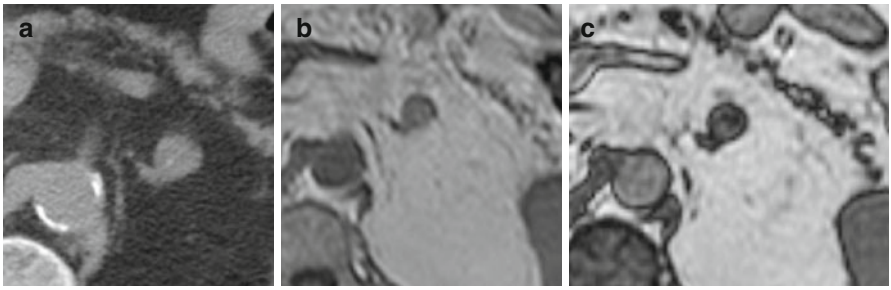


Fig. 5.18 CT and chemical shift MRI of a lipid poor adrenal adenoma. (**a**) Pre contrast CT showing a small homogenous left adrenal mass with a CT attenuation value of 20HU. An attenuation value greater than 10HU indicates an indeterminate mass. (**b**) In phase MRI of the adrenal mass. (**c**) Out-of-phase MRI showing loss of signal intensity in the adrenal mass, in keeping with a benign adenoma

washout patterns [30, 31]. Adenomas typically enhance early with rapid contrast medium washout, compared with non-adenomas which washout over a longer time period. By taking attenuation value measurements of the adrenal lesion at 0 s (unenhanced), 60 s (initial enhancement) and 15 min (delayed enhancement) following contrast medium administration, the absolute and relative percentage contrast washout can be calculated as follows;

$$\text{absolute percentage washout} = \left(\text{initial} - \text{delayed} / \text{initial} - \text{unenhanced}\right) \text{x}\, 100$$

$$\text{relative washout} = \left(\text{initial} - \text{delayed} / \text{initial}\right) \text{x}\, 100.$$

Absolute percentage washout of >60 % and relative percentage washout >40 % are used to make a diagnosis of adrenal adenoma with sensitivity and specificity of 88 % and 96 % and 96 % and 100 % respectively [30, 31]. Chemical shift sequences on MRI are used to characterize atypical, lipid poor adenomas which remain indeterminate by contrast medium washout criteria on CT (Fig. 5.18), or if CT and iodine based contrast media is contraindicated.

New guidelines published by the American College of Radiology Incidentally detected Abdominal and Pelvic Lesions Committee, suggest that for lesions >4 cm in size which do not have typical imaging features seen in myelolipomas, adenomas, cysts etc., adrenal resection should be considered after biochemical evaluation to exclude phaeochromocytomas, without any other additional imaging workup [32]

Tumour Staging by CT

Tumour staging is vital to predict prognosis and for planning the treatment strategy. Staging of the primary tumour with reference to its size, evidence of invasion of local structures, nodal involvement and distant metastases forms the basis of

the internationally accepted TNM classification system. While not specifically a radiological classification system, CT is well placed to demonstrate these features well. However, the sensitivity and specificity of the accuracy of CT varies with tumour type and location.

Local Assessment of the Primary Tumour

CT is well suited to assess certain urologic tumours, in particular, renal cell carcinoma, adrenal and large bladder cancers. Superficial bladder tumours not invading the muscle layer, localised prostate carcinomas, and testicular tumours are best assessed with cystoscopy, MRI or ultrasound respectively. Local tumour invasion is diagnosed on CT where tumour is seen extending into surrounding fat or adjacent organs. Loss of the fat plane between tumour and adjacent structures is not always a reliable indicator of invasion. This is particularly the case in the pelvis where clear fat planes are not normally visible on CT between the posterior bladder wall, prostate, cervix, uterus and rectum. Locally advanced bladder or prostate carcinoma is best diagnosed on MRI when enhancing soft tissue is seen directly invading adjacent structures. Other clues may be present which raise the suspicion of local tumour extension. For example, tumour involvement of the ureteric orifices in the bladder may be suspected in the presence of hydronephrosis. The good contrast resolution of CT enables visualisation of abnormally placed pockets of gas, in the bladder or vagina for example, which may raise the suspicion of vesicovaginal or colovesical fistulae secondary to tumour invasion.

Lymph Nodes

The detection of tumour extension to lymph nodes by CT is dependent on an assessment of lymph node size. A short axis diameter of above 1 cm is considered abnormal in the upper retroperitoneum, and above 8 mm within the pelvis.

These measurements are however somewhat arbitrary and normal or reactive nodes may frequently be larger. The limitations of using size criteria have been evaluated in renal cell carcinoma where nodes greater than 1 cm contain normal or hyperplastic lymphoid tissue in up to 43 % of cases [33, 34]. The presence of enlarged reactive local nodes is increased further in the presence of tumour necrosis and venous invasion [35]. Similarly, micrometastases within normal sized lymph nodes accounts for false negative rates of up to 4 % in one series [35]. Other features to suggest lymph node involvement include, round rather than oval shape, irregular contour, attenuation and contrast enhancement similar to the primary tumour, and necrosis.

Knowledge of the lymphatic drainage pathways of different tumour is essential in the CT evaluation for lymphadenopathy and particular attention should be paid to the retroperitneum in the case of testicular carcinoma and the pelvic side walls in the case of bladder and prostate carcinomas.

Distant Metastases

Unlike ultrasound and MRI, CT has the advantage of being able to image a large volume of the patient in a single scan. It is therefore the ideal imaging modality to detect distant metastases.

Scans of the thorax and liver are included as part of the standard staging for renal, adrenal and testicular malignancies and scan technique is optimized to demonstrate lesions in different sites, as discussed above. Bone metastasis will be diagnosed on CT if present in the areas covered in the scan and when the images are viewed on settings optimised for visualising bone ('bone windows'). They may be visible as sclerotic or lucent defects in the bone, which may or may not expand the bone contour. Attention should be paid to the bones, particularly vertebrae, in patients with renal cell, testicular and prostate carcinomas. Renal and testicular cancer metastases are classically lytic lesions whilst prostatic metastasis are sclerotic lesions. CT of the brain following intravenous injection of contrast medium may be performed acutely in patients presenting with neurological signs to exclude brain metastases, particularly those with testicular germ cell and renal cell carcinomas. In this group, MRI is more sensitive but is reserved for those with clinical suspicion and a negative CT and is only performed routinely in those patients considered at high risk of developing brain metastases.

Tumour Staging: Disease Specific Considerations

Renal Cell Carcinoma

The widespread use of cross sectional imaging has resulted in the detection of earlier stage renal cell carcinomas. Accurate preoperative staging is essential to plan an appropriate management strategy. The differentiation between tumours limited to the kidney (T1-2) and tumours with perinephric invasion (T3) can be difficult on imaging although it is not clinically significant in patients treated with radical nephrectomy. However, since the introduction of nephron- sparing surgery and radiofrequency ablation for low stage tumours it is now essential that this distinction is made preoperatively. The most reliable indicator is the presence of focal soft tissue within the perinephric fat, measuring up to 1 cm being 98 % specific for diagnosing stage IIIa disease. However this sign is not often seen [36]. The presence of soft tissue stranding extending into the perinephric fat is suggestive of tumour invasion, or it can also be due to tumour induced fibrosis, oedema and inflammation. This finding is present in up to 50 % of those with stage I tumour confined to the kidney [36]. Gerota's fascia is well visualised on CT in most patients and tumour extension beyond is diagnostic of stage 4 disease (Figs. 5.19 and 5.20).

The presence of tumour invasion into the renal vein occurs in up to 25 % of patients with renal cell carcinoma and into the IVC in up to 10 % [37, 38]. Estimation

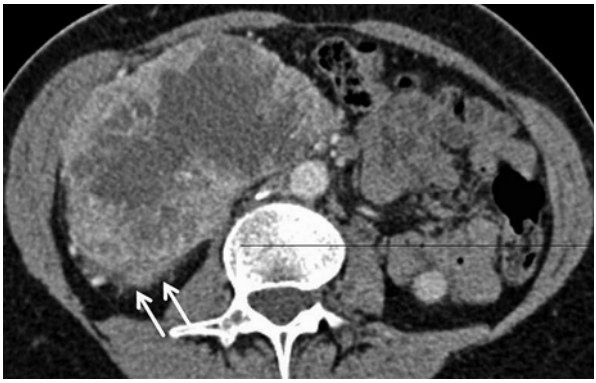


Fig. 5.19 RCC with peripnephric changes. Post contrast enhanced CT of a large right sided renal carcinoma. Along the posterior margin, tumour stranding is seen in the perinephric fat (*arrows*) in keeping with a T3a carcinoma

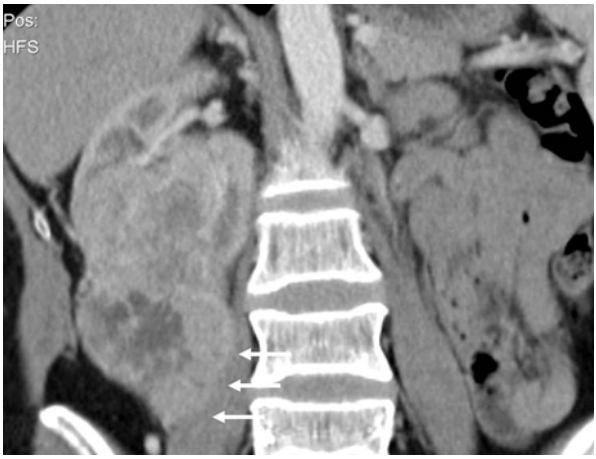


Fig. 5.20 RCC invading the psoas. Large right renal cell carcinoma arising from the lower pole, invading the right psoas muscle (*arrows*) in keeping with a T4 carcinoma

of the upper extent of intracaval tumour is essential for appropriate surgical planning. Indirect signs of IVC invasion include vessel enlargement and the presence of collateral vessels (Fig. 5.21). The most reliable sign is visualization of a persistent filling defect on contrast medium enhanced images (Fig. 5.22). Images must be obtained during peak enhancement of the renal vein and IVC and are acquired at 60 s post intravenous contrast medium administration. CT has been reported to detect intracaval tumour with a sensitivity of 78 % and specificity of 96 % [36] and up to 100 % accuracy has been reported with newer MDCT techniques [38]. Venous invasion is also commonly seen in adrenal carcinomas, with the same implications for surgical planning when there is extension in the IVC. Supra-hepatic caval tumour extension and invasion of the IVC wall can be difficult to distinguish on CT and if suspected an MRI should be performed. A transoesophageal echocardiogram can help to asses the tumour extension into the right atrium.

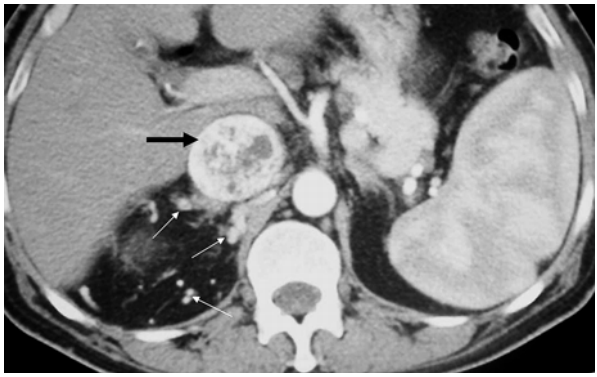


Fig. 5.21 Signs of IVC invasion: IVC expansion. Post contrast CT in a patient with right sided renal carcinoma. The IVC is expanded (*black arrow*) and multiple collaterals are present in the retroperitoneum (*white arrows*)

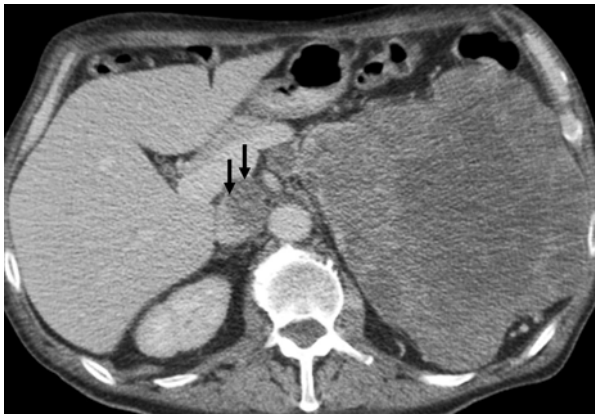


Fig. 5.22 Signs of IVC invasion: filling defect. Post contrast enhanced CT showing a very large carcinoma in the left kidney. The images are acquired at 90 s after contrast administration, thereby opacifying the IVC. A large filling defect is present in the IVC (*arrows*). The filling defects in this phase within the IVC is consistent with thrombus. Enhancement of thrombus indicates tumour thrombus

Urothelial Cancer

Imaging of the bladder with CT is ideally achieved with a full bladder and intravenous contrast medium. Tumour within the bladder enhances to the same degree or greater than that of normal bladder wall. Tumours may be multifocal and are visualized as either plaque like thickening of the bladder wall or mass like soft tissue protruding into the bladder lumen. The important role of CT in bladder cancer staging is distinguishing between tumour confined to the bladder wall and those which have invaded thorough the wall, into the perivesical fat (stage T3). Full thickness bladder wall invasion is indicated by an irregular outer contour of the tumour and stranding of the adjacent perivesical fat (Fig. 5.23). Invasion into adjacent structures indicates stage T4 disease.

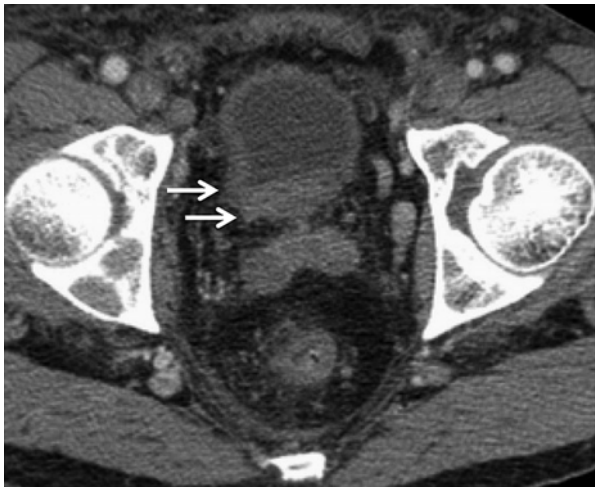


Fig. 5.23 Bladder TCC stage 3a on CT. Large right sided and posterior bladder wall TCC. There is full thickness invasion and stranding (*arrows*) in the peri-vesical fat highly suggestive of tumour invasion

Upper tract TCC can be visualized with CT IVU using the technique described earlier. Focal TCCs may be seen as soft tissue filling defects within a dilated renal pelvis or calyces. Stage T1 and T2 tumours invading the subepithelial connective tissue and muscularis layer respectively cannot be differentiated from each other with CT. Tumour invasion into the renal parenchyma or periureteric fat indicated stage T3 disease and is visualized as areas of poorer enhancement compared to normal renal tissue or nodular projections in the peri-nephric space. (Fig. 5.24).

Tumour invasion through the renal parenchyma and into the perinephric fat indicates stage T4 disease (Fig. 5.25). As with bladder TCC the importance in radiology is in detecting distant and multifocal disease with careful attention made to the contralateral kidney, ureter and bladder.

Testicular Cancer

The role of CT in the management of malignant testicular tumours is to stage the nodal disease accurately and to detect the presence of distant metastases in lungs, liver, bone and brain. Nearly 95 % of testicular tumours are germ cell tumours and these have a predictable pattern of lymphatic spread. Right sided tumours spread to right sided retroperitoneal nodes; pre, para, retro and aortocaval nodes and right renal hilar nodes, while left sided tumours spread to the left retroperitoneum; pre and left para aortic and left renal hilum [39]. The pattern is so consistent that enlarged contralateral nodes in the absence of ipsilateral nodal enlargement are

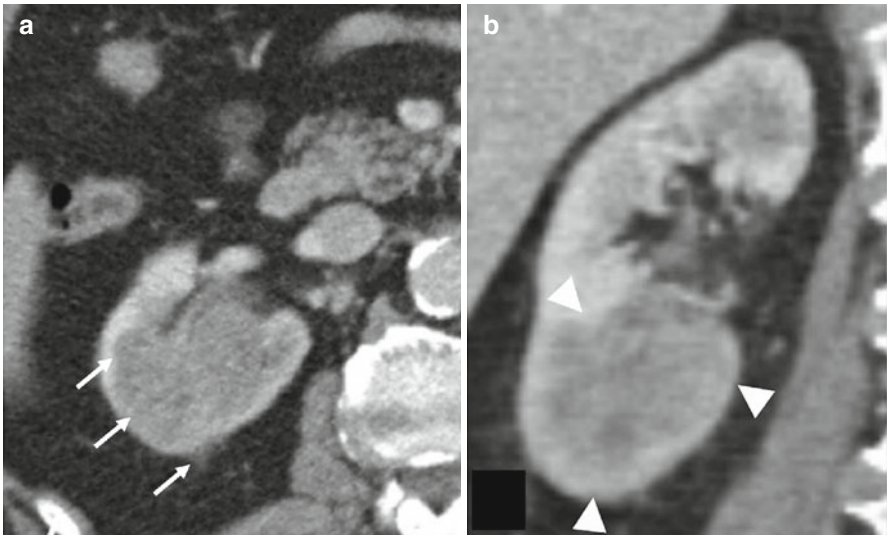


Fig. 5.24 Upper tract transitional cell carcinoma: T3a. (**a**) Axial post contrast CT showing an ill defined diffuse mass replacing the lower pole of the right kidney. The mass is central, replaces the collecting system and invades the renal parenchyma. Small tumour nodules are also seen in the perinephric space in keeping with a T3a transitional cell carcinoma (*arrows*). (**b**) Coronal post contrast reconstructed CT demonstrating the transitional cell carcinoma invades the renal sinus and the full thickness of the renal cortex (*arrowheads*)

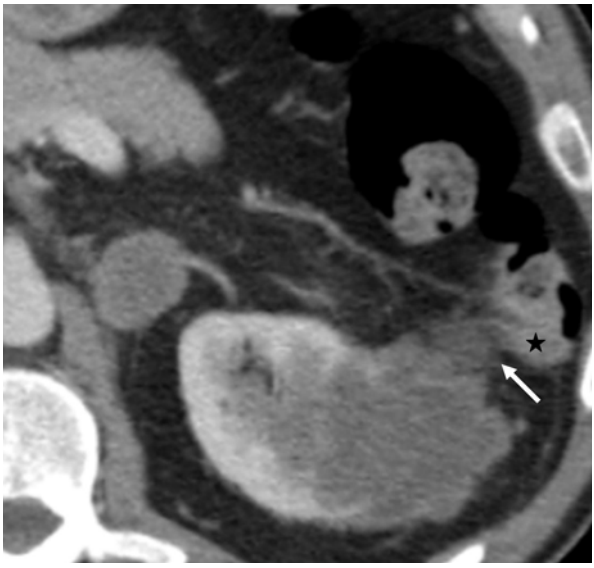


Fig. 5.25 Upper tract transitional cell carcinoma: T4. Axial post contrast image demonstrating a large upper tract transitional cell carcinoma invading the full thickness of the renal parenchyma and extending into the perinephric fat. Direct tumour invasion (*arrows*) is seen into the splenic flexure (*asterisk*) in keeping with a T4 carcinoma

unlikely to be due to tumour. Extension to contralateral nodal groups can be seen in the presence of bulky ipsilateral nodes, greater than 2 cm, and cross over is seen more commonly from right to left sided adenopathy [40]. Extension to lateral nodal

groups anterior to the psoas muscle (echelon nodes) is uncommon but well recognised in testicular carcinoma [41]. Retroperitoneal lymphadenopathy can be mimicked by the presence of unopacified bowel loops or variations in normal vascular anatomy, such as a retro-aortic renal vein or double IVC and can be a potential diagnostic pitfall, particularly if good oral and intravenous contrast enhancement is not achieved. Nodal extension to pelvic nodes is only seen in the presence of massive retroperitoneal lymphadenopathy. Supradiphragmatic extension can occur directly from the retroperitoneum via retrocrual extension and into the posterior mediastinum, or via the thoracic duct to the supraclavicular fossa. These areas should be included in the scan when retroperitoneal lymphadenopathy is present. The lungs are the commonest site of haematogenous disseminated and nodules as small as 3 mm are easily visualised with CT. Disease surveillance however is usually with chest x-ray.

CT Guided Intervention

The good spatial resolution of CT facilitates its use for a variety of image-guided procedures including fine needle aspiration, biopsy and drain insertion. These procedures can usually be performed under local anaesthetic and with minimal distress to the patient.

Technique

Patient positioning on the scan table is critical and should be both optimal for the procedure and comfortable for the patient as it must be maintained throughout the procedure.

A scan through the relevant area is performed initially and oral or intravenous contrast may be used when it is necessary to highlight neighboring vessels or bowel. A reference image is selected from which a direct and safe needle pathway from the skin to the lesion can be identified. Using the guide laser on the CT scanner the selected point can be identified on the patient and marked on the skin. During needle insertion repeated scans through the area can be obtained to establish exact position of the needle tip and ensure correct pathway. CT can be used to guide procedures in areas which are difficult to visualize with ultrasound, particularly the retroperitoneum, chest and deep pelvis.

CT is also used to guide radiofrequency ablation and cryotherapy of renal masses suspected to be RCC. This role is discussed in Chap. 23.

Surgical Planning

Knowledge of the spatial relationships of the tumour to other structures, particularly vessels, is an important consideration for surgical planning. It is important to document the presence of accessory renal arteries or normal variations in the location of

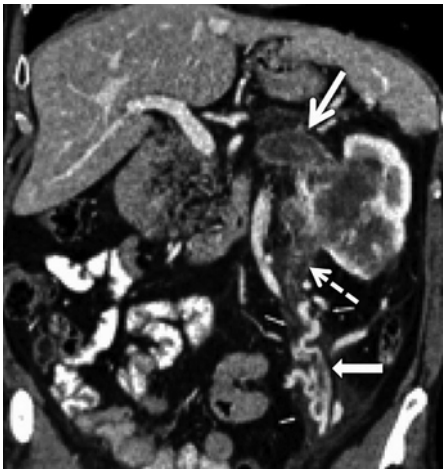


Fig. 5.26 Left sided RCC. Large infiltrative tumour, invading the left renal hilum. The coronal reconstruction demonstrates invasion of the renal vein (*arrow*) and left testicular vein (*dashed arrow*). There is a resultant left sided varicocoele, seen in the abdomen and pelvis (*block arrow*) extending into the scrotum

the renal vein prior to surgery. Multidetector CT (MDCT) enables accurate CT angiographic images of the renal vascular supply to be generated via a variety of techniques. Maximum intensity projection (MIP) images are commonly used to reconstruct angiographic images from pixels with the maximum attenuation value. 3-dimensional (3D) images can be generated which allow the image to be viewed in multiple planes (Figs. 5.12 and 5.26). 3D volume rendered imaging creates a 3D image from the entire data set without preliminary editing and enables the spatial relationship of the tumour to surrounding structures to be displayed. Overlapping structures can be separated out to improve visualisation. 3D volume rendered angiography has been shown to be as accurate as conventional angiography in depicting renal vascularity [42]. 3D images display anatomical detail in a format comparable to surgical appearances compared to conventional axial imaging.

Accurate staging information is essential for the selection of appropriate patients for nephron sparing surgery. It is important to identify patients with bilateral or multifocal tumours, those with stage I disease confined to the kidney, and those without invasion of the collecting system or vascular structures. Lesions most suitable for nephron-sparing surgery are small (usually <4 cm), peripherally located, preferably exophytic, and away from the collecting system and renal hilum. These features are well demonstrated with 3D CT. [43–45].

Imaging in the Post-operative Period

CT is useful in the evaluation of the postoperative patient. A degree of free fluid and inflammatory change will be present in the abdomen or retroperitoneum in the immediate post operative period, along with pockets of gas, particularly following laparoscopic surgery. However, increasing or new intra-abdominal gas and fluid might suggest the presence of anastomotic dehiscence for example following

cystectomy and ileal conduit formation. The detection of an anastomotic leak can be improved with the introduction of 20–50 ml of dilute (2 %) water-soluble contrast medium via the stoma or rectum, where appropriate, prior to CT scanning.

Limitations of visualising deeper portions of the abdomen with ultrasound make CT the more appropriate imaging modality when infected collections are suspected clinically. An abscess can be identified by presence of a focal collection of fluid with an enhancing rim and/or pockets of gas within. Surgeons frequently use oxidized regenerated cellulose (Surgicel) and leave it in the operative bed to achieve intra-operative haemostasis. The immediate post-operative appearance of the inserted Surgicel can mimic that of an abscess and can appear as linear collections of gas within masses of mixed attenuation. Having details of the operative procedure will help differentiate the presence of Surgicel in the operative bed from an abscess [46]. CT can also be used to guide drain insertion into a collection, or plan ultrasound guided or surgical drainage where most appropriate.

Tumour Volume Measurements

The aim of radiotherapy is to maximally irradiate tumour, bladder and prostate in particular, while keeping dose to surrounding normal tissues, rectum and small bowel, at a minimum. Advances in radiotherapy technology have made it possible to more accurately irradiate smaller volumes of tumour with higher doses. Conformal radiotherapy uses multiple collimators to shape the radiation beam much more closely to the contours of the tumour volume while reducing the dose to the surrounding area [47]. Intensity modulated radiotherapy (IMRT) is a more recent form of conformal radiotherapy in which the quantity of radiation across the beam in varied, enabling greater control of the shape of the radiation beam. The radiation beam can be varied to allow higher doses to different areas within the tumour volume [47]. It is important that the CT performed for radiotherapy planning is performed with the same technique and conditions to that later used to administer treatment. Differences in equipment, respiration, oral contrast administered and degree of bladder filling can result in variations in tumour position and volume of tissue within the radiation field. The prostate gland can alter in position within the bony pelvis by 9 mm or more between radiotherapy fractions due to changes in bladder filling [48, 49]. Image guided radiotherapy (IGRT) allows the radiation beam to be altered depending upon day-to-day movement of the prostate gland. This is done by placing intraprostatic fiducial markers (e.g. gold seeds) that serve as surrogates for prostate position, and this in conjunction with IGRT has enhanced the ability to target the prostate despite daily variations with increased accuracy. These techniques are currently being used in the treatment of pelvic malignancy including prostate and bladder carcinomas and require accurate localisation of the tumour margin in order to map out the specific treatment area. CT is principally used although techniques are being developed using MRI image fusion with radiotherapy planning CT for accurate tumour volume co-location.

Magnetic Resonance Imaging

Basic Principles

Magnetic Resonance Imaging (MRI) is a non-ionising radiation method utilising magnetic fields and radiofrequency waves to induce and detect a signal from different body tissues which is then converted into a grey scale image. An MRI scanner consists of a large bore circular magnet. When a patient is placed within it, spinning (precessing) hydrogen ions (protons) in water and lipid molecules of the body tissues are aligned producing a net longitudinal magnetisation along the line of the magnet field. A radiofrequency (RF) pulse at a specific frequency is applied which induces a proportion of precessing, aligned protons to change alignment and flip through an angle, the size of which is determined by the strength and duration of the RF pulse. The net magnetisation is hence tipped into a direction in the transverse plane and induces a small voltage or signal, which can be detected by a receiver coil placed around the patient. When the RF pulse is switched off, the net magnetization begins to decay generating a signal. This signal is amplified and processed into the pixel grey scale level of the MRI image. The strength of the signal partly depends on the proton density of the tissue but more significantly on the time for the transverse magnetisation to decay and the longitudinal magnetisation to re-grow. This is dependent on two methods of energy loss, or relaxation. The T1 relaxation represents recovery of the longitudinal magnetization and depends on the time taken for the excited protons to give up energy and realign themselves along the line of the magnetic field. T1 relaxation is increased by the rapid jostling of heavy molecules within tissues removing energy from the excited protons. Tissues with protons attached to heavy molecules such as proteins or fat have a shorter T1 relaxation time than lightweight molecules containing a high proportion of free water.

T2 relaxation represents decay of the transverse magnetisation and relies on progressive dephasing of excited protons once the RF pulse is switched off. This depends on the variation of local magnetic fields in different tissues which is greatest in solids and rigid large molecules which have a very short T2 compared with free water. Rigid or fixed macromolecules such as those in bone, calculi and metallic clips are relatively immobile and do not generate a signal. By varying time between RF pulses and time to collect the signal, images are produced when the difference of the signal produced by different tissues is greatest. Images are generated with either more T1 or T2 effects or weighting.

Advantages and Disadvantages of MRI Over CT

Compared with CT, MRI produces images which reflect molecular differences between tissues rather than just tissue density and therefore generates a much greater grey scale range of soft tissue contrast. Images can also be generated in any

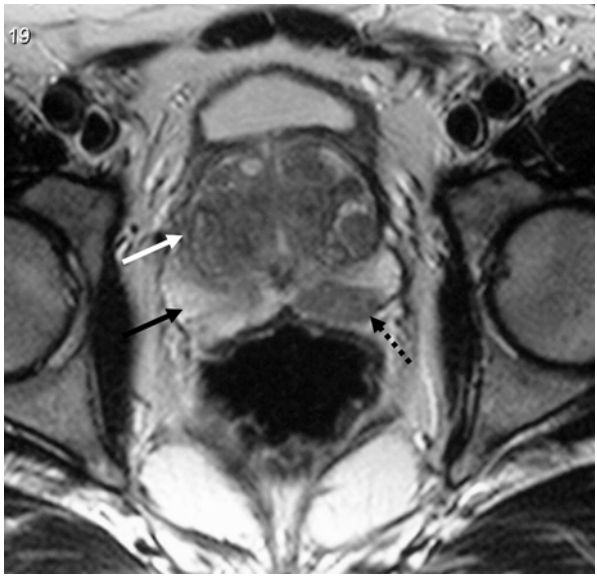


Fig. 5.27 T2 weighted MRI prostate. Axial T2 weighted high resolution image of the mid prostate gland. The normal peripheral zone has a homogenous, high T2 signal intensity (*black arrow*) whilst the central gland has lower T2 signal intensity with nodular changes proportional to the degree of benign prostatic hyperplasia (*white arrow*). Within the left peripheral zone, a typical low signal intensity carcinoma is demonstrated (*dashed arrow*)

plane and at any angle. MRI is particularly useful for imaging the pelvis where contrast and spatial resolution of organs is generally limited with CT. With MRI, molecular differences in the zonal architecture of the prostate can be delineated, for example, and clear distinction between the central and peripheral zones of the gland can be demonstrated (Fig. 5.27). The development of local pelvic RF transmit/receiver coils have enabled imaging to be targeted at a much smaller field of view resulting in improved signal to noise ratio and spatial resolution. This has greatly facilitated the use of MRI in the staging of pelvic malignancy.

Intra-cavity receiver coils have also been developed which are placed into the rectum and produce images with much greater signal-noise ratio. The imaged field of view is much smaller with an endorectal coil but greater resolution can be achieved in the areas imaged. These coils are used particularly to visualize the anal sphincter, prostate zonal anatomy and for rectal cancer staging.

At clinical strengths, MRI does not use ionising radiation and at present poses no known risks to patients. This makes MRI of value where it is desirable to limit radiation exposure, in particular in children or young adults, and patients who require long term follow up surveillance imaging.

MR imaging involves obtaining multiple sequences and planes which is much more time consuming than CT. The imaging sequences obtained are specific to the organ and specialist training of the radiographers and radiologists is essential. Image quality will be degraded by patient movement and respiration and is therefore more dependent on patient cooperation and studies may be limited in sick patients or those requiring continuous monitoring. Some patients are unable to tolerate MRI and find the enclosed confines of the scanner claustrophobic. This may be overcome by using an open bore magnet which is available in some specialist centres.

Technique and Patient Preparation

The patient should be informed that the scan may take up to 30–45min to perform, during which time they will be required to lie still within the scanner. During the scan, loud 'knocking' noises will be heard as radiofrequency pulses are switched on and off. Pelvic MRI for bladder and prostate imaging is best performed with a moderately full bladder, although over distension can result in patient movement artefact. Ideally the patient is asked to void approximately 2 h before the scan. Bowel peristalsis can also create movement artefact and degrade the images. For renal and adrenal MRI an antispasmodic agent such as, buscopan or glucagons is administered immediately prior to the scan [50].

The diagnostic ability of MRI has been enhanced with the now standard use of Gadolinium chelate based intravenous contrast agents. Like iodinated contrast medium used in CT, injected gadolinium circulates within the vascular system and is taken up in vascularised tissue and tumours. Within the magnetic field of the MRI scanner, gadolinium has a paramagnetic effect, causing shortening of the T1 and T2 relaxation times. This is best appreciated on sequences weighted for T1 effects where the signal is increased. Thus, on T1 weighted imaging, vascularized tissue increases in signal intensity following gadolinium administration. Unlike iodinated contrast agents, the incidence of allergic reactions is extremely rare.

Safety Considerations

Ferromagnetic objects placed in or near the magnetic field are attracted to the magnet and can move. This may convert unfixed external objects into potentially hazardous projectiles. Objects within the body such as aneurysm or other surgical clips might be displaced or rotated in body tissues. The current practice is to use MRI-compatible non-magnetic surgical objects where possible. It is important for the MR operator to check the compatibility of surgically inserted materials, particularly those inserted more recently. Joint prostheses are firmly fixed and don't generally cause a problem, although the susceptibility artefact induced by metallic hip prostheses may degrade images of the pelvis. MRI is contraindicated in patients with implantable cardiac pacemakers, neurostimulator devices, cochlear implants, certain types of aneurysm clips and intraocular metallic foreign bodies.

Patients with chronic kidney disease (Stage 4–5) with a GFR of <30 ml/min, those with renal impairment who have had or awaiting liver transplants, those undergoing haemodialysis or peritoneal dialysis, when exposed to gadolinium based contrast agents are at high risk of developing a debilitating fibrosing systemic disease called Nephrogenic systemic fibrosis (NSF). This is thought to be caused by the prolonged presence of gadolinium in the vascular space due to impaired renal clearance. The gadolinium leaks into the extracellular space setting up an irreversible inflammatory reaction. The disease primarily causes patchy fibrosis of the skin and joints, but may also affect the heart, lungs, liver, nerves, dura mater and muscle and may result in increased mortality [51–54]. The risk of NSF is lower for patients with stage 3 chronic kidney disease (GFR 30–59 ml/min) and children under 1 year

due to their immature renal function. It is therefore essential to check patients' serum creatinine and estimated GFR (eGFR levels) before undergoing MRI examination. No cases of NSF have been reported in patients with GFR >60 ml/min [54].

MRI in Urologic Cancers

The main indications for the use of MRI in urologic oncology are summarized in Table 5.5. Because of resource and time implications MRI is often reserved for specific problem-solving such as the characterization of lesions detected by other imaging modalities. This is particularly the case for those renal and adrenal lesions which remain indeterminate on CT, or in whom CT is contraindicated. MRI may also be performed to exclude hepatic metastases in a patient with an indeterminate liver lesion who is being considered for surgery.

Table 5.5 Role of MRI in urologic malignancy

A. Kidney
1. Characterization of focal renal lesions
2. Tumour staging Patients where CT is contraindicated Specific problem solving (a) perinephric invasion (b) local organ invasion (c) venous invasion including IVC wall invasion
3. Follow up/ surveillance: to reduce radiation burden in high risk groups e.g.: VHL
B. Adrenal
1. Characterisation of adrenal mass lesion: Adenoma versus metastasis/ primary adrenal adenocarcinoma
2. Characterisation of functional adrenal mass: Adenoma *versus* adrenal adenocarcinoma
3. Local staging of primary adrenal carcinoma
C. Bladder
1. Local staging
2. Identification of suspected vaginovesical, rectovesical or other fistulae
3. Radiotherapy planning
D. Prostate
1. Local staging Extracapsular invasion Seminal vesicle invasion Nodal staging Multiparametric MRI for tumour detection and localisation
2. Spine MRI: suspected cord compression in patients with bone metastases
E. Testes
No role in assessment of local tumour
Brain and spine MRI for detection of metastases

The exception is for local staging of prostate and bladder carcinoma. MRI is recommended for local staging of muscle invasive bladder cancer and prostate carcinoma in patients being considered for radical treatment. MRI is sensitive for the detection of pelvic fistulae which may arise as a complication of a pelvic tumour, surgery or radiotherapy, and MRI is the imaging investigation of choice for this.

Lesion Characterization

Renal Lesions

Solid renal mass lesions are frequently isointense to renal parenchyma on T1 and hyperintense T2 weighted MRI. Following the administration of Gadolinium they enhance more than renal parenchyma and become more conspicuous [55]. This is particularly important for the detection of small (<3 cm) renal cell carcinomas which are usually solid. MRI is useful for surveillance imaging in high risk patients. In particular, patients with Von Hippel Lindau syndrome, for example, have a propensity to develop renal cell carcinomas, often from a relatively young age and on a background of multiple renal cysts (Fig. 5.28). They frequently develop small (<3 cm) early renal cell carcinomas which are slow growing. MRI is often the imaging method of choice for follow up in these patients.

Adrenal Lesions

MRI techniques have been developed to aid characterization of adrenal lesions. Differentiation of benign from malignant lesions relies on the detection of intracellular lipid, seen almost exclusively within adenomas [28]. This can be reliably detected on MRI with the use of a chemical shift imaging technique. This exploits the normal difference in precessional frequency between fat and water protons

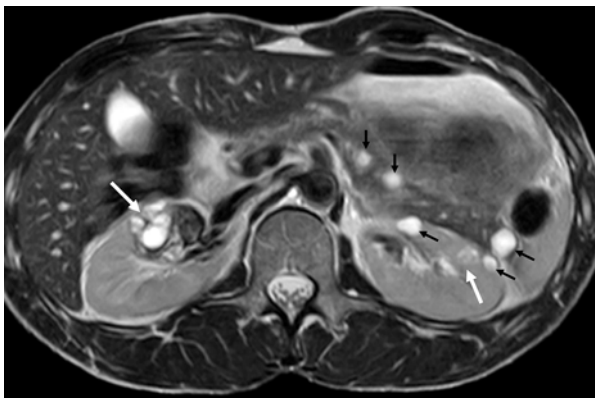


Fig. 5.28 Renal MRI in VHL. Axial T2 weighted MRI image from a male 22 year old patient with Von Hippel Lindau (VHL) syndrome. There are bilateral cystic renal cell carcinomas (*white arrows*) seen as complex cystic masses. Multiple simple cysts are also present within both kidneys and the pancreas (*black arrows*) commonly present in VHL syndrome

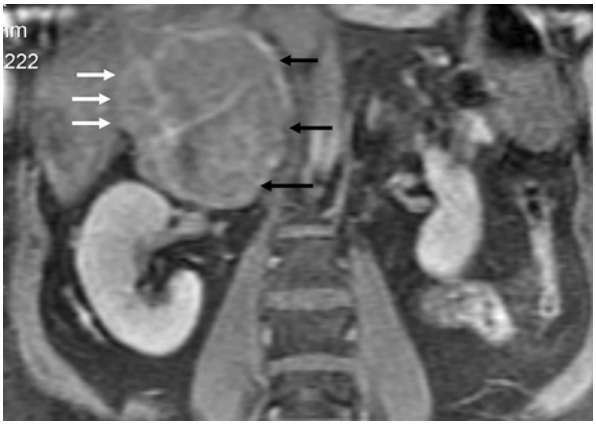


Fig. 5.29 Adrenal cortical carcinoma. Coronal T1 weighted post gadolinium MRI in a 26 year old male patient. A large heterogenous right supra-renal mass is demonstrated (*black arrows*). A clear plane of separation is present between the upper pole of the kidney and the mass, congruous with an adrenal mass. The mass shows invasion of the inferior margin of the liver (*white arrows*). Histology confirmed an adrenal cortical carcinoma with direct hepatic invasion

within a given voxel. The protons can be made to precess, or spin, at the same frequency and are 'in phase' with each other and an additive signal is produced. When they are made to precess out of phase the signal is reduced in those voxels which contain both fat and water protons. In the case of adrenal adenomas, the lesion looses signal on the out of phase images compared with the in phase (Fig. 5.18). Adenomas can be diagnosed with up to 100 % specificity [56] and thus can be distinguished from metastases and primary adrenal carcinoma. Primary adrenocortical carcinomas are usually large at presentation, heterogeneous and enhance post Gadolinium administration (Fig. 5.29).

Tumour Staging

Bladder

MRI has the advantage over CT for staging of muscle invasive bladder carcinoma in that it can identify invasion of the deep muscle [50]. It cannot however, differentiate superficial muscle invasion from submucosal invasion. The bladder wall muscle is seen as low signal intensity on T2 weighted images and disruption of this line indicates muscle invasion (Fig. 5.30). MRI is unable to distinguish between T1 and T2 tumours and is inaccurate in assessing T2a versus T2b disease. Its strength is in the demonstration of T3 disease. MRI has better sensitivity for the detection of perivesical fat and surrounding organ invasion, compared with CT. Both T1 and T2 weighted sequences demonstrate T3b disease due to the high signal contrast between tumour and the pelvic fat. MRI is also superior to CT in detecting local organ invasion due

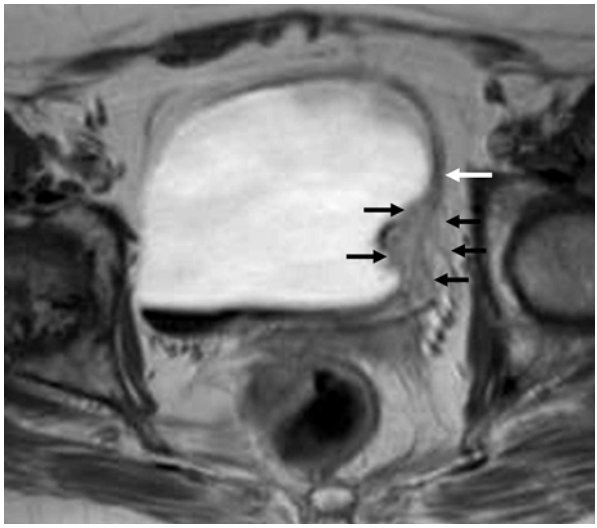


Fig. 5.30 MRI of bladder TCC: T3b carcinoma. Axial T2 weighted image of the bladder with a muscle invasive transitional cell carcinoma along the left lateral bladder wall (*black arrows*). The mass invades the full thickness of the bladder wall which has a low T2 signal intensity (*white arrows*). Tumour is also seen directly invading into the peri-vesical fat in keeping with stage T3b carcinoma

to its superior contrast resolution. The overall accuracy of MRI in staging bladder cancer is 75–85 % and is therefore the modality of choice for local staging of muscle invasive bladder cancer [50].

Patients with pathological T2 stage disease on MRI, are at risk of lymphatic and haematogenous extension and full N and M stage requires CT of the lungs and liver.

Prostate

High resolution T2 weighted imaging of the prostate gland in multiple planes enables the zonal anatomy of the prostate gland to be well demonstrated [57, 58]. The peripheral zone is usually thinner and of higher signal intensity compared with the heterogeneous, lower signal intensity central zone. Prostate carcinoma can be identified as low signal intensity within the peripheral zone (Fig. 5.27). However, this appearance is not specific and can also be seen with chronic inflammation and fibrosis, making detection and delineation of the tumour difficult (Fig. 5.31). Low signal change can also be seen in the peripheral zone due to post biopsy haemorrhage and is confirmed on T1 weighted imaging as high signal foci . The presence of haemorrhage makes it difficult to localize the tumour and reduces staging accuracy when MRI is performed less than 3 weeks post biopsy [59]. Tumours arising within the central zone cannot be differentiated from the markedly heterogeneous appearance of the central zone in co-existent benign prostatic hypertrophy. Tumour localization by MRI is reserved for patients with elevated PSA but previous negative biopsy, and in selected patients MRI has been shown to have a sensitivity and positive predictive value of 83 and 50 % respectively [60].

The principle role of MRI of the prostate, however, is in local tumour staging in patients with histologically proven carcinoma who are being considered for radical

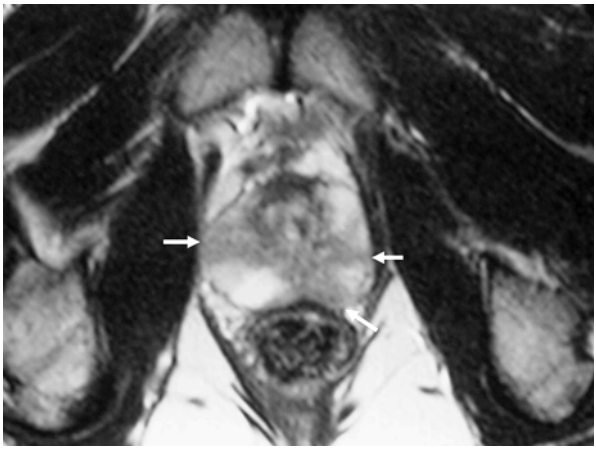


Fig. 5.31 MRI prostate: Non specific prostatitis. Axial T2 weighted image showing multiple bilateral areas of low T2 signal intensity within the peripheral zone of the prostate gland (*white arrows*). Extended biopsies of the prostate gland demonstrated prostatitis only with no foci of carcinoma

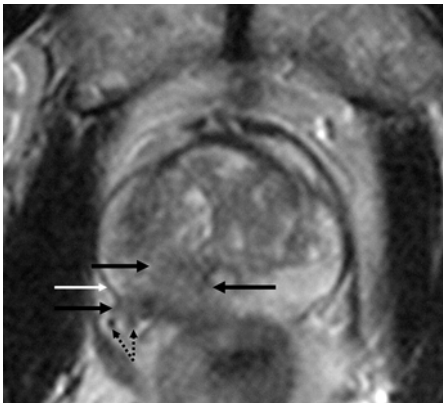


Fig. 5.32 Extracapsular invasion of the prostatic capsule. Axial T2 weighted image of the prostate demonstrating a large focus of carcinoma in the midline and right peripheral zone (*black arrows*). The prostate capsule is well seen (*white arrow*). The tumour in the peripheral zone invades the capsule and extends into the peri-prostatic fat encasing the right neuro-vascular bundle (*dashed arrows*)

surgery or radiotherapy. The accuracy of prostate cancer staging varies but may be up to 88 % with endorectal coil MRI [61]. The detection of extrascapsular extension and seminal vesicle invasion is of particular importance for treatment planning because of their prognostic implications. Features suggesting extracapsular invasion include interruption of the low signal peripheral capsule with a bulging tumour contour but the most predictive features of invasion are asymmetry of the neurovascular bundles and obliteration of the rectoprostatic angle, with specificity of up to 95 % but poor sensitivity of 38 % [62]. The location of the neurovascular bundles are an important site of invasion and can be seen posterolaterally in the 5 and 7 o'clock positions. Loss of the normal rectoprostatic angle at this point is suspicious for tumour extension (Fig. 5.32). Seminal vesicle invasion is suggested when replacement of their normal high signal intensity with low signal intensity tumour is seen (Fig. 5.33). Previous pelvic irradiation, age related atrophy and other benign conditions (e.g.: amyloid) may render the seminal vesicles fibrotic and of low signal intensity. MRI is also important in detection of local tumour invasion into the bladder or rectum.

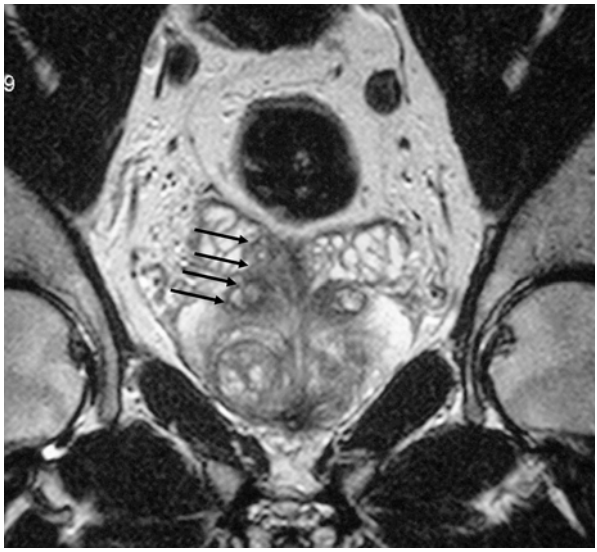


Fig. 5.33 Seminal vesical invasion: T3b carcinoma of the prostate. Coronal T2 weighted image with a tumour focus in the right prostate base, invading the medial aspect of the right seminal vesical. The normal high T2 signal intensity of the seminal vesical is replaced by the low T2 signal intensity of the tumour (*black arrows*)

Multiparametric MRI (MPMri)

Conventional MRI sequences using T1 and T2 weighted images have several limitations in evaluating prostatic disease. It cannot distinguish between tumour, protatitis, haemorrhage and treatment effects. Some tumours are iso-intense to the normal peripheral zone on T2W imaging and central gland tumours are indistinguishable from the normal heterogeneous central gland. After hormonal and radical radiotherapy treatment, the whole prostate gland loses normal zonal anatomy and the peripheral gland loses normal MR signal.

The role of MRI in prostate cancer is evolving with proposed indications which include detecting prostate cancer, localising cancer in the prostate for localised therapies such as HIFU, predicting the aggressiveness of the tumour, detecting recurrence within the prostate following radical radiotherapy and predicting treatment response. For these extended applications, MPMri, in addition to conventional MRI, has been proposed. This includes the use of diffusion weighted imaging (DWI), dynamic contrast enhancement (DCE) and MR spectroscpopy (MRS).

Diffusion weighted imaging MRI technique relies on Brownian motion of molecules and capillary perfusion. It uses balanced positive and negative MR gradients to diphase and then subsequently rephase water protons before signal detection. When no restriction of Brownian motion of water protons occurs, protons move away and no MR signal is acquired . In areas of restricted water motion, rephasing occurs and there is signal acquisition. Restriction of protons occurs in areas of high cellular density or in the presence of extracellular macromolecules. Hence on DW images, areas of restricted diffusion, usually tumours, appear of higher signal intensity. In clinical practice, diffusion can be quantified as ‘apparent’ diffusion coefficient (ADC) value. This is an ‘apparent’ value as the true coefficient is dependent on

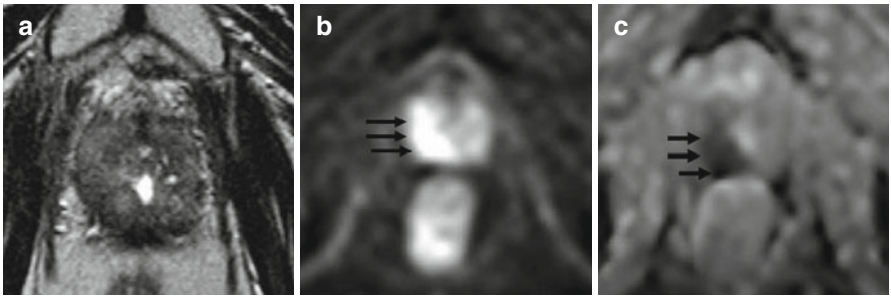


Fig. 5.34 Local recurrence following radical radiotherapy. (**a**) Axial T2 weighted image in a patient following radical radiotherapy treatment. The prostate has a diffuse intermediate T2 signal intensity with complete loss of zonal anatomy. A small localized recurrence within the prostate would be masked by the intermediate signal. (**b**) Axial diffusion weighted image b = 800. The diffusion weighed image demonstrates differential restriction of diffusion within the prostate (*black arrows*). This restricted diffusion is highly suggestive of recurrent disease in the prostate. (**c**) Axial ADC map of the prostate. The ADC image maps the areas of restricted diffusion. A guided biopsy of the sites of restriction (*black arrows*) confirmed recurrent disease in the prostate

temperature, perfusion, motion etc. When used as an adjunct to conventional T2 weighted images, in detection and localization of primary prostate cancer, DWI improves the sensitivity (81 % versus 54 %) compared to T2W sequences alone. There is only a minimal loss of specificity with DWI, 84 % compared to 91 % on T2 weighted images [63, 64]. These results apply to lesions greater than 4 mm in size and Gleeson grade >6. This improvement of tumour detection within the prostate has an important application in guiding TRUS biopsies, detection of local recurrence following radical radiotherapy for salvage local therapies (Fig. 5.34).

During the last decade, dynamic contrast-enhanced MRI has emerged as one of the main techniques used in MPMri of the prostate gland. Dynamic contrast enhanced MRI developed from earlier simpler studies which demonstrated prostate cancer enhanced and washed out earlier than benign prostatic peripheral zone tissue. Fast T1 sequences allow evaluation of contrast dynamics in the prostate following a rapid injection of a gadolinium bolus, reflecting prostate microvascularity and angiogenesis. A rapid continuous series of images obtained (1–7 min) through the whole prostate allows a continuous time assessment of the contrast dynamics in the prostate. These are used to generate an enhancement curves followed by quantitative or semi-quantitative evaluation of the contrast wash-in and wash-out rates. Prostate cancer has higher magnitude of enhancement and a higher wash-in and washout rate compared to benign tissue. The rate of enhancement reflects vascular volume and tissue permeability (corresponds to higher tumour grade). The peak enhancement reflects extravascular/extracellular leakage. Relative peak enhancement has been shown to have the best correlation with malignancy in the peripheral zone [65] (Fig. 5.35).

MR spectroscopy is a 3-dimensional technique for plotting relative concentrations of chemical compounds within the prostate gland by mapping signal intensities of chemicals resonating at different frequencies [66]. Important prostate

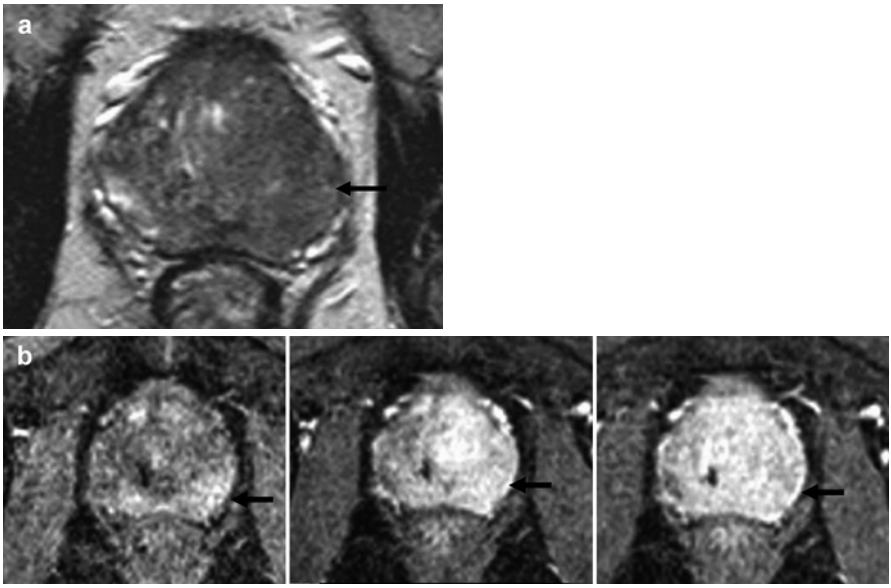


Fig. 5.35 Dynamic contrast enhancement of prostate cancer. (**a**) Axial T2 weighted image in a patient suspected of local recurrent disease (**b**) selected images from the dynamic contrast enhanced sequence at 20, 60 and 120s showing typical early tumoural enhancement in the left sided peripheral zone (*black arrows*)

metabolites are Polyamines, Choline which resonate at 3.25 ppm, Creatine resonates at 3.05 ppm and Citrate resonates at 2.62 ppm. In normal peripheral zone a relatively high peak of citrate is seen compared to that of choline. Choline is a normal constituent of cell membranes and in areas of high tumour cell turnover, a relative increase in the concentration of choline is seen, with reduction of choline. This leads to a reversal of the normal choline: citrate ratio. Spatial mapping of such peaks within the prostate gland are used to plot the location and estimate the extent of tumour (Fig. 5.36). When used in conjunction with standard endorectal or pelvic phased array prostate MR, this technique has been shown to improve tumour localisation [67], increase staging accuracy and reduce interobserver variability. The ability of MRS to identify cancer is dependent on (i) **tumor size**; cancers < 0.5 cm in diameter may be missed whereas those > 0.5 cm are identified with increasing accuracy, (ii) **tumour grade**; higher grades (Gleason score 8–10) are better imaged than lower grade tumours [68].

The increased sensitivity of MPMri in tumour detection and localization provide a useful guide to biopsy of the prostate in patients with rising PSA but previous negative biopsies. The fusion of ultrasound and MPMri software allows the benefits of both techniques to be harnessed in increasing the positive yield of prostatic biopsies. Magnetic resonance imaging/ultrasound fusion guided biopsies can detect more cancers per core than standard 12-core transrectal ultrasound biopsy for all levels of suspicion on magnetic resonance imaging [69].

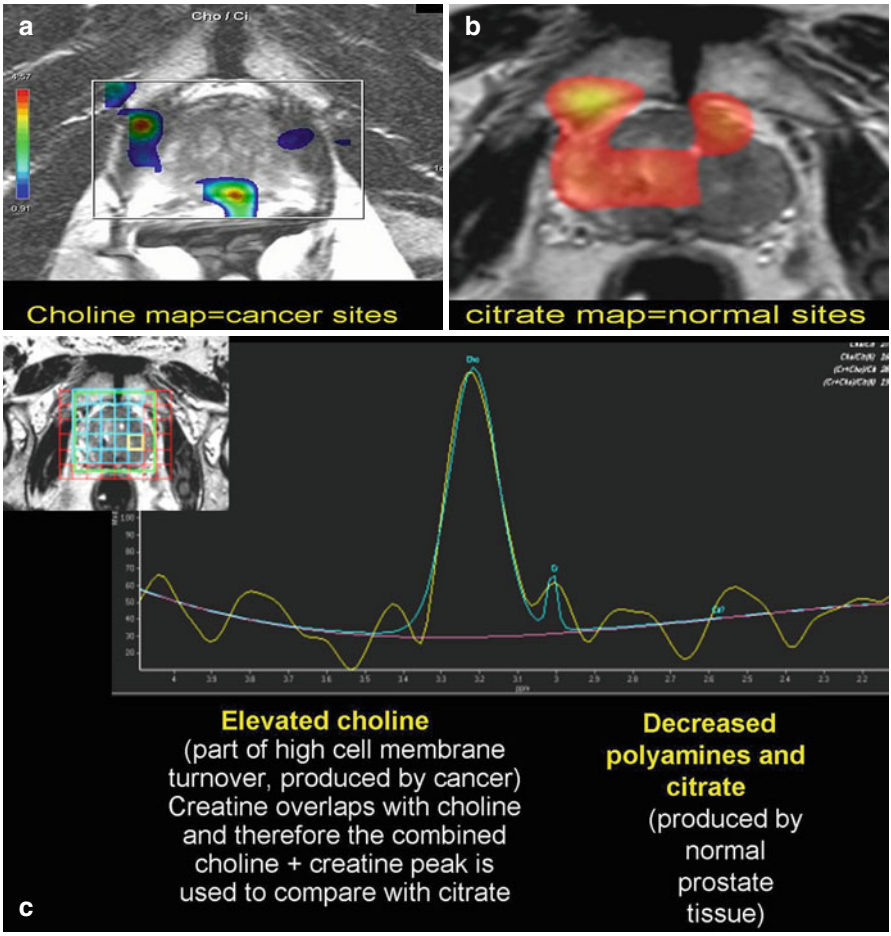


Fig. 5.36 Spectroscopy citrate and choline maps. (**a**) Spectroscopic data acquired through the prostate can be displayed over conventional T2 weighted images. Sites with high levels of choline have been displayed as blue and correspond to tumour sites in both peripheral zones. (**b**) Similarly, citrate maps can also be created, demonstrating areas of normal prostatic tissue. An extensive tumour is seen in the left peripheral zone with no citrate substrate. (**c**) Spectroscopic data can also be displayed as a spectroscopic trace of substrates in each voxel. An elevated choline plus creatine peak and a reduction in the citrate and polyamines corresponds to tumour

Specific Problem-Solving in Renal and Adrenal Carcinoma Staging

In the case of renal and adrenal staging, MRI is usually reserved for resolving specific problems not answered with CT. The multiplanar imaging ability of MRI can help delineate the organ of origin of a large suprarenal or renal angle mass. Similarly, local organ invasion may be better differentiated with MRI where accuracy rates of

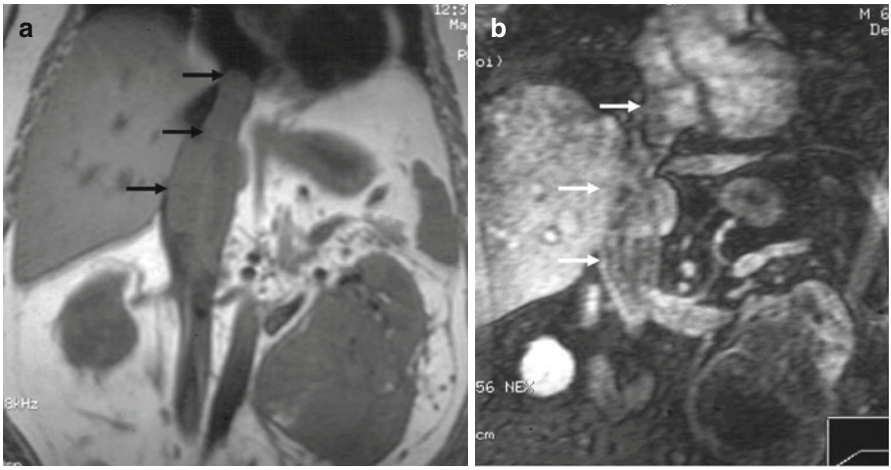


Fig. 5.37 IVC thrombus on MRI. (**a**) Coronal T1 weighted MRI. A large left lower pole carcinoma with expansion of left renal vein and IVC (*arrows*). The upper level of thrombus is well visualized within the supra-diaphragmatic IVC. (**b**) Coronal T1 weighted MRI post gadolinium enhanced image showing non-enhancing thrombus within the IVC (*arrows*)

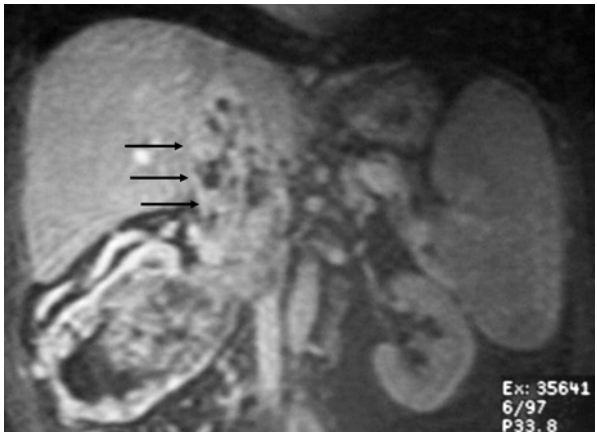


Fig. 5.38 IVC wall invasion on MRI. Coronal T1 weighted image following intravenous gadolinium enhancement. The wall of the IVC is invaded by the enhancing tumour thrombus within the lumen of the IVC (*arrows*). Both the wall and the tumour have heterogenous enhancement and no nomal IVC wall is seen at the site of the luminal tumour. These features are highly specific for IVC wall invasion

up to 100 % have been reported [70] for renal cell carcinoma. The main role of MRI in renal and adrenal staging is in the diagnosis of venous tumour thrombosis, and the delineation the uppermost level of extension. The suprahepatic IVC and right atrium, which may be difficult to visualise on CT, are well seen with MRI (fig. 5.37). Enhancement of thrombus following Gadolinium administration enables distinction between bland and tumour thrombus to be made [71]. Direct tumour thrombus invasion of the caval wall can also be diagnosed with 92 to 94 % accuracy [71, 72] with contrast enhanced MRI (Fig. 5.38). Gadolinium-enhanced 3-dimensional MRI studies can be used to generate renal angiographic images and provide a preoperative vascular roadmap for potentially resectable tumours.

Conclusion

Ultrasound remains an important first line investigation in the detection of renal and testicular cancer, in children and pregnant women. The main imaging modality for uro-oncological cancer staging, treatment planning and surveillance is CT. MRI is used mainly as a problem solving tool for renal and testicular cancer but has the best imaging performance for the local staging of bladder and prostate cancer. Along with the myriad of traditional applications of imaging, advances in multiparametric MRI, multi-detector CT and 3D ultrasound, continue to widen the horizons of cross-sectional imaging. Image guided therapy for renal and prostate cancer are now well established. MRI is being advocated to guide prostate biopsy and stratify treatment options. Advances in MPMri will continue to see increasing applications in the management of patients with prostate cancer.

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Chapter 6
Nuclear Medicine in Urological Cancer

John Buscombe

Introduction

In nuclear medicine administering to the patient orally or intravenously a radioactive tracer material visualizes the target organ. Imaging is performed with a gamma camera, which is able to form an image from the gamma photons emitted, by the radioactive tracer material. There are a wide range of applications for radiopharmaceuticals in the investigation and management of urological cancers. The advantage is that nuclear medicine techniques allow physiological processes to be followed in a non-invasive way, which can not only be done with imaging but by measuring the clearance of radioactivity from the blood or the appearance of radioactivity in urine.

The information provided is different from that obtained by other forms of radiology in that it is primarily physiological and not anatomical. Therefore the results of nuclear medicine results are complementary to other forms of radiology and can often be combined to improve diagnostic yield as can be seen in PET-CT. The type of study used will depend on the clinical situation and the question the clinician needs answering.

Atomic Structure and Radioactivity

All matter is made up of atoms. Each atom is made up of a nucleus, which is positively charged and surrounded by negatively charged electrons. The nucleus is made from positive charged protons and neutral neutrons. The number of protons and neutrons determine the atomic weight of the atom. The number of protons

J. Buscombe, MD, FRCP
Department of Nuclear Medicine, Addenbrookes Hospital,
Hills Road, Cambridge CB2 0QQ, UK
e-mail: john.buscombe@addenbrookes.nhs.uk

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determines the atomic number and the chemical nature of the atom. A single element will have the same number of protons as any other atom of the same element. This is seen simply with hydrogen, in its simplest form Hydrogen has a single proton only so its atomic weight is 1 and its atomic number is 1. However there are two other forms of hydrogen each of these are called the isotopes of hydrogen the first is deuterium which has a proton and a neutron in the nucleus. The atomic weight is now 2 but atomic number remains 1. Likewise tritium has an atomic weight of 3 with 2 neutrons and one proton but atomic number remains 1. Though they have different atomic weight chemically hydrogen, deuterium and tritium all have the same chemical qualities.

The addition of neutrons (and in some cases removing neutrons) results in the nucleus being unstable and it can spontaneously break apart releasing energy. This is called radioactive decay and the isotopes that undergo these changes are called radioisotopes.

Finally when radioactive decay occurs the resulting isotope may itself not be stable and may have a transitory phase before decaying to a more stable form called the metastable form and marked with the letter "m". Therefore a radioisotope may have both a metastable form such as Tc-99m with a half-life of 6 h and a more stable form Tc-99 with a half-life of thousands of years. These different forms of the same radioisotope are called radionuclides.

Positrons

A variation on radioactive decay is the fate of nuclei, which are proton rich. When these decay they produce a positively charged electron called a positron. This will travel a short distance typically 0.5–1 mm in tissue where it meets an electron. When the two combine to annihilate each other and all their mass is converted into energy. As the mass of a positron and electron cannot be changed the energy released is defined by Einstein's equation $E = mc^2$ in this case the energy is 1,022 keV and is released as 2 gamma rays each of energy 511 keV. These can then be picked up by the ring of detectors in a positron emission tomography (PET) machine.

The Tracer Principle

All nuclear medicine studies independent of their simplicity are based on de Heversey's tracer principle. In a nuclear medicine study a small amount of a radioactive tracer is administered to the patient to track a specific physiological process without having a pharmacological action, which may change the effect you are observing. To do this tiny amounts of a radioactive tracer are used, often less than a billionth of a gram. Then the radioactivity in a particular fluid in the body is measured or imaged with an external imaging devise. These radioactive substances are called radiopharmaceuticals.

Tracers Used in Nuclear Medicine

There is a range of radiopharmaceuticals used in assessment of a patient's renal tract. These can be split into three groups:

1. Those with poor imaging characteristics used for *in vitro* testing.
2. Those that can be used for imaging using gamma camera.
3. Those that are positron emitter and can be imaged using PET.

Most rely on gamma ray emission as they decay to be detected either in a well counter or on an imaging device. When imaging the renal tract directly most of the agents used are highly hydrophilic allowing for rapid excretion through the kidneys. In the case of Diethylenetriaminepentaacetic acid (DTPA) excretion is purely glomerular, with hippuran it is purely tubular whereas with mercaptoacetylglycylglycylglycine (MAG3) it is both ways. In addition to the pharmaceutical there also needs to be an isotope. Together they make a specific radiopharmaceutical, which is designed to perform a specific task such as look at renal blood, flow, uptake and excretion as in the case of DTPA.

Radionuclides

The first used isotopes tended to be those, which were produced as a by-product of the fission of Uranium-238. The most common of these is Iodine-131. On its own it is of little use in urology but when added to hippuran to produce Iodine-131 hippuran (also written by convention as I-131 hippuran or ^{131}I-hippuran). It is possible using either blood samples to measure the clearance of the agent from the blood to give the effective renal plasma flow (EPRF). Using sodium iodide scintillation probes and later an Anger gamma camera, it is possible to measure uptake of the I-131 hippuran into the kidney and its excretion. The images are of poor quality and the radiation dose is high but this remains a valid test though often a different isotope of Iodine (I-123 or ^{123}I) is now used as it gives slightly better images and at a lower radiation dose.

Technetium 99m

Technetium 99m (Tc-99m or ^{99}Tc^{m}) is the most commonly used isotope in nuclear medicine; however it is an artificial isotope with a very short half-life of only 6.02 h. This is a metastable form of technetium-99 with the conventionally written as ^{99}Tc^{m}. This isotope is the decay product (called a daughter) of another isotope molybdenum-99 (^{99}Mo) which is a product of nuclear fission of ^{238}U. However, to get sufficient quantities for medical use worldwide special high neutron flux reactors

are used because on any given day about one million $^{99}Tc^{m}$ tests are performed for various different reasons worldwide.

Almost all the ^{99}Mo is created in just four reactors (one in Canada, one in South Africa and two in Europe). All but the South African reactors are over 40 years old and due for de-commissioning. The age of the reactors meant that twice since 2009 there have been multiple breakdowns and there has been little or no ^{99}Mo produced. This resulted in many millions of nuclear medicine studies being cancelled worldwide. At present there is no long-term solution to this problem and ^{99}Mo supplies remain fragile.

As the half life of $^{99}Tc^{m}$ is so short it is best to have the equipment to separate $^{99}Tc^{m}$ from the parent ^{99}Mo based as close to the patient as possible. Many hospitals will have their own $^{99}Tc^{m}/^{99}Mo$ generator on site and it can be used once or twice a day for about 1 week.

The $^{99}Tc^{m}$ is drawn off as a column of insoluble molybdenum oxide and is oxidised to valency-7 (therefore is chemically soluble sodium pertechnetate). Then using transitional metal chemistry it can be added to vials containing the required pharmaceutical with buffers and a reducing agent to allow for binding. Most of these radiopharmaceuticals take 10–30 min to prepare depending on whether or not the product has to be boiled. Again worldwide over 80 % of all nuclear medicine tests use this isotope and these techniques are widely spread in developing countries.

Physical Characteristics

The $^{99}Tc^{m}$ produces a single burst of radiation when it decays, called its characteristic radiation. This radionuclide has energy of 140 KeV. This is ideal for the simple gamma cameras used based on a sodium-iodide scintillator. The range of radiopharmaceuticals that are available for use in urological cancers is wide and described in Table 6.1. It should be noted by the use of a variety of radiopharmaceuticals the same radionuclide can be used for a wide range of indications.

Table 6.1 Commonly used radiopharmaceuticals in urological cancer

Radiopharmaceutical agent	Indication
$^{99}Tc^{m}$ Diethylene Triamine-pentaacetic acid (DTPA)	Measurement of GFR, renography
$^{99}Tc^{m}$ Mercaptoacetylgly-cylglycylglycine (MAG3)	Clearance studies, renography
$^{99}Tc^{m}$ dimercaptosuccinic acid (DMSA)	Divided renal function, characterization of renal space occupying lesion
$^{99}Tc^{m}$ methyl di-phosphonate (MDP)	Assessment of bone metastases, renography
$^{99}Tc^{m}$ labelled red cells	Assessment of cardiac function (pre and post chemotherapy)

Measurement of Glomerular Filtration Rate

For *in vitro* testing of renal physiology, a long living isotope is preferable, attached to a product, which is excreted via a single part of the nephron. For this Chromium-51 (^{51}Cr) is ideal when attached to ethylenediaminetetracetic acid (EDTA) which is filtered by the glomerulus and not re-absorbed. The gamma irradiation is not good for imaging but in small quantities such as 3–4 MBq will be measured efficiently in a well counter and therefore can be used via the radio-activity in sequential blood specimens to calculate the glomerular filtration rate (GFR). This is used in assessment of renal function during chemotherapy but in combination with $^{99}Tc^{m}$ DMSA can be used to predict residual renal function after nephrectomy.

Positron Emitters

The second main class of imaging radiopharmaceuticals are those that are positron emitters. Positrons are positively charged electrons emitted during decay of proton rich nuclei. To obtain these isotopes means adding protons or proton rich nuclei to the nucleus of the target atom. This cannot be done in a reactor instead a machine called a cyclotron accelerates the These positively charged particles, such as protons or alpha particles to close to the speed of light and then bombards them into a precise target. The resulting positron emitting isotopes tend to be of low atomic number such as oxygen nitrogen or fluorine. These have short half-lives so have to be used close to the site of production. For example, the most commonly used of these positron emitters is fluorine-18 (^{18}F). This has a 2-h half-life and as after production some time will be taken up combining the positron emitter with a physiologically useful organic molecule such as glucose to make FDG. It is generally considered practical if the images are performed within a 2-h radius of production. This might mean 30 miles by road transport in a big city but 600 miles when the product can be moved by air.

Imaging with Positrons

All positron emitters produce two 511 kEV gamma rays after their annihilation with an electron. The two gamma rays travel at 180° and can be identified by a paired detection system. Though traditional gamma cameras can be used the 511 jeV energy is a little high for them to work efficiently so a special crystal such as Beryllium-Germanium-Oxide (BGO) is used. These are set in a ring to collect the pairs of 511 keV photons, called co-incidence events. This enabled a 3 dimensional map of positron emission to be produced. This type of machine is a positron emission tomography (PET) camera. The most common form available at present is a combination

of a PET machine and CT. The CT component allows accurate localisation of any site of abnormal uptake and is also used to correct the PET image for any attenuation of the gamma signal through the patient. In the last 12 months PET combined with MRI has also been launched. This technique must be considered experimental and there has been no evidence that it will be of use in urological cancers.

Therapy Isotopes

The third type of radiopharmaceutical has a particulate form of emission such as a beta or alpha particle. These have mass and therefore can deliver a higher radiation dose to any tissue they interact with but cannot be used for imaging unless there is an accompanying gamma emission. In urological cancers there use until recently has been limited to pain relief from bone metastases, however new agents which directly target renal cancer are entering phase II and phase III clinical trials.

Imaging Devices

To be able to image radiopharmaceuticals efficiently, a range of imaging devices have been produced. They all relay on the same principle. They use a scintillator, which is a type of crystal, which is temporarily energised by being hit by a gamma ray resulting in the production of visible light. This is picked up by a photo-multiplier tube (PMT), which converts this signal into the electrical energy, which is amplified and then passed on to a computer. The simplest form of such a system is found in a well gamma counter which can be used to measure small amounts of radioactivity in blood.

The Anger Camera

Invented in 1959 by Hal Anger, the gamma camera uses a large single scintillation crystal often 40×60 cm and about 2 cm thick. To pick up the light signal as array of 30–70 PMTs are needed and are normally hexagonal so they fit together in a honey-comb fashion to ensure the surface is covered. As the amount of light produced by the scintillation crystal is small both the scintillation crystal and PMTs are held in a light proof box. Gamma rays cannot be focused like light so any scattered photos would degrade the image and make it look more "fuzzy". To remove these scattered photons the gamma rays pass through a series of parallel lead lined tubes called a collimator. The width of the septa in the collimator is determined by the energy of the gamma rays and divided into "low energy" (0–180 keV), medium energy (180–300 keV) and high energy (>300 keV). The computer that is attached to the gamma

camera system then determines where on the crystal a gamma ray arrived and its energy. These camera cameras can be mounted on gantries that can move along the patient to perform whole body images and rotate around the patient producing a three-dimensional image called single photon emission computed tomography (SPECT). The associated computer system can detect a series of images (every 0.5 s upwards) of a particular part of the body. This is called a dynamic image then the computer can calculate the activity of a radiopharmaceutical at any area of interest to perform a time activity curve as seen in renography.

Positron Emission Tomography (PET) Imaging

PET imaging does not need collimation, as a scattered gamma ray will be deflected much like a billiard ball hitting one another. Therefore it will not arrive 180° from its partner gamma ray released at the same time and will not make a co-incidence event and will not be recorded. As no lead collimation is needed in PET less gamma rays are stopped and the system is more efficient than a standard gamma camera.

Tomography

Both SPECT and PET are excellent methods to look at functional images of the body and are finding increasing roles in the imaging of urological cancers. However spatial resolution is limited to about 7 mm for SPECT and 3 mm for PET, though these figures are optimistic and describe the best attainable. Also identifying the site of any abnormal uptake can be difficult due to the lack of anatomical markers. Therefore both SPECT and PET machines have been added to CT scanners to allow for simultaneous SPECT/CT and PET/CT a technique called image registration.

Radiation Dosimetry

The radiation burden for nuclear medicine tests tends to lie in the low to medium band compared to other radiological studies The unit of measurement for radiation is the Sievert (Sv) which equals a joule of received energy per kg of tissue Clearly as this is a lot of energy normally a mSv is used.

Residents of London receive on average 2–5 mSv of radiation per year. Residents of Cornwall or Aberdeen who live on granite may receive an annual radiation dose of 5–10 mSv due to Radon gas seeping into their home. The area of the world with the highest annual background radiation dose is the Southern Caucasus with an annual radiation rate of 25 mSv. The radiation dose from X-rays studies may vary depending on the number of views taken, energy of the X-ray beam and exposure time. In Nuclear

Table 6.2 Radiation dose for investigations commonly used in urological cancer

Investigation	Radiation dose measured as effective dose equivalent (mSv)
3 MBq ^{51}Cr-EDTA for GFR	0.006
100 MBq ^{99}Tc^{m} MAG3 renogram	0.7
400 MBq ^{18}F FDG PET scan	10
KUB plane X-ray	1–3
Spiral CT of kidneys with contrast	3–24
IVU-6 image	1–6

Based on data from Ref. [1]

Medicine the radiation dose is determined by the activity of radioisotope given. In the UK this is itself governed by a statuary instrument and administered through a committee of the Department of Health called the Administration of Radioactive Substances Advisory Committee (ARSAC) who publish typical maximum activities and radiation doses received (Table 6.2) [1]. A few radiological investigations are included for comparison. However, it can be seen that the excess radiation of a single nuclear medicine test is not great compared to background radiation.

Assessment of Renal Function

The most commonly used isotopic test for the assessment of renal function is the measurement of GFR with a radiopharmaceutical, which is exclusively filtered in the glomerulus. There are several agents which can do this including ^{99}Tc^{m}-DTPA. However the short half-life of ^{99}Tc^{m} at 6 h means that any counts must be decay corrected and correct timing of samples taken is vital. Also in patients with impaired GFR (that is below 30 ml/min), a 24-h sample is needed, which is not practical with ^{99}Tc^{m}-labeled pharmaceuticals. The method of choice then is to use ^{51}Cr-EDTA, which has a half-life of 27 days. This helps make counting simple with no real need to decay correct and samples may be counted 2–3 days after the test has been performed. In addition taking a late sample at 24 h is simple.

The standard method is to take a background sample and then three samples 2, 3 and 4 h after injection of 2–4 MBq of ^{51}Cr-EDTA. The activity in a millilitre of plasma is then plotted on a graph and the rate of reduction of counts gives the GFR. However, a simpler 1 blood sample method and some mathematical modelling by Martenssen et al. [2] has shown that if the GFR is more than 50 ml/min then it is just as accurate as a three sample method. Likewise if the GFR is less than 30 ml/min, a 24 sample should be added. As it may not be possible to pre-predict the exact GFR before a test is done then more than one method may be needed. The creatinine clearance or estimated GFR can be used as a guide but may be inaccurate if the patient is in a catabolic state from malnutrition (the anorexia of cancer or post-chemotherapy), or has impaired renal function or has suffered a recent muscle injury including an operation. Also the GFR is more accurate for sequential measurements especially if potentially nephrotoxic treatment is being given [3, 4].

The main use of a GFR in urological cancer management is the correct dosing of nephrotoxic chemotherapy (especially platinum based drugs) before and during treatment. The combination of the GFR and divided renal function as determined by a $^{99}Tc^{m}$ DMSA study can be used to predict post nephrectomy renal function. The EPRF may be a better measure of early drug induced renal toxicity than GFR but it has not been accepted into standard clinical practice.

Cardiac Assessment

Though not directly connected to the urological system, a well functioning heart it is required for the efficient treatment of some patients. Many nephrologists think that the heart is there merely to perfuse the kidneys and there is some element of truth in this. However, there are two specific areas in which assessment of the heart using radionuclide techniques may be of particular value. The first is a general assessment of myocardial perfusion before any major surgery such as nephrectomy as not only is cancer more common in the elderly but so is heart disease. Therefore the high negative predictive value of stress and rest myocardial perfusion scintigraphy using $^{99}Tc^{m}$-methyliso-butyliso nitrile (MIBI), $^{99}Tc^{m}$-tetrofosmin or thallous-201 chloride ($^{201}TlCl$) will determine, if normal with no evidence for myocardial ischaemia that a major operation can proceed without risk to the patient.

In addition gated blood pool imaging using $^{99}Tc^{m}$-labeled red blood cells allow an accurate determination of left ventricular ejection fraction (LVEF) which is less dependent of left ventricular geometry than stress echocardiography and may be more accurate in serial studies [5]. This is used to assess the LVEF before and after chemotherapy with cardiotoxic drugs of doxorubicin type and may be of particular use if the patient has co-existent hypertension and or diabetes for which the commonly used nomograms for maximal tolerated drug may not apply.

Renography

Renography, acquired by dynamic gamma camera imaging normally with 300 MBq $^{99}Tc^{m}$-DTPA or preferably with 100 MBq $^{99}Tc^{m}$-MAG3 again are not primary methods used to assess urological cancers. However, they have two main roles. Firstly, in combination with a GFR it may be used to determine the expected result of a nephrectomy on residual renal function. For example, if a renogram demonstrates that each kidney contributes 50 % of renal function and the total GFR is 80 ml/min, removal of one kidney will result in a residual GFR of 40 ml/min. Interestingly as the most common agent used for bone imaging $^{99}Tc^{m}$-MDP is up to 80 % excreted in the kidneys during the first 20 min post injection it may be possible to combine a $^{99}Tc^{m}$-MDP renogram with a staging bone scan, which if combined with a GFR may provide all the staging required for the patient, in nuclear medicine terms, quickly and efficiently with reduced cost and radiation dose to the patient.

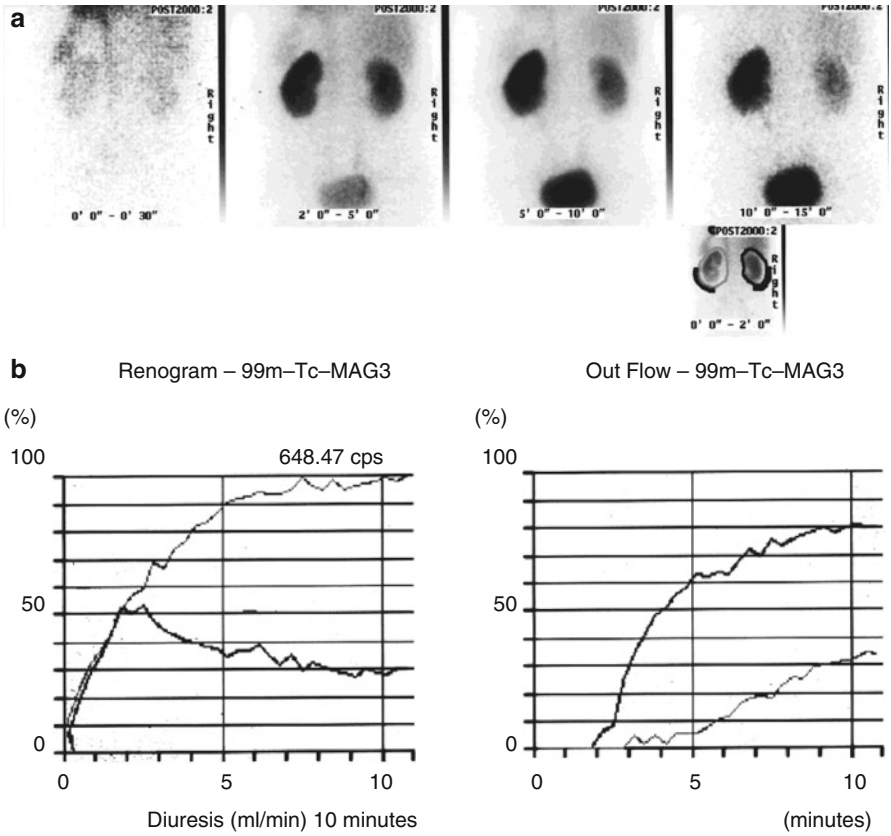

Fig. 6.1 (**a**) A series of static images of two kidneys imaged after injection of Tc-99m MAG3. The right kidney clears but the left kidney retains activity. (**b**) The renogram curves shows the left kidney (*unbold line*) confirms a rising curve and low output confirming obstruction on the left

The second use of renography is to assess renal function if there is pelvic tumor, which is suspected of blocking one or both ureters, in which case a high urine flow rate needs to be achieved to prevent false positive studies due to ureteric dilatation form old obstruction. Frusemide can be given at any time during the renogram but if ureteric obstruction is suspected giving the Frusemide 15 min before the imaging agent (the Manchester protocol or F-15 protocol) means that the maximum diuresis occurs when the imaging agent in injected [6]. A flat or rising excretion phase curve suggests partial or complete obstruction of the ureter on that side (Fig. 6.1). If the ureter is stented or a nephrostomy placed the F-15 renogram should be repeated about 48 h later to determine if the kidney is now clearing. The divided function on the affected side will give some idea of the age of the obstruction, but if it is within a few days, the function of the affected kidney would not have been reduced by a huge margin and relief of the obstruction should result is a rapid return to full function of that kidney. If the function of the obstructed kidney is poor then a full recovery becomes less likely.

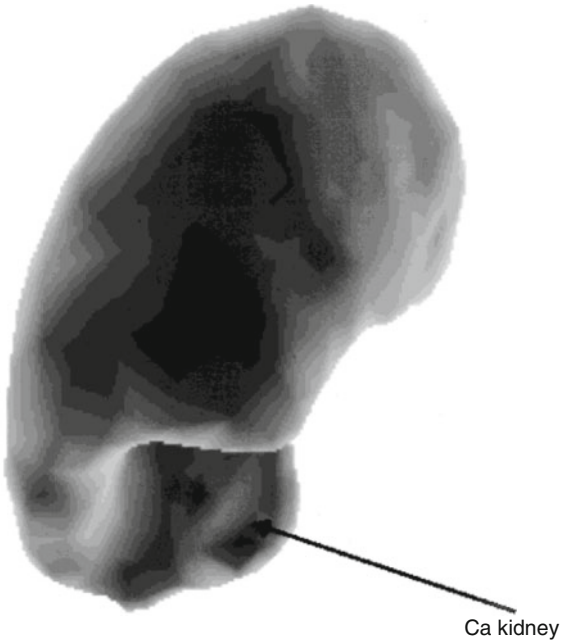

Fig. 6.2 Tc-99m DMSA SPECT study showing a defect near the lower pole (*arrowed*) consistent with a renal tumour

Ureteric Obstruction

In very acute obstruction, which is complete, the renogram with $^{99}Tc^{m}$-MAG3 demonstrates not hold up in the renal pelvis but in the kidney parenchyma-a sort of "shock kidney" picture. The clues are divided function is normal, the other kidney drains and ultrasound suggests a dilated collecting system. If this pattern is seen early drainage procedures work well, often without any residual loss of function on the affected side.

Static Imaging of the Kidneys

Static renal scintigraphy in Europe is performed using $^{99}Tc^{m}$-DMSA. This radiopharmaceutical is filtered by the glomerulus and re-absorbed in the tubules and effectively maps working nephrons (Fig. 6.2). As such it can be used to characterise space-occupying lesions seen on other imaging such as ultrasound or CT. A study showing uptake of $^{99}Tc^{m}$-DMSA is useful in showing that cancer in unlikely. However a defect may be due to cancer, scar, infarct or cyst. More commonly

DMSA imaging is used in combination with a GFR to calculate residual renal function after nephrectomy or renal call carcinoma.

Imaging normally involves a series of static images including a posterior image and right and left posterior obliques performed 2.5–3 h after injection of about 150 MBq of $^{99}Tc^{m}$-DMSA. SPECT imaging can also be performed producing 3-dimensional images of the kidney (Fig. 6.3). It could be of additional use if patient suffers from congenital recurrent potentially bilateral renal cell carcinomas in which case an assessment of residual working renal tissue can be made by the surgeon if they will attempt to maintain some working renal tissue.

Bone Scanning

Bone scintigraphy is probably the test that most often associated with urological cancers. It is primarily used in prostate cancer but has a role in bladder and renal cell cancers well. The mechanism by which bone scintigraphy works is that 550 MBq $^{99}Tc^{m}$-MDP (or one of its close associates) is injected into the vein and 3 h later a static bone scan is performed. This can be done as a series of "spot" views or as a whole body image. With both methods it is essential that the parts of the skeleton that includes the red bone marrow, namely the skull, spine, ribs, sternum, scapulae, the pelvis, proximal humeri and proximal femora be covered (Fig. 6.3). The aetiology of bone metastases being primarily through haematogenous spread any metastases tends to be deposited in the red marrow containing bones. The $^{99}Tc^{m}$-MDP does not attach directly to the metastases but is actually incorporated into new bone formation around the metastasis as the bone tries vainly to repair the injury caused to itself by the metastatic cancer deposit. This laying down of new bone may be seen as increased density on X-ray and is therefore described as sclerotic type metastases. Purely lytic lesions will vary rarely have increased uptake of $^{99}Tc^{m}$-MDP. Fortunately in almost all cases urological cancer metastases are slow growing and tend to produce sclerotic lesions, which may be seen on radiology but the radiological changes may lag behind the scintigraphic changes by 6 months. The actual target cell for the $^{99}Tc^{m}$-MDP is unclear and could be either the osteoblast or the fibroblast or both.

Sensitivity and Specificity

Although the sensitivity and specificity are rarely formally tested it has been assumed from clinical experience that bone scintigraphy is sensitive but not specific. This is generally the case, though methods which look at bone marrow disease such as magnetic resonance imaging MRI may be able to see metastases in the spine, pelvis or long bones before they become apparent on bone scintigraphy, again by as much as 6 months. The main difficulty with bone scintigraphy has been the non-specific uptake of the $^{99}Tc^{m}$-MDP to any injury however trivial. Bone is slow to heal

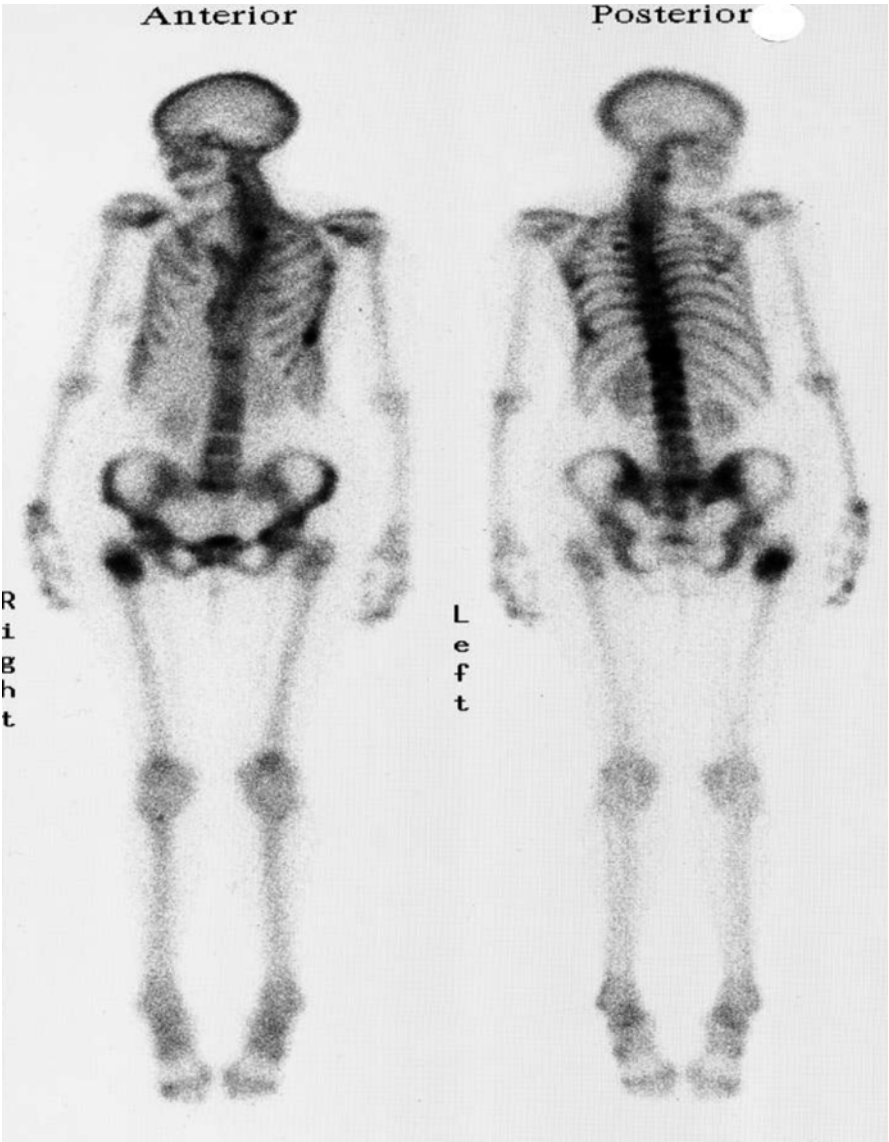

Fig. 6.3 Whole body Tc-99m MDP image showing a single metastases in the proximal right femur

and defects can be active for over 12 months. Typically the problem is in the ribs where trivial injuries such as walking into a door handle 9 months before may not be remembered. Also in older men who smoke spontaneous cough fractures are often seen in winter and early spring. Other causes of significant trauma include falls, which if accompanied by a stroke or excessive alcohol may not be remembered by the patients. This type of trauma often produces a characteristic appearance on the bone scintigram with a linear uptake of equal intensity across several ribs. If multiple, such injuries are seen with different intensities in which case then frequent falls (from a cardiovascular or alcoholic cause) can be assumed. If these are ruled out then a more sinister non-accidental injury any need to be considered especially if the patient is incapacitated due to co-morbidity and needs help from caregivers.

The other area of non-specific uptake is in the spine. Metastases tend to favour the body of the vertebra and the pedicles producing areas of focal uptake within the vertebra. Degenerative disease tends to affect the body of the vertebra adjacent to the discs, the facet joints and anteriorly on the body if there is an active osteophyte. Correlative radiology confirming these areas show degenerative disease is sufficient. If however the X-ray or CT is normal then metastases cannot be excluded and MRI or even bone biopsy may be needed. If there is uptake across the vertebral body with a smooth outline a collapsed vertebrae may need to be considered. Often these, which are osteoporotic in nature, often affect more than one vertebra and do so at different times. This will lead to a number of vertebrae having increased uptake at various intensities often along with some cough and rib fractures. To the unwary observer they look like multiple bone metastases but are not. The accuracy of bone scintigraphy may be helped by SPECT-CT [7].

Paget's disease also commonly occurs in the elderly male especially those from a North European background. Which is just the same population that suffers more from prostate cancer. The scintigraphic appearances are characteristic of active Paget's disease in the whole of one bone (mono-ostotic) or more than one bone (polyostotic) is involved [8]. In active Paget's disease uptake is intense throughout the bone, which is also expanded and in the case of the long bones bowed. If the long bones are involved then Paget's is the most likely explanation, however in pelvic disease Paget's can look like very sclerotic metastases on both scintigraphy and radiography. This confusion can be increased if the patient has a high PSA suggesting high cancer load. A trial of anti-androgens may help but it is possible for both diseases to co-exist.

Diffusely increased uptake in the bones with little or no urinary activity but affecting the distal long bones equally to the axial skeleton may be due to a metabolic bone disease. Commonly this is due to hyperparathyroidism but also, surprisingly, a high proportion due to osteomalacia.

Patterns of Abnormality

With prostate cancer the primary site for metastases beyond the loco-regional area is bone. Therefore sequential bone scinigraphies can help map out the progress of disease and the effect of any interventions. The disease load *at diagnosis* can also predict the outcome. Of the methods used to grade bone scans the easiest and most

Table 6.3 Soloway grading of bone metastases *at diagnosis*

Grade	Appearance on bone scintigraphy
0	Normal, no metastases
1	1–5 lesions compatible with bone metastases
2	6–20 lesions compatible with bone metastases
3	More than 20 lesions but not a "super-scan"
4	A "superscan" with more than 75 % of axial skeleton, proximal humeri and femora involved

Based on data from Ref. [9]

Table 6.4 Survival by Solway grade

Solway grade	Survival at 3 years (%)	Survival at 5 years (%)
0	97	96
1	78	68
2–4	44	21

Based on data from Ref. [10]

robust is the one by Soloway et al. (Table 6.3) [9]. This has been shown with the Gleason score to be the one of the best predictors of survival (Table 6.4) [10].

The pattern described as a "superscan" is an unusual variant in bone imaging of prostate cancer. In the case of the superscan there is contiguous or almost contiguous metastases in the red marrow containing bone (Fig. 6.4). All the injected $^{99}Tc^{m}$-MDP is deposited in these bones specifically the ribs, sternum, scapulae, spine at least part of the skull, the pelvis, proximal humeri and femora but not the distal long bones which are often invisible. It is likely that such a patient would also have a PSA greater than 1,000 and may have impaired bone marrow function.

In the 6 weeks following manipulation of androgens by drugs or surgery there may be an increase/start of bone pain accompanied by an apparent worsening of the bone scan this is a "flare" reaction. Therefore bone scanning should be avoided in this period but if done and a flare reaction suspected repeated 3 months later when it should return to its normal activity.

Other Urological Cancers

Bladder and renal cell cancers (RCC) seldom produce such a florid reaction in the bones; often only 2–3 lesions being seen before death from extensive soft tissue disease. However RCC metastases occur in unlikely places. An example being a patient presenting with a single metastases in the right patella with no further sites of disease for many years. These metastases are painful so any areas causing pain in these patients should always be imaged even if it is outside the normal area for metastases. A further rare appearance has been increased activity in the cortex of the tibiae, fibulae and distal tibiae, sometimes called tram-lining. Though variously named it is known as hypertrophic pulmonary osteo-arthropathy (HPAO) and may be painful or not. Though normally associated with small cell lung cancer it has been seen with pulmonary metastases from testicular and renal tumours.

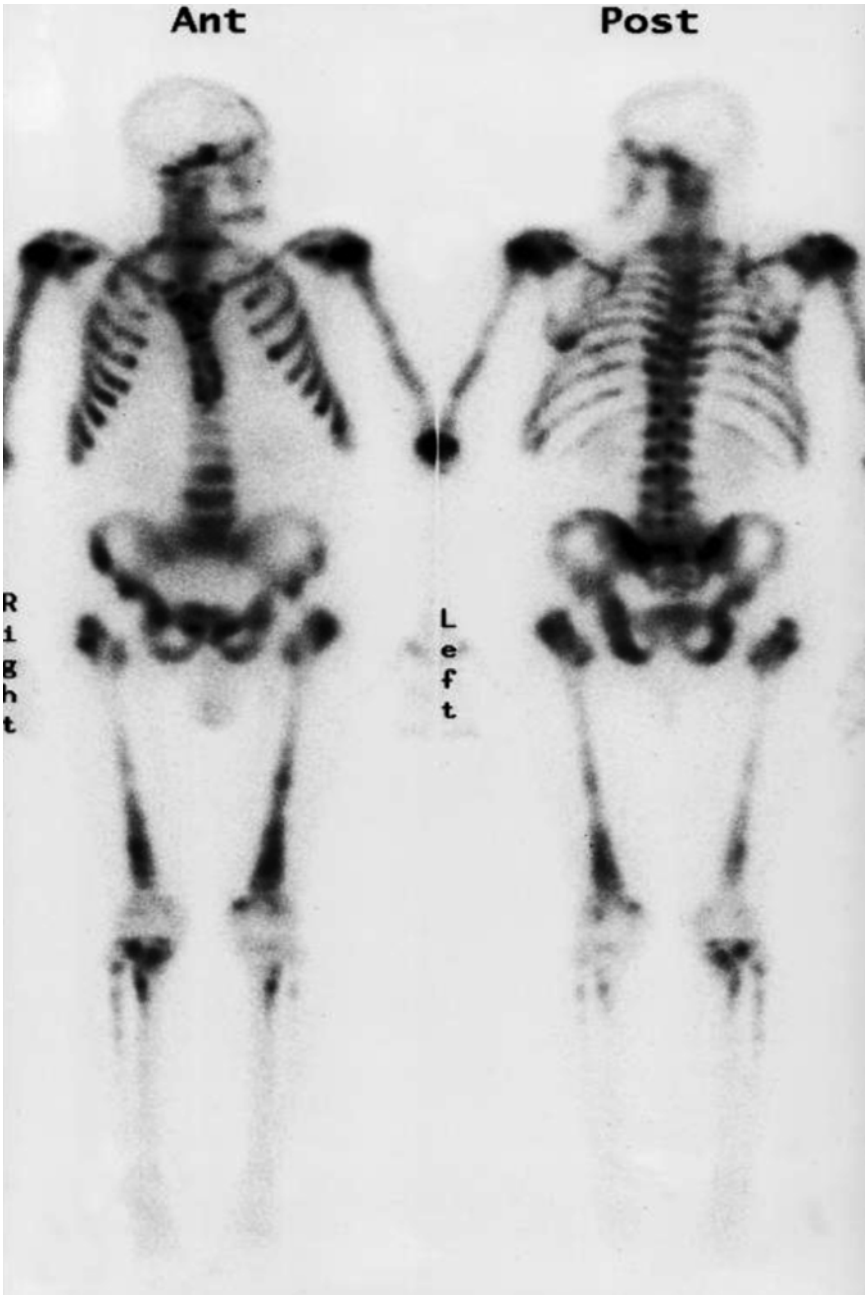

Fig. 6.4 Whole body Tc-99m MDP showing widespread bone metastases. The lack of renal or bladder activity means this can be described as a "superscan"

Which Patient Should Undergo Bone Scintigraphy?

Does every man with prostate cancer need a bone scintigraphy at diagnosis? The answer is plainly no. If the PSA is less than 10 and the Gleason score less than 3 + 3 the yield in a patient without bone pain does not justify a bone scan [11]. However if the patient has bone pain a bone scintigram should be considered because if he has degenerative disease this will act as a baseline scan for comparison as new lesions tend to be metastatic. For a PSA greater than 20 and a Gleason score of 3 + 4 a bone scintigraphy, at least at diagnosis, should be performed. However this is a guideline and bone scintigraphy is cheap and normally readily available, therefore the threshold for use should be low [12].

In renal, bladder and testicular cancer the case is less clear. For renal and bladder a bone scan may be useful before surgery with curative intent. If not it should be directed by the patient's symptoms. However, pre-surgical screening of testicular and renal cancers may be better done by using PET than a bone scintigraphy.

Alternative Methods

The role of the bone scintigraphy in routine assessment of bone metastases has been questioned. In particular there is good evidence that whole body MRI especially with diffusion weighted imaging (DWI) is highly accurate for bone metastases in prostate cancer especially those with sclerotic lesions [13]. There is a clear advantage in not using ionising radiation though that may be less of an issue in the normal population with metastatic prostate cancer where the rate of cancer induction 20 years hence is less worrisome. The scanning may take 60–70 min roughly twice the time of a bone scintigraphy so there could be an issue of cost and accessibility.

Therapy for Pain Relief

The same mechanism by which $^{99}Tc^{m}$-MDP is taken into the bone around metastases can be exploited by therapeutic radiopharmaceuticals. There are three main groups of radiopharmaceuticals used.

1. Phosphorus-32 (P-32) which is built into hydroxyapatite,
2. Analogues of calcium.
3. Di-phosphonates

Radiophosphorus is cheap but the long penetrating beta particle of P-32 (^{32}P) means that it often results in significant bone marrow toxicity and repeat treatments cannot be given. Strontium-89 (^{89}Sr) is a calcium analogue and Samarium-153

lexidronate (^{153}Sm-lexidronate),- a diphosphonate. Both of these latter agents produce good pain relief in 80 % of patients though the onset of pain relief is faster at 7–10 days after injection of ^{153}Sm-lexidronate though re-treatment is often needed after 3 months.

^{89}Sr has a longer onset of action related to its longer physical half-life, but re-treatment is not normally needed for 6 months. In both agents a "flare" reaction may occur 24–48 h before pain relief. Though these treatments are primarily directed towards pain relief there is some evidence that repeat treatments can result in delay in advance or even retreat in bone metastases.

In continental Europe rhenium-186 diphosphonates (^{186}Re-HEDP) are used instead of ^{153}Sm-EDTMP [14]. A different approach has been the use of radium-223. This is an pure alpha emitter and radium is a calcium analogue. It is given in small quantities over 4–6 cycles at 4 weekly intervals and not only produced pain relief but there is evidence it prolongs overall survival [15]

Sentinel Node

Since Cabanas described the principle of sentinel node drainage 40 years ago in carcinoma of the penis it has been widely used in many cancers such as melanoma and breast. The sentinel node principle states that every tumour has a logical lymph drainage to a particular first lymph node-the sentinel node [16]. Other nodes and therefore other metastases are only involved after the sentinel node. Therefore if this node is identified and removed the possibility of cancer spreading beyond that node is very low. This node can be identified best by injecting a radio-colloid of about 100 nm such as ^{99}Tc^{m}-nanocoll peri-tumourly in the sub-dermas. Using a combination of imaging and a hand held gamma probe the node can be identified and removed for histological assessment. This process may be aided by addition of blue dye and accurate localisations of >98 % have been obtained in other organs. Interest had therefore been re-kindled in its use in penile cancer.

There has also been interest in using sentinel node imaging in high risk but possibly curable prostate cancer with one group in Germany claiming an accuracy of 96 % in their experience of over 2,000 patients [17]. The technique is technically difficult and has not been widely adopted.

Positron Emission Tomography (PET)

Positron emission tomography (PET) is normally performed with ^{18}F-fluor-deoxyglucose (FDG). This acts as a false substrate for glucose metabolism which is increased in cancers compared to normal tissues. However this will depend on the metabolic rate of the cancer being imaged. Unfortunately the most common Urological cancer from the prostate appears to have a low metabolic rate and as a consequence ^{18}F-FDG is rarely positive in this disease and therefore is of little use.

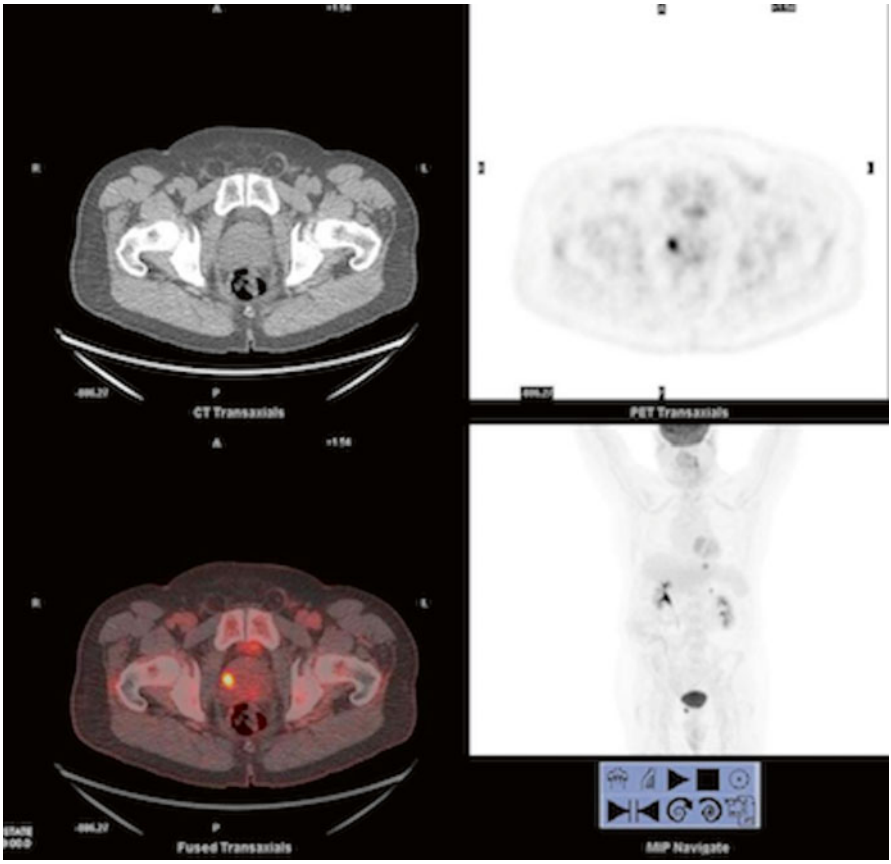

Fig. 6.5 F-18 FDG PET CT the *top right hand image* shows a CT at the level of the prostate, the *top right image* shows a "hot spot" on the F-18 FDG scan. The *lower left image* is a fused image showing focal uptake in the right side of the prostate. A small primary cancer is likely. The whole body image confirms this in the only site of cancer

Likewise ^{18}F-FDG is excreted via the kidneys so that it may be difficult to differentiate a renal primary from background renal activity. Though is an FDG PET scan is being performed for another indication and focal uptake of FDG is seen in the prostate, this can demonstrate not only the presence of possibly an unexpected prostatic primary but as it is FDG avid the more aggressive tumour type and further investigation is obligatory (Fig. 6.5). In renal and bladder cancers uptake of FDG can be variable but there is good evidence that ^{18}F-FDG PET is superior to CT in identifying lymph node disease in such a way that management was changed in 35 % of patients. Overall accuracy in staging has been found to be 89 % [18].

Testicular Cancer

Again as there is high levels of ^{18}F-FDG in the bladder little work has been done in bladder cancer, though theoretically using catheters and bladder washout, bladder tumours could be better delineated. In testicular cancer, ^{18}F-FDG PET has been shown to have a very high accuracy in testicular cancers. In seminomas multi-centre trials have shown a sensitivity of 89 % and specificity of 100 % [19]. One area in which PET has been found to be useful it to look for cancer in those patients with rising tumour markers but CT/MRI negative. Again the most likely area found to be abnormal are lymph nodes which appear on CT or MRI to be less than 1 cm and morphologically normal.

Other Positron Emission Tomography Tracers

To overcome the problem of carcinoma of the prostate having a low metabolic rate work has looked at the increased uptake of amino-acids in cancers with promising results for ^{18}F-choline or ^{11}C-methionine, though the very short half life of ^{11}C means that imaging can only occur in hospitals with their own cyclotron [20]. More recently there has been renewed interest with ^{11}C-choline and ^{18}F-choline. With the short half life of only 20 min limited imaging with ^{11}C-Choline has been proposed looking at extent of primary disease and locoregional nodes. However, the high cost of ^{11}C which must be produced near the PET scanner. It is proposed to use ^{18}F-choline for staging of distant metastases but neither agent is in routine clinical use.

Antibody Imaging

After 30 years of false starts antibodies have finally entered medicine for both imaging and therapy. In North America there has been an antibody used which is directed against prostate membrane specific antigen (PSMA) in prostate cancer. This is labelled with indium-111 (^{111}In) and designated at CYT-356 and is commonly called “Prostoscint” [21]. It has been shown to have a sensitivity of 86 % in nodal disease but only 55 % for bone disease. It has developed a role in characterising the nature of pelvic lymph nodes, which are equivocal on MRI. At present it is not available in the European Union on a routine basis. It is most likely this technique will be replaced by a PET technique.

Antibody Therapy

A final development has been the use of antibodies labelled with therapeutic isotopes which emit beta particles such as yttrium-90 (^{90}Y) and lutetium-177 (^{177}Lu) [22]. These radiometals offer stable labelling of biomolecules via a linker molecule.

New antibodies have been developed for example J591 which a genetically humanised antibody directed against prostate specific prostate antigen, thought to be more specific of liver and growing prostate cancer than prostate specific antigen which can remain expressed on dead tissue. After imaging with an ^{111}indium labelled version of the antibody to ensure localisation on the tumour a therapeutic dose can be given. In 29 patients treated with 300–1,200 MBq ^{90}Y-J591. At the higher activities there were 40–90 % reduction in measurable tumour and 70–85 % reduction in PSA. After a single treatment this was maintained for 6 months. Funding is being sought for further development of this agent.

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Chapter 7
Clinical Emergencies in Genito-Urinary Cancers

Lewis Chan and Andrew J. Richards

Bleeding from Urinary Tract

Profuse Haematuria

Painful or painless haematuria is an important symptom in genitourinary malignancy and warrants a thorough evaluation. It is unusual for gross haematuria to present as an acute emergency unless it is associated with other symptoms such as loin pain or urinary retention.

Causes

Upper Urinary Tract

- Transitional cell carcinoma (renal pelvis, ureter)
- Renal cell carcinoma
- Metastatic tumours in the kidney
- Retroperitoneal tumours (testis, lymphoma, sarcoma)
- Iatrogenic: percutaneous surgery/nephrostomy

L. Chan, FRACS, DDU (✉)
Department of Urology, Concord Repatriation General Hospital,
Level 4 West, Main Building, Hospital Road, Concord, NSW 2139, Australia
e-mail: lwlchan@optusnet.com.au

A.J. Richards, MBBS, FRACS
Department of Urology, Prince of Wales Hospital, University of New South Wales,
Randwick, NSW, Australia

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Lower Urinary Tract

- Urothelial carcinoma of bladder
- Pelvic cancer: cervix, rectum (with fistula to bladder), urethra and prostate
- Iatrogenic [radiation cystitis, cyclophosphamide cystitis, postoperative, e.g. transurethral resection of prostate (TURP) or bladder tumor (TURBT)]
- Vaginal or cervical haemorrhage in a woman
- Bleeding from a fistula from another pelvic malignancy
- Systemic disorders – e.g. disseminated intravascular coagulation

Clinical Presentation

Patients who present with haematuria may have associated lower urinary tract symptoms (frequency, urgency, dysuria) or clot retention. In upper tract bleeding patients may present with ureteric colic/loin pain due to blood clots in the ureter. Unusually a patient may present with shock secondary to excessive loss of blood or associated sepsis. In some patients there may be associated renal failure due to blockage of both ureters.

Investigations

These have been described in detail in Chap. 5. Baseline investigations include full blood count, coagulation screen, electrolytes, urea, creatinine and eGFR. A midstream urine (MSU) sample is sent to the laboratory to rule out infection. When the diagnosis is not known, urine cytology or bladder tumour antigen testing is quite useful investigation. Imaging should include ultrasound or computed tomography (CT) scan of the upper urinary tract, and rigid cystoscopy to evaluate the bladder and urethra.

Management

Fluid Resuscitation

Accurate assessment of hemodynamic status is the key to management of patients with profuse haematuria. Intravenous fluids and blood transfusion should take into account the age of the patient, site of bleeding, degree of anemia, hemodynamic stability, and presence of coexisting cardiac, pulmonary or vascular conditions.

Transfusing one unit of red cells increases the hemoglobin by approximately 1 g/dL and the hematocrit by 2–3 % in the average 70 kg adult. Adequate oxygen-carrying capacity can be met by a hemoglobin of 7 g/dL (a hematocrit value of approximately 21 %) or even less when the intravascular volume is adequate for perfusion.

Catheter Irrigation

A three-way irrigation catheter with large eyes and 30 cc balloon [usually size 20 or 22 French] is placed to allow bladder washout followed by setup of continuous bladder irrigation if the patient is in clot retention.

Rigid Cystoscopy and bladder lavage to evacuate clots may be necessary after the patient's condition is stabilized. This will also help in the diagnosis of the cause of the bleeding.

Haemorrhagic Cystitis

This condition is seen in patients who had pelvic irradiation or systemic treatment with oxazophosphorine alkylating agents (cyclophosphamide, ifosfamide) and warrants special mention. In a series of 1,784 patients treated with radiotherapy for carcinoma of cervix, the incidence of haemorrhagic cystitis was 6.5 % and the median interval before bleeding occurred was 35.5 months [1]. However, common urological causes of haematuria such as bladder stones, urinary infections should be kept in mind. Management is based on the severity of haematuria, treatment facilities available, risks and severity of complications, as well as the prognosis of the patient.

Placement of a large catheter (usually 22F 3-way irrigation catheter as above) to allow bladder irrigation is the basic management in all patients. Periodic evacuation of clots is necessary in most cases. Coagulation defects if present should be corrected. Cystoscopic assessment under anaesthesia allows diathermy of bleeding areas, resection of tumour, and washout of clots. Intravesical irrigation with 1 % alum (50 g alum/5 L sterile water), via 3-way catheter at 250–300 mL/h is generally a safe, effective and well-tolerated method of treatment [2]. It is important to make sure that the renal function is not compromised as alum induced encephalopathy can occur in patients with renal failure [3]. Intravesical irrigation of alum has also been used for intractable haemorrhage from carcinoma of prostate after radiotherapy [4]. Oral sodium pentosanpolysulphate (100 mg tds) has been used successfully in bleeding secondary to pelvic radiation. The dosage is gradually reduced to a maintenance dose of 100 mg until the cessation of bleeding [5].

Hyperbaric oxygen treatment is effective in 80–90 % of cases but is not widely available. Intravesical formalin and silver nitrate have an efficacy of 70 % in intractable haematuria but there is risk of serious complications [6].

Embolization of internal iliac artery (unilaterally or bilaterally) under local anesthesia may control bleeding [7]. Complications of embolization include gluteal pain and dislodgement of atherosclerotic plaques with distal embolization.

Surgical Measures

In initial stages cystoscopy, bladder wash out, diathermy of bleeding vessels and irrigation may help in controlling the bleeding. In refractory cases when conservative

measures fail, surgical procedures such as urinary diversion and cystectomy may be necessary.

Urinary Retention

Urinary retention may occur due to bladder outlet obstruction or detrusor failure. This may be acute, chronic or acute-on-chronic retention.

Causes

1. Obstruction: Bladder outlet obstruction may be due to locally advanced prostate or bladder cancer, coexistent benign prostatic hypertrophy (BPH), or urethral stricture. Clot retention may occur due to bleeding from a tumour or haemorrhagic cystitis related to radiation or cyclophosphamide. Other less common causes include urethral cancer, phimosis, advanced penile or vaginal cancer or a tumour at the base of the bladder causing outlet obstruction.
2. Detrusor failure: Urinary retention can also be caused by the inability of the detrusor muscle to contract (underactive or acontractile bladder) resulting from previous pelvic surgery/radiation, spinal or meningeal metastases or neuropathy from chemotherapy ***BEWARE***: *Urinary retention may be the first sign of spinal cord compression particularly in prostate cancer*.
3. Other causes include drugs (e.g. Antidepressants, opiates, analgesics and antipsychotics), constipation, poor mobility and urinary infection.
4. Iatrogenic: post brachytherapy for prostate cancer.

Clinical Presentation

Acute painful retention is of short duration and is usually due to bladder outlet obstruction.

Chronic retention may present with symptoms of overflow incontinence, nocturnal enuresis, worsening lower urinary tract symptoms (LUTS), urinary tract infection or uremia. Physical examination may reveal a palpable bladder or localised pelvic/suprapubic discomfort.

Investigations

- Serum Electrolytes, urea, creatinine, calcium, prostate-specific antigen (PSA), MSU, urine cytology
- Renal ultrasound (to check for hydronephrosis/obstructive uropathy)

Other investigations may include CT scan, transrectal ultrasound (TRUS), and biopsy of prostate (if prostate cancer is suspected) and MRI of spine (if there is a concern about spinal cord compression).

Management of Acute Retention

The discomfort and pain of acute urinary retention is relieved by immediate placement of urethral or suprapubic catheter (SPC). However, an SPC should be avoided in cancer of the bladder.

In patients with large volume retention there may be haematuria following bladder decompression. Using a large caliber (e.g. 18 or 20F) catheter reduces the problem of intermittent catheter blockage by clots. There is no evidence to suggest that clamping the catheter is useful in reducing the risk of bleeding.

If there is evidence of neurological signs indicating spinal cord compression, urgent MRI of the spine and neurological assessment are necessary (see below).

A trial without a catheter can be arranged once all the predisposing factors including mobility and constipation are optimized.

It is usually necessary to wait at least 2–3 days after acute retention before attempting a trial without catheter. Patients with chronic retention may need surgical intervention (TURP or TURBT) but in cases of obstructive nephropathy with renal impairment surgery may need to wait for 2–3 weeks until biochemistry is normalised. A short course of α-blockers (tamsulosin or alfuzocin) may increase the chance of a successful trial of void if retention is thought to be uncomplicated and due to BPH.

Management of Chronic Retention

Post-obstructive diuresis may occur following bladder decompression by catheter if there is renal failure. This is due to loss of concentrating ability of the kidneys and is managed as follows:

- Closely monitor intake/output and clinical state of hydration
- Replacing urinary volume losses with normal saline/Hartman's solution intravenously.
- Check Electrolytes regularly: watch serum levels of Na, K and Mg particularly, as patients can become hypokalaemic rapidly and require K replacement
- Admit patient to a high-dependency (critical care) ward if significant difficulties with fluid or electrolyte balance and involve a renal physician early.
- In patients who are fit enough to take oral fluids, IV fluid replacement can be slowed early.
- Avoid "pushing" the diuresis by giving too much IV fluid, especially when the creatinine has normalised
- Once the general condition is stabilized, surgical intervention (e.g. TURP) may be necessary to relieve the obstruction. Patients with detrusor failure who are unable to void may be managed by long-term catheter or clean intermittent self-catheterisation.

Anuria Due to Malignant Obstruction

Causes

Ureteric obstruction can result from the following:

- Muscle invasive TCC at the base of bladder involving the trigone
- Locally advanced prostate cancer
- Bilateral ureteric TCC
- Other pelvic malignancies (colorectal, gynaecological)
- Retroperitoneal lymphadenopathy (e.g. haematological malignancy – lymphoma, testicular cancer)
- Clot obstruction in a single kidney
- Rarely benign ureteric stricture after radiotherapy for pelvic tumours
- Iatrogenic: surgical damage to the ureters

Investigations

The following investigations are necessary initially to plan the management:

Electrolytes, urea and creatinine, MSU, arterial blood gases
Ultrasound or non-contrast CT scan of urinary tract

Principles of Management

- Placement of urethral catheter will differentiate urinary retention/bladder outlet obstruction from ureteric obstruction. Most patients have some dehydration and will need fluid resuscitation/rehydration.
- Imaging of upper urinary tract (ultrasound and/or noncontrast CT scan). The findings of hydronephrosis with an empty bladder would indicate supravesical obstruction whereas a distended bladder with bilateral hydronephrosis implies bladder outlet obstruction.
- Percutaneous nephrostomy followed by antegrade insertion of ureteric stent

(cystoscopy and retrograde ureteric stenting is usually difficult if not impossible especially in cases of locally advanced prostate cancer or a urothelial cancer of the bladder). Usually the kidney, which has a better function is drained first.

It is important to watch for post-obstructive diuresis once drainage is secured especially in cases of bilateral ureteric obstruction. In severe cases initial dialysis may be necessary if there is significant fluid retention and metabolic acidosis. This is discussed in Chap. 9. Close monitoring of fluid and electrolyte balance with correction of abnormalities and associated acidosis is necessary if the patient is in renal failure.

Spinal Cord Compression

Spinal cord compression should be recognized and treated promptly as it can lead to significant morbidity. Compression of the spinal cord (and its blood supply causing ischaemia) is caused by metastases in the epidural space or the vertebral bodies.

This affects 5–10 % of patients with metastatic prostate cancer in the vertebral column.

Other genitourinary cancers including TCC, renal carcinoma and testicular tumours can also cause cord compression.

Presentation

Although back pain may precede compression symptoms by months, the progression to neurological dysfunction is generally of short duration. Localizing back pain and tenderness may be absent especially in chronic spinal cord compression. Urinary retention and constipation may be the first signs of cord compression. Neurological signs depend on the level of lesion(s).

Clinical assessment should include vital signs, full neurological assessment, palpation of back for tenderness, abdominal examination for distended bladder, and rectal examination for constipation (from associated neurogenic bowel dysfunction).

Diagnosis

Sudden development of lower motor neurone type symptoms raises the possibility of the cord compression. The presentation of cauda equina lesions is gradual, with affected ankle and knee jerks, saddle anaesthesia, urinary and faecal retention or overflow incontinence. High-level spinal cord lesions may manifest with earlier motor and sensory signs.

Investigations and Management

It is important to ascertain the diagnosis of the primary tumour as the treatment differs according to the pathological origin of the cancer. If suspected, the management of spinal cord compression is multidisciplinary involving the oncologist, neurologist, radiotherapist and neurosurgeon [8]. Urgent MRI (if available and preferred investigation) or CT myelogram will help to assess the nature of the compression. Intravenous dexamethasone (4–24 mg every 6 h) is started immediately once

cord compression is suspected. Constipation is treated with laxatives or enemas, and urinary bladder is decompressed with a catheter if the patient is in retention. Other measures include analgesics and careful nursing of the pressure areas of the back and limbs.

Spinal cord compression may be relieved by neurosurgical decompression or by radiotherapy. Surgery (laminectomy or direct decompressive surgical resection) is indicated for the younger patient with a relatively good prognosis, early presentation, and a single level of compression. It is also indicated if radiation fails or if the spine is unstable. It has been shown that surgery followed by radiation is more effective than radiation alone in treating certain patients suffering from spinal cord compression caused by metastatic cancer [9]. The outcome is related to the degree of neurological impairment at presentation, duration/degree of cord compression and bulk of disease. Most patients who are ambulant at presentation will remain ambulant while <40 % who are not ambulant regain mobility. **Spinal cord compression is a surgical emergency**, **because of risk of damage to local vasculature and ischaemia**, **and intervention should not be delayed for convenience – viz. surgery should not wait until the next day**!

Patients with spinal cord compression from metastatic prostate cancer have a poor outlook. Patients with spinal metastasis need close observation to prevent development of cord compression. In patients with hormone-resistant metastatic prostate cancer, persistent back pain can be a sign of impending compression and imaging studies (bone scan, spine CT scan or MRI) may help to confirm the diagnosis. In such cases prophylactic local radiotherapy to the spine in the areas of bony metastases is justifiable [10].

Acute Symptoms of Testicular Cancer

Testicular cancer may present as an acute scrotal pathology or with symptoms of systemic metastases. Haemorrhage into testicular cancer may present as acute scrotal pain or swelling. There may be a history of associated minor trauma. Metastatic disease may manifest as dyspnoea (extensive chest metastases), lower extremity swelling [retroperitoneal lymphadenopathy/inferior vena cava (IVC) obstruction], and renal and gastrointestinal disturbances. In rare instances spinal cord compression due to spinal metastases may occur. There may be a history of cryptorchidism/surgery for undescended testis, infertility or testicular swelling.

Ultrasound of scrotum and testes may show haemorrhage in a testicular lesion with retroperitoneal node enlargement on abdominal CT scan. CT scan of abdomen and chest is helpful in staging. Testicular tumour markers including α-fetoprotein (AFP), beta subunit of human chorionic gonadotrophin (HCG) and Lactic dehydrogenase (LDH) are assessed.

Management

Once the initial assessment is made and if the tumour is localised radical inguinal orchidectomy is the initial step in the management. This is followed by a CT scan of chest and abdomen to accurately stage the extent of the disease. In the presence of extensive metastases, chemotherapy may need to precede inguinal orchidectomy. Neurological symptoms arising due to spinal cord compression are usually treated by chemotherapy, although occasionally surgical decompression is required urgently.

Malignant Priapism

Priapism is a persistent erection not accompanied by sexual desire or stimulation lasting for more than 6 h and typically involving only the corpus cavernosa [11]. For clinical management purposes priapism is classified as low-flow and high-flow types. Low flow priapism is more common and is due to occlusion of venous outflow from the corpus cavernosa. This causes pain and ischemia of the corporal smooth muscle. High-flow priapism is rare and is usually due to continuous arterial blood flow into the sinusoidal spaces of the corpora. This may occur with vascular injury following pelvic trauma.

Priapism may be caused by vasoactive drugs (such as intracavernosal prostaglandin injections) used for treatment of erectile problems, hematological causes associated with hyperviscosity (e.g. sickle cell disease), trauma and neurological conditions.

The pelvic malignancies (bladder, prostate cancer) can rarely cause priapism due to direct invasion of the base of penis. Although the exact mechanism is not known, one possible explanation is venous occlusion and stasis with resultant low-flow priapism. Other cancers (renal, colonic, melanoma and leukaemia) can also cause priapism. In a patient presenting with priapism of unknown cause it is important to rule out malignancy.

Treatment

If the patient has a known pre-existing malignancy contributing to priapism, the treatment is supportive and conservative whenever possible. In addition to treating the priapism, effort is made to treat the causative factor without any delay. Cavernosal blood sample for blood gases helps in differentiating high and low flow priapism. In low flow priapism, the blood gases have values similar to those of venous blood.

Cavernosal aspiration of sludged blood followed by intracavernosal phenylephrine (200 μg), an α-adrenoreceptor agonist, is the first-line treatment in low-flow priapism. This may result in some detumescence and the same dosage (200 μg) can be repeated. The patient should have blood pressure and electrocardiogram monitoring. Methylene blue injection has been advocated [12]. This is supposed to inhibit cyclic guanosine monophosphate (cGMP), preventing smooth muscle relaxation. If these simple measures fail, then surgical shunting is necessary although this may not be effective in malignant priapism. The commonest procedure is the Winter's shunt which utilizes a Tru-cut biopsy needle to create a communication between the glans and corpus cavernosa [13].

Perioperative Hypotension in Adrenal Neoplasms

Causes

1. Hypotension may be due to common postoperative causes such as blood loss, hypovolaemia, cardiogenic shock or sepsis.
2. The remaining adrenal tissue may not be able to respond to the stress of surgery (especially in presence of preoperative adrenal suppression). This often becomes apparent after perioperative hydrocortisone has worn off.
3. In the setting of phaeochromocytoma, hypotension can be related to decreased intravascular volume or catecholamine withdrawal after removal of tumour and can be prevented by volume expansion prior to surgery.

Diagnosis

Knowing the pathology of adrenal lesion, perioperative medication (especially steroids, antihypertensives and antibiotics) helps in assessment of the cause of hypotension. Clinical signs of bleeding or hypovolemia, cardiogenic shock, sepsis or anaphylaxis will help to differentiate among other causes of hypotension.

Management

Management should be according to the underlying cause (transfuse and volume replacement if hypovolaemic, inotropes if cardiogenic shock etc). If thought to be addisonian, give 100 mg IV hydrocortisone. There is usually a component of hypovolaemia and fluid replacement with close monitoring of hemodynamic status and urine output is necessary in most cases.

Prevention

Consultation with anaesthetist and endocrinologist regarding pre-operative admission, anti-hypertensives (alpha or beta-blockade), cortisone replacement and fluid replacement is vital prior to surgery for adrenal tumours especially phaeochromocytoma. These patients require close intra- and postoperative monitoring.

Malignancy Associated Hypercalcemia

Causes

Hypercalcemia is commonly due to hyperparathyroidism or malignancy. The mechanism for malignancy-associated hypercalcemia include- local paracrine stimulation of osteoclasts by bone metastasis leading to increased bone reabsorption (osteolytic) and calcium mobilization. In addition, there may be inadequate calcium clearance in the kidneys. Malignant cells may secrete parathyroid hormone (PTH) – like protein (PTHrP) [14], which increases serum calcium levels in the absence of demonstrable bony lesions. Hypercalcaemia usually occurs in the setting of advanced disease (Renal cancer, TCC bladder, carcinoma of the penis and uncommonly in prostate cancer). This may also be a paraneoplastic syndrome associated with renal cancer

Clinical Presentation

Patients may present with vague abdominal pain, anorexia, diarrhoea, thirst, polyuria or nocturia. Other manifestations include bony pain, psychological disturbance, nephrocalcinosis and urinary calculi if chronic hypercalcaemia. If very severe, hypercalcaemia may lead to obtundation or death.

Diagnosis

Normal calcium levels vary between 2.25 and 2.57 mmol/L for men and 2.22 and 2.54 mmol/L for women. It is important to note that the serum protein concentrations affect serum calcium levels but not unbound fraction of calcium. So it is necessary to correct the total plasma calcium concentration for the percent calcium level measured at normal albumin levels:

$$\begin{aligned}&\text{Total Serum Calcium}\left(\text{Corrected for Albumin Level}\right)\\&=\left(\text{Normal Albumin}-\text{Patient s Albumin}\right)\times 0.8\\&\quad+\text{Patient s Measured Total Calcium}\end{aligned}$$

Other laboratory investigations include renal function studies (creatinine, urea, and electrolytes including magnesium and phosphate), PTH, serum 1,25-dihydroxyvitamin D, and immunoreactive PTH (iPTH).

Management

Hydration with intravenous normal saline is the mainstay of treatment together with frusemide (not thiazides). Intravenous bisphosphonates (pamidronate) is indicated if there is lack of response to hydration, very high calcium levels, obtundation or severe symptoms. Patients with renal failure may need dialysis.

Calcitonin is a very expensive option; it works very quickly but exhibits tachyphylaxis.

Treatment of underlying disease would depend on stage of tumour, patient co-morbidities and prognosis (e.g. localised renal carcinoma vs. end stage metastatic bladder TCC). Ongoing control may involve oral bisphosphonates or periodic IV treatments [15, 16].

Post-operative Emergencies

Treatment of urogenital malignancy often involves major surgical procedures (e.g. radical prostatectomy, cystoprostatectomy and nephrectomy). As the incidence of many urological cancers increase with advancing age, surgery is being considered for a growing number of older patients often with multiple co-morbidities and less able to cope with post-operative complications. Some of these patients may well be nursed in high dependency units as indicated. An understanding of the common post-operative emergencies related to the surgical procedure is essential for satisfactory perioperative management and achieving good outcomes.

Bleeding

Pelvic surgery may be associated with major blood loss. Postoperative monitoring of vital signs and early recognition of ongoing blood loss is essential. Warning signs (apart from haemodynamic instability) include high drainage output, poor perfusion, low urine output despite adequate intraoperative fluid replacement. Correction

of coagulopathy is important especially if there has been significant intraoperative transfusion requirement.

Visceral injuries: Leakage due to bowel injury or urinary leak from anastomosis (vesico-urethral) is the most dreaded complication of abdominal urological surgery. The first important aspect is to recognise and correct it if possible. Initial postoperative observation will help to detect such problem early.

Sepsis

This is associated with significant morbidity and mortality especially in the elderly patient. Common causes for postoperative fever include pulmonary atelectasis and catheter/line associated infections. Specific causes related to uro-oncological surgery include

- Wound infection
- Infected deep- seated collections (e.g. pelvic lymphocoele, haematoma)
- Urinoma (leakage from uretero-intestinal anastomosis, veisco-urethral anastomosis after pelvic surgery or renal collecting system following partial nephrectomy)

It is important to remember that an infected collection requires urgent surgical or radiological drainage rather than prolonged antibiotic therapy

- Peritonitis -This may occur from leakage from an intestinal anastomosis (e.g. Following cystectomy and urinary diversion) or inadvertent injury to bowel during open or laparoscopic surgery and usually require surgical exploration

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Chapter 8
Clinical Aspects of Urological Cancers Including Haematuria and Haematospermia

Kim Mammen

Cancer does not have universal symptoms and in some cases it may remain completely silent until its stage has advanced and it has clinically manifested. For the patient learning that they have a cancer is a difficult and at times a devastating experience. Like many cancers early diagnosis of urological cancers leads to a curative management without compromising quality of life. The diagnosis therefore depends on a high index of suspicion. Any cancer management starts with clinicopathological diagnosis followed by staging and specific treatment. This chapter will highlight clinical aspects of urological cancers.

Worldwide Incidence of Urological Cancers

For most cancers the incidence and details of morbidity and mortality usually come from the data accrued in the western world and there is no exception for genitourinary tumours. In the year 2002 alone it is estimated that there were 10.9 million new cases worldwide, 6.7 million deaths, and 24.6 million persons living with cancer (within 5 years of diagnosis) [1]. Incidence of urological cancers worldwide is outlined in Table 8.1. These figures really indicate a mixture of data extrapolated from limited samples.

Incidence rates of prostate cancer in 2008 were highest in Australia/New Zealand, Western and Northern Europe and North America and lowest in Asia [2]. In both sexes bladder cancer is one of the major GU cancers. The details of epidemiology and aetiology have been discussed in respective chapters. This chapter will focus on clinical aspects of genitourinary tumours.

K. Mammen, MS, MCh, FRCS, FACS
Department of Urology, Christian Medical College and Hospital,
Brown Road, Ludhiana 141008, India
e-mail: kjmammen@gmail.com

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Table 8.1 Incidence worldwide 2012

Organ	No. of cases in 2012 (in 1,000s)	Percent of all cancers
Prostate	1,112	7.9
Testis	55	0.4
Kidney	338	2.4
Bladder	430	3.1

Based on data from Ref. [2]

Symptoms Associated with Genito-urinary Cancers

Presenting symptoms of genito-urinary cancers fall into three categories:

- Lower urinary tract symptoms related prostate and bladder
- Abdominal masses/swellings of testes and
- Haematuria. This will be discussed below along with other symptoms, which are less common presentations.

Haematuria

It is one of the commonest symptoms investigated in its various forms in the urology department. It can manifest in renal, bladder and prostate cancers. Diagnosis and management of haematuria will be discussed later in this chapter.

Loin/Back Pain

It usually manifests in an obstructed or a stretched kidney. Patients with upper tract urothelial tumour and renal cancer may present with loin pain and visible haematuria. The classical 'triad' of flank pain, haematuria and abdominal mass with renal carcinoma is a rare presentation now because of early detection of renal tumours by imaging. Loin pain is not that commonly seen in transitional cell carcinoma of the ureter in spite of obstruction probably because of gradual ureteric obstruction. Differential diagnosis includes pelvi-ureteric junction obstruction, stone disease, sloughed renal papilla. Prostate cancer patients with metastasis in the spine may also present with back pain.

Suprapubic/Vesical Pain

This is usually manifested in acute urinary retention or in bladder carcinoma in situ. Occasionally suprapubic pain is associated with urethral pain particularly in bladder neck or prostatic lesions.

Lower Urinary Tract Symptoms (LUTS)

Urinary frequency, hesitancy, urgency, sensation of incomplete voiding indicate bladder outlet obstruction, which may be due to benign enlargement of prostate or prostate cancer. Irritative bladder symptoms including urgency and frequency may indicate carcinoma in situ of the bladder. Similarly urethral pain in absence of infection may be an indication of a sinister pathology. Urinary incontinence in prostate cancer may signify tumour infiltration of external sphincter.

Testicular Symptoms

Testicular cancer can present with testicular pain particularly if there is haemorrhage or a rapidly expanding tumour. The most common presenting symptom is painless swelling or nodule of one testis. Patients with cancer in atrophic testes might present with progressive testicular enlargement. Dull ache or heavy sensation in the lower abdomen could be presenting symptom. Progressive enlargement of testis following trauma should be evaluated to rule out testicular cancer.

Penile Symptoms

The presentation of penile cancer is highly variable. The lesion may present anything between a small popular lesion to a large fungating ulcer. The commonest site is glans and prepuce. The first presentation could be phimosis or balanitis like symptoms with or without purulent discharge.

Haematospermia

Presence of blood in the semen is distressing for the patients and generally does not have a sinister cause. This is again discussed in detail later in this chapter.

Urethral Symptoms

Diminished stream, straining to void and other obstructive voiding symptoms may be the presenting symptoms of urethral carcinoma. Frequency, nocturia, and other irritative voiding symptoms are reported in association with bladder carcinoma *in situ*. Severe urgency might progress to urge incontinence and distortion of the urethral anatomy in females might lead to stress urinary incontinence. Urethral discharge, purulent or otherwise could be the sign of urethral or penile malignancy.

Urinary retention from progressive malignant urethral stricture disease may occur. There might be hard nodular mass may be palpable along the urethra. Hematuria, urethral or vaginal spotting may be seen in late disease. Purulent, foul-smelling/watery discharge, hematospermia, perineal/suprapubic/urethral pain, dyspareunia, priapism also may be presenting symptoms of urethral cancer. Patients with penile cancer may present with phimosis or painless ulcer.

Bone and Neurological Symptoms

Prostate cancer spreads to axial skeleton and first presentation of metastasis could be back pain. Characteristically the pain may get worse even after resting. Nerve root compression pain usually radiates along the course of the nerve. Bone metastasis itself is not threatening but its morbidity stems from the various complications that arise as a result of bony metastases. Skeletal-related events (sres) include debilitating bone pain in up to 80 % of patients with bone metastases, impaired mobility in 65–75 %, vertebral collapse or deformity in 18 %, hypercalcemia in 10–15 %, spinal cord compression in 12 % of prostate cancer patients, and pathologic fracture in 9 % [3–6]. These complications may cause deformity, postural problems, and loss of motor and sensory function (neurologic impairment), leading to decreased overall quality of life (qol) [7].

Paraneoplastic syndromes (PNS) are sometimes seen in prostate and renal cancers. PNS are much less common than direct, metastatic, and treatment related complications of cancer. Paraneoplastic syndromes are a group of rare disorders that are triggered by an abnormal response of the immune system to a cancer [8]. Essentially PNS are nonmetastatic manifestations of a cancerous growth. The presenting symptoms may be endocrine, neuromuscular or musculoskeletal, cardiovascular, cutaneous, hematologic, gastrointestinal, renal, or miscellaneous in nature [9]. Unexplained fever in renal cancer is an example of PNS. Various cytokines normally produced by the kidney (i.e. prostaglandins, renin, and erythropoietin) may be produced in excess quantities, and other substances that the kidney does not usually secrete (i.e. parathyroid hormone-like chemicals, glucagon, and insulin) may be produced. Intrinsic production of such substances leads to manifestation of paraneoplastic syndromes.

The presentation of paraneoplastic syndrome in renal cancer includes anaemia, polycythemia, hypertension, hypoglycemia, Cushing's syndrome, hypercalcemia, erythrocytosis, and nonmetastatic hepatic dysfunction (i.e. Stauffer's syndrome). In a study of 1,046 renal cancer patients in the UCLA, Kim et al. observed that hypoalbuminemia, weight loss, anorexia and malaise were the predictors of poor survival that were independent of stage, grade and performance status [10].

Uraemic symptoms can occur from ureteral obstruction caused by local prostate growth, infiltrating bladder cancer or retroperitoneal lymph nodal metastasis. In fact in some unfortunate patients with advanced disease, uremia could be the first manifestation of advanced urological malignancy. The term uremia refers to a syndrome characterized by fluid, electrolytes and metabolic abnormalities including acidosis and accumulation of nitrogenous products. Bilateral ureteric involvement in bladder and prostatic malignancies may be associated with anuria.

Miscellaneous metastatic symptoms due to metastases include cachexia, fever, and night sweats. Metastasis from renal cell carcinoma occurs to lung, soft tissues, bone, liver, cutaneous sites, and central nervous system. Similarly in prostate cancer bony metastasis, anemia and weight loss indicate advanced disease.

Other relevant history: Functional status and co-morbidity are two important aspects that have to be assessed in cancer patients. The Karnofsky Performance Status Scale (KPS) and more recently WHO performance status have been used to quantify the functional status of cancer patients. However, limited data exist documenting its reliability and validity [11]. Similarly medical conditions such as diabetes, stroke, cardiovascular are also important in determining the course of the disease and consideration of various modalities of treatment. History of previous abdominal surgery, peritonitis and difficult anaesthesia is important in patients undergoing major renal or bladder surgery.

Physical Examination

Examination of the patient with suspected urological cancer starts with a cursory look regarding their height, build, obesity, breathing and nourishment. Gynaecomastia may be seen in patients with testicular cancer. Anaemia, weight loss may be seen in renal and prostate cancer. A detailed abdominal examination including genitalia is necessary. Rectal examination in men is important in suspected bladder and prostate cancers. In women vaginal examination may be necessary to carry out bimanual assessment. Attention should be given to the consistency of prostate gland, along with the seminal vesicles and adjacent organs. Hard nodule or surface on rectal examination in men indicates prostatic malignancy. Obliteration of the lateral sulcus or seminal vesicular involvement and restricted mobility of the prostate indicates locally advanced disease. Rectal wall mobility and fixation to the anterior structures is also noted. Normal physical examination does not exclude urological cancer.

Examination of the testes usually starts with the assessment of normal testis first and later the affected testis is looked for abnormal areas and involvement of the spermatic cord. In all suspected testicular tumour patients, testis should be palpated carefully and at no stage the testis is squeezed.

Neurological examination, including determination of external anal sphincter tone, should be done to help detect possible spinal cord involvement/pathological fracture of vertebra.

Haematuria

Haematuria is defined as the presence of blood in the urine on visual inspection (visible haematuria) or quantified on urine analysis (invisible haematuria). Presence of blood in the urine is significant if there are greater than three red blood cells (RBCs)

per high power microscopic field on urine sediment examination from two of three properly collected urinalysis specimens [12]. Haematuria of any degree should not be ignored regardless of the quantity of blood. It is considered to be of malignant origin until proven otherwise. In the vast majority of patients microscopic haematuria is detected by dipstick testing (see later). Different dipstick kits vary in their sensitivity to detect blood, but most dipsticks will detect 8 RBCs/HPF. Dipstick haematuria of '3+' equates to approximately 500 RBCs/ml. As dipstick testing is less sensitive compared to urine microscopy, a positive test should be confirmed with a second test and followed by urine microscopy.

Gross (or frank or visible) haematuria is blood in the urine in sufficient quantity to be visible to the naked eye. In fact, visible blood in the urine is thought to be the first presentation in 85 and 40 % of patients with bladder and renal cancers, respectively [13]. It indicates the risk of significant sinister underlying disease i.e. urothelial cancer.

Other Forms of Haematuria

Exercise Haematuria

Microscopic or gross haematuria may occur immediately following non-contact strenuous exercise such as running, cycling or swimming. Although the exact cause is not known this may be due to microcontusions resulting from trauma of the posterior bladder wall against the trigone of the partially filled urinary bladder. It usually resolves with rest in 48–72 h.

Pseudohaematuria

It occurs following ingestion of certain foods (carrots, beetroots, blackberries, riboflavin, vitamin A), drugs (chloroquine, phenacetin, sulfonamides, phenazopyridine, sulfasalazine, rifampin, laxatives containing phenolphthalein).

Factitious Haematuria

It is an extremely rare condition where patients have pathological desire to feign ill health and undergo investigations (Munchausens syndrome). Patients show haematuria by contaminating urine samples with venous blood. It is usually seen in analgesics abusers especially people addicted to opiate drugs.

Postcoital (Post-ejaculatory) Haematuria

It is a rare condition where painless haematuria occurs in men immediately after sexual intercourse. A urethral vascular lesion is usually associated, especially haemangioma. Haematuria may be associated with haematospermia in such a setting.

Causes of Haematuria

Systemic causes: Systemic disorders include Systemic lupus erythematosus (SLE), Henoch- Schönlein purpura (HSP), malaria, sickle cell disease, coagulopathies, endometriosis and alcohol abuse (papillary necrosis).

Drugs

Interstitial nephritis can be caused by penicillin, nonsteroidal antiinflammatory drugs (NSAIDs), cephalosporins, and frusemide. Nephrotoxic drugs include aminoglycosides and cyclosporine. Drug-induced hemorrhagic cystitis can be caused by cyclophosphamide and methicillin. Ketamine, a hallucinogenic drug and short acting anaesthetic causes severe voiding dysfunctional symptoms including haematuria. There is no evidence at present that this drug carcinogenic [14].

Anticoagulation

Anticoagulation should not be discounted as the source of bleeding, as significant urinary tract disease may be present in up to 30 % of patients [15]. The majority of patients have no diagnosis found after thorough evaluation. Table 8.2 lists the urological causes of haematuria.

Table 8.2 Urological causes of Haematuria

Renal	Congenital: PUJ obstruction, arteriovenous (AV) malformations, cystic renal disease (adult polycystic kidney disease, APKD), medullary sponge kidney, renal cysts
	Genetic: renal tubular acidosis type I, cystinuria, von Hippel–Lindau disease, Alport disease, thin basement membrane disease
	Trauma: iatrogenic (nephrostomy) Neoplastic: Renal cell carcinoma, transitional cell carcinoma, angiomyolipoma Metabolic: calculi Infection: pyelonephritis, genitourinary tuberculosis Inflammatory diseases: interstitial nephritis, poststreptococcal glomerulonephritis, IgA
	Nephropathy, Goodpasture's syndrome Radiation: nephritis Vascular: renovascular arterial disease, renal vein thrombosis, left renal vein hypertension due to nutcracker syndrome renal infarction: compression of left renal vein between superior mesenteric artery and aorta, hemangiomas, renal papillary necrosis Foreign bodies: stent, nephrostomy
Ureteral	Ureteral Calculi, neoplastic (transitional cell carcinoma, TCC), trauma (including iatrogenic), foreign bodies (stent)
Urinary bladder	Bladder Neoplastic (TCC, squamous cell, adenocarcinoma, neuroendocrine tumors); anatomic (diverticulae, vesicoureteric reflux); infection (hemorrhagic cystitis, schistosomiasis); metabolic (calculi), post– acute urinary retention (decompression bleeding), trauma
Prostate	Prostate Benign prostatic hyperplasia, carcinoma, infection (prostatitis), metabolic (calculi) Urethra Hemangioma, tumor, stone, stricture, trauma, foreign bodies (catheter, stents, inserted bodies), iatrogenic (instrumentation)

Clinical Evaluation

Patients, who are 40 years of age or older, have a higher risk of urological malignancy. The incidence of significant pathology is lower in women. It is important to differentiate rectal and vaginal bleeding from hematuria. Gross hematuria with clots demonstrates significant bleeding and increases the likelihood of malignancy.

The timing of hematuria can give a clue to the anatomical site of bleeding: hematuria at the start of micturition (initial) indicates urethral bleeding; hematuria occurring throughout micturition (total) comes from the bladder or upper tracts; and hematuria at the end of micturition (terminal) indicates that the bleeding is in the prostatic urethra or bladder neck.

Hematuria associated with colicky abdominal flank pain and passage of stringy clots is indicative of upper tract bleeding. Constant severe lower abdominal pain may be due to clot retention. Prostatic bleeding due to benign prostatic hypertrophy (BPH) or urethral stricture is usually associated with lower urinary tract symptoms (LUTS). Dysuria, urgency, and incontinence may be due to prostatitis or urinary tract infection.

Systemic Symptoms

Loss of appetite, weight loss, and night sweats could be due to underlying carcinoma. Recent history of an upper respiratory tract infection is associated with nephrological causes of hematuria such as poststreptococcal glomerulonephritis. A viral illness with hemoptysis and abnormal renal function is typical of Goodpasture's syndrome. Timing of the menstrual period must be noted along with any history of endometriosis. Unprotected sexual intercourse increases the likelihood of acquiring sexually transmitted infections.

A history of previous instrumentation may lead to a history of urethral stricture. Pelvic radiotherapy could cause radiation cystitis. Chronic atrial fibrillation or recent myocardial infarct may result in renal emboli and hematuria. In endemic regions a history of tuberculosis may indicate genitourinary tuberculosis. Urological cancer may be prevalent in first-degree relatives (prostate, renal cancer-von Hippel-Lindau disease). A family history of urolithiasis may point toward calculi as the cause of hematuria.

Clinical assessment of hemodynamic status is essential against a background of significant gross hematuria. Other features such as fever, sepsis, lymphadenopathy, hypertension (due to glomerulonephritis, renal parenchymal disease, renal failure, renal cystic disease, or vascular disease) and pulse rhythm (atrial fibrillation) will give clues to the diagnosis. Generalized edema may be due to glomerular disease.

Abdominal examination is done to rule out renal and bladder masses. Rectal examination helps in assessing the size, consistency, nodules, and tenderness of the prostate gland and finding rectal bleeding. The genitalia should be examined for

signs of infection, bleeding, or discharge. In men, the penis is examined for growths, meatal stenosis, and phimosis.

Laboratory Investigations

Mid-stream Urine (MSU)

For optimal analysis, a clean catch mid-stream urine specimen non-contaminated from external genitalia should be obtained and examined within 1 h or refrigerated at 4 °C. False negative results arise when urine is stored at room temperature for longer than an hour due to changes in pH and disintegration of white or red cells.

Dipstix (Dipstick) Testing

The dipstick test is based upon the liberation of oxygen from peroxide in the reagent strip because of the peroxidase like activity of heme from erythrocytes, free haemoglobin and myoglobin. The reaction causes the reagent strip to change colour and turn green. The degree of colour change is related to the amount of heme, haemoglobin and myoglobin in the urine. Intact red cells cause a punctate colour change on the strip whereas free haemoglobin leads to uniform staining. When >250 RBCs/ml is present in the urine, the number of punctate dots increases to become uniform.

The overall sensitivity for the dispstick compared to phase contrast microscopy is over 90 % with specificity ranging from 65 to 90 % [16]. False negative results occur in the presence of acidic urine (pH <5), high levels of ascorbic acid or certain drugs (captopril, rifampicin, phenolphthalein).

Free myoglobin, haemoglobin, povidone and microbial peroxidase from bacterial infection can lead to false positive readings. False positive readings are much less common than false-negative results, and up to 40 % of patients with dipstick haematuria may not have haematuria confirmed on bright-field urine microscopy [16]. A positive dipstick result in the presence of a negative urine microscopy or repeated dipstick test should not be discounted. The ideal standard for urine microscopy is phase-contrast microscopy, which is often not the standard investigation in most centres. One positive dipstick result, even if intermittent, should be considered worthy of full investigation, especially if risk factors for malignancy are present. The combination of proteinuria indicates a likely glomerular origin for the haematuria.

Microscopy

The two main methods of microscopic examination of urine are bright field microscopy and phase contrast microscopy.

Red Blood Cells (RBCs)

Bright-field microscopy: This is the direct examination of centrifuged urinary sediment under a cover slip (sediment count), which is reported as the number of RBCs per high power field (HPF). The upper limit of normal of RBC excretion in the urine is approximately equal to 2 RBCs/HPF.

The speed of centrifugation, its timing the volume in which sediment is re-suspended, and the power of the HPF vary from laboratory to laboratory. Another method of analyzing RBCs in the urine is by using counting chambers in the microscope, which determine the number of RBCs per milliliter of urine. The chamber count has greater sensitivity and precision than the sediment count but the sediment count is easier to perform, less time consuming and more cost effective.

Phase-contrast microscopy: This is regarded as the gold standard microscopic examination. It is able to show components in a cell or bacteria that would be difficult to see in an ordinary light microscope. Not only are RBCs detected better, their morphology can be better determined with the phase contrast microscopy.

Circular isomorphic erythrocytes are characteristic of nonglomerular bleeding, whilst glomerular bleeding results in dysmorphic erythrocytes associated with proteinuria and RBC casts.

White Blood Cells (WBCs)

Presence of greater than 10 WBCs/HPF is seen in significant inflammation. Persistent pyuria with a negative culture may be indicative of urolithiasis, tuberculosis or tumour.

Casts

A cast is a protein coagulum that is formed in the renal tubule and traps any tubular luminal contents within the matrix. Haematuria of glomerular origin is associated with casts. RBC casts are diagnostic of glomerular bleeding. WBC casts may also be found in acute glomerluonephritis, pyelonephritis and tubulointerstitial nephritis.

Crystals

Crystals of urate, calcium oxalate or triple phosphate may be seen in those with urinary tract stones.

Culture

Urine specimens should be cultured within 24 h of collection. Urinary tract infection is present when $>10^5$ colony forming units (CFU)/ml is detected in a mid-stream specimen of urine.

Cytology

Cytological analysis of urine may detect transitional cell carcinoma (TCC) but is highly operator dependent. Sensitivity is much higher for high grade lesions and carcinoma in situ (CIS). The specificity and sensitivity for the low grade tumours is 4 and 31 % respectively [17]. Voided urine sensitivity may be improved if the first and second voided morning specimens over three consecutive days are analysed. Barbotage cytology at cystoscopy also increases sensitivity.

Cytology does not add much in the diagnostic work up of transitional cell carcinomas, as most lesions are picked up on imaging or endoscopy. Cytology results do not change the course of investigations and management in haematuria patients but may add information when endoscopy is negative.

Tumor Markers

Urinary cytological markers can be used as a reasonable adjunct to the diagnosis of bladder cancers. These include bladder tumour antigen tests (BTA), ImmunoCyt (Scimedx Corp, Dnville, NJ, USA), nuclear matrix protein 22 (NMP22) tests, UroVysion (Abbott Molecular, Inc., Des Plaines, IL, USA) which could lead to a decrease in diagnostic cystoscopies, however more trials are needed to support these early promising findings [18]. Table 8.3 summarizes the sensitivity and specificity of the various urinary markers and conventional urinary cytology [19].

Serum Analyses

Screening laboratory tests typically consist of coagulation studies, a complete blood count, serum chemistries (renal function studies and eGFR), and serologic studies for glomerular causes of hematuria as directed by the medical history. Serum glucose should be checked to exclude diabetes (papillary necrosis). The prostate-specific antigen (PSA) in men should be checked to exclude prostate causes.

Table 8.3 Sensitivity and specificity of urinary markers

Marker	Studies	Sensitivity % (range %)	Specificity % (range %)
BTA stat	17	58 (29–74)	73 (56–86)
NMP22 Elisa	16	69 (47–100)	73 (55–98)
NMP22 POC	2	62 (50–86)	86 (77–87)
uCyt +/Immunocyt	8	77 (52–100)	74 (62–82)
FISH UroVysion	6	66 (30–86)	83 (66–96)
Microsatellite	7	73 (58–92)	76 (73–100)
Cytology	26	35 (13–75)	94 (85–100)

Adapted from Khadra et al. [19]. With permission from Elsevier

Imaging in Haematuria

Different imaging modalities vary in sensitivity for detecting different pathology and are described in detail in Chap. 5. The modality chosen is based upon its diagnostic strengths balanced against the risks of the investigation (for e.g. radiation, contrast reaction), availability of equipment and expertise to interpret image findings. The primary goal of imaging should be to exclude neoplastic disease of the urinary tract.

Ultrasound

Ultrasound is excellent at detecting and characterising renal cystic masses. It is also excellent at assessing renal morphology, structure and vasculature, and detecting hydronephrosis. It can assess bladder wall morphology, detect large bladder tumours and assess bladder emptying. Nevertheless, ultrasound is less sensitive than IVU in diagnosing urothelial tumours.

The study by Khadra et al. showed that if only ultrasound had been used, 43 % of tumours would have been missed [19]. Ultrasound has a lower sensitivity for detecting renal tumours less than 3 cm in size. Compared to CT, sensitivity and specificity of ultrasound for detecting renal masses between 2–3 cm is 82 % and 91 % respectively [20]. The sensitivity for detecting calculi is also low, ranging from 37 to 64 % and this is even poorer when compared with non-contrast helical CT (NCHCT) as the reference standard, with a sensitivity of 24 % and a specificity of 90 %. Stones in the pelvicalyceal system can be reliably identified only if they are larger than 5 mm [21]. The advantages of ultrasound include it being non-ionizing, safe, easy to use, cheap, portable and widely available. Therefore in pregnant women, it is the investigation of choice. The drawback of ultrasound is that it is very much operator dependent and the spatial resolution of images are poor compared to CT.

Computerized Tomography (CT)/CT Urography/Intavenous Urography

Historically intravenous urography with or without ultrasound (US) was the investigation of choice for many years and may be so even now in some places. CT is more sensitive than IVU (intravenous urography) or ultrasound in detecting small renal lesions. Non contrast high resolution CT (NCHCT) has overtaken IVU as the investigation of choice for diagnosing urinary tract calculi. Its other advantage is its ability to detect radiolucent stones. Traditionally CT has had a higher radiation dose compared to IVU, which discouraged its greater use. However, modern NCHCT protocols can achieve radiation doses that approach the dose of the IVU. Apart from the radiation burden and cost, disadvantages of CT include its limited availability especially in an acute setting, and the need for specialists to interpret the images. In last 10 years, computerised tomography Intravenous urography (CT-IVU) has mostly replaced conventional IVU and is the most commonly used modality to identify any possible upper or lower tract lesions i.e. arising from kidney down to bladder as urothelial cancer could be multifocal. It permits staging and assessment of the upper urinary tract in a single examination [22].

Compared to ultrasound, the IVU is better at detecting TCC, which usually manifests as a filling defect, in the intrarenal collecting system, pelvis and ureter. It cannot distinguish solid from cystic masses, which require further evaluation with ultrasound, CT or MRI. Ultrasound or IVU on its own is likely to miss upper urinary tract tumours. The detection rate is highest when both investigations are performed. The IVU has a lower cost and radiation dose compared to CT. However, the radiation dose to the patient is significant (3–4.5 mSV equivalent to 80 chest x-rays). It takes longer to perform than CT or ultrasound. Adverse reaction due to contrast media such as vomiting or urticaria may occur in up to 4 % of patients with a smaller proportion developing anaphylactic reaction which can be fatal. Diabetic patients on metformin require cessation of metformin before and 48 h after the investigation in order to avoid renal failure and lactic acidosis.

Magnetic Resonance Imaging (MRI)

The detection rate of MRI for renal masses is comparable to CT. The slightly poorer resolution of the urinary tract on MRI compared to CT has meant that CT is more widely used compared to MRI. However, MRI has certain advantages over CT. MR urography does not require potentially nephrotoxic contrast media and therefore can be used in patients irrespective of renal function. Similar to CT, it can also combine angiography and urography in the same examination. The disadvantages of MRI are its high capital cost and limited availability. Patients with claustrophobia or metal implants are not suitable for scanning.

Virtual Endoscopy

Volume rendered three-dimensional (3D) reconstruction of CT and MR data can be explored with the technique of perspective rendering in which the computer simulates an endoscopic view of a hollow viscus or body cavity – the so-called "virtual endoscopy". Virtual endoscopy has inherent advantages in that it is non-invasive and therefore avoids the risk of perforation, stricture formation or infection.

The role of virtual ureterorenoscopy and cystoscopy in the evaluation of the urinary tract is still being defined, but it is likely that it will be useful in evaluating patients where endoscopy is difficult either due to anatomy or disease (e.g. strictures) [23]. Virtual cystoscopy can be successfully used for noninvasive detection of bladder lesions with a sensitivity of 90 % and specificity of 94 % [24]. Virtual cystoscopy however can miss out carcinoma in situ and flat bladder lesions. Battista et al. [25]. concluded that virtual ureteroscopy provides superior anatomic information to that obtained by axial CT.

Endoscopy/Upper Tract Imaging

It is ideal if results of upper tract imaging are available before endoscopy so that appropriate endoscopic examination of the uretero-pelvi-calyceal system could be organized.

Flexible Endoscopy

The diagnostic accuracy of flexible cystoscopy is equivalent to that of rigid cystoscopy if the urine is clear. For lesions at the anterior bladder neck, it may be superior to rigid cystoscopy. Flexible cystoscopy is well tolerated procedure, does not require a general anaesthestic and causes less pain and complications. It can be performed in an office setting by a doctor or nurse, thus allowing rapid evaluation of the lower tract.

Rigid Endoscopy

For the vast majority of patients flexible cystoscopy should be the preferred investigation. The indications for rigid cystoscopy include persistent gross haematuria, diagnostic uncertainty at flexible cystoscopy and where access to the bladder is restricted due to disease (urethral stricture, large prostate).

Ureterorenoscopy

Evidence of upper tract abnormality on imaging may warrant further evaluation by diagnostic upper tract endoscopy and/or retrograde ureteropyelopraphy or simply called retrograde pyelography (RPG). Diagnostic ureterorenoscopy is then indicated for diagnosis and in suspected upper tract TCC, for biopsy confirmation and cellular staging.

Retrograde Ureteropyelopgraphy

At the time of cystoscopy it can confirm the presence of a known or suspected filling defect on IVU or discover further abnormalities.

Upper Tract Urine Brush Cytology

The diagnostic yield of cytology can be significantly increased if selective upper tract urine cytology is performed using a ureteric catheter (aspiration or saline barbotage cytology). Brush cytology is a specific and more sensitive sampling method than irrigation or catheterized urine in detecting TCC of the upper urinary tract. Brush cytology does not appear to be successful in diagnosing dysplasia or CIS. As with urinary cytology in general, the technique is less effective in diagnosing low grade (I and II) lesions [26]. Retrograde brushings can also increase the sensitivity and specificity of cytological analysis.

Renal Biopsy

Microscopic haematuria in the presence of proteinuria (>500 mg of protein in the urine/24 h collection), dysmorphic RBCs, RBC casts or an elevated serum creatinine level should be evaluated by a nephrologist for renal parenchymal disease. The limit of detection of standard urine dipsticks for proteinuria is 300 mg/L (0.3 mg/ml). Haematuria of urological origin does not elevate protein concentration greater than 200–300 mg/dl (+2 to +3 on disptick).

Management

For ascertaining the exact cause and site of haematuria detailed investigations and imaging as mentioned before in this chapter are required along with cystourethroscopy. The cause is to be treated accordingly after diagnosis of the pathology.

Haematuria should be treated on priority by an urologist except only in situations as mentioned below:

Haematuria in the Presence of a Positive Urine Culture

Although men should be investigated after a single episode, women should be treated with culture specific antibiotics. Persistent haematuria after treatment with no evidence of urine infection warrants investigation. Microscopic haematuria in women who have repeated urinary tract infections should be investigated.

Asymptomatic Microscopic Haematuria (AMH)

Urological cancer has been detected in between 0.5 and 8.3 % of patients with AMH [16]. The risk of cancer increases with age and where there is a history of exposure to carcinogens.

American Urological Association (AUA) Guidelines

The AUA best practice policy on the evaluation of AMH has divided patients with AMH into high and low risk group [12]. A single episode of either dipstick or urine microscopy haematuria in a patient with any of these risk factors should prompt thorough first line evaluation consisting of urine cytology, upper tract imaging and lower tract endoscopy. Patients with AMH and a low risk of malignancy do not necessarily require all of these investigations. In these patients, imaging of the upper tract is the primary investigation followed by cystoscopy if imaging is abnormal. If upper tract imaging is normal, urine cytology should be evaluated, followed by cystoscopy if cytology is abnormal or atypical. Table 8.4 summarizes the risk factors for urothelial cancer.

For upper tract imaging, the choice now is CT-IVU over IVU, ultrasound and CT for high risk patients unless there are specific contraindications. An ultrasound and plain abdominal radiograph may be sufficient in low risk patients. High-risk patients allergic to contrast medium are recommended to undergo retrograde ureteropyelography in replacement of IVU or CT-IVU.

Gross Haematuria

The immediate consequences of gross haematuria are haemodynamic compromise and clot retention. Patients haemodynamically unstable or in urinary retention require emergency admission to hospital. Significant haemodynamic compromise requires blood transfusion and close monitoring. This conservative approach is sufficient in managing the acute consequences of gross haematuria in the vast majority of patients.

Upper tract imaging and urine cytology may be carried out in the interim period whilst the haematuria is resolving. If the urine becomes clear, a flexible cystoscopy can be carried out under local anaesthesia to assess the lower tract. Rigid cystoscopy under general anaesthesia should be done where bleeding has not ceased.

Benign Lateralising Haematuria (BLH)

BLH is a diagnostic and therapeutic challenge. As first and second line investigations fail to identify a suitable cause for the bleeding, ureterorenoscopy (URS) assumes a pivotal role in diagnosis and therapy. URS usually identifies the bleeding

Table 8.4 Risk factors for urothelial cancer

(a) Age >40 years
(b) Chronic smoking
(c) Occupational exposure to chemicals (benzenes, aromatic amines, aniline dyes)
(d) Cyclophosphamide therapy
(e) History of pelvic irradiation
(f) Recurrent urinary tract infection
(g) Analgesic abuse
(h) Schistosomiasis of the bladder
(i) Family history of cancer (Lynch syndrome)

to be emanating from a vascular lesion in the kidney, and through a combination of direct vision and biopsy, malignant lesions are ruled out.

Haemangiomas may appear as either as small red or bluish spots at the tip or base of a papilla or as larger bulbous erythematous lesions on a papillary tip. Endoscopic treatment is the mainstay of the management for BLH. Patients with discrete lesions are more amenable to treatment. Up to 50 % undergoing URS will have a discrete vascular lesion that can be treated. Conservative treatment of patients with chronic unilateral hematuria should always be considered. Laser ureteroscopic treatment is an excellent method and should be considered as the first option for the management of chronic unilateral hematuria [27].

Intractable Haematuria

Severe haematuria may occur as a result of radiation cystitis, bladder carcinoma, cyclophosphamide-induced cystitis and severe infection. Rarely, fulguration of the bleeding lesion and subsequent irrigation in the ward through a three-way urethral catheter fails to stop bleeding a life-threatening situation can develop, when blood transfusion fails. Patients with massive uncontrollable haematuria are usually elderly and unfit for cystectomy as a treatment. The management of such patients is discussed in Chap. 7.

Follow Up

Urological

The concern with investigating haematuria is that malignancy may be missed. Data from studies on following up patients with normal initial evaluation have demonstrated that the prevalence of malignancy is more or less non-existent. In a 10–20 years follow up assessment of 191 patients with unexplained microhematuria genitourinary malignancies did not develop in any of the patients evaluated after the first diagnostic investigation [28]. In the large study by Khadra et al. [19] subsequent

follow up of patients with no abnormal findings revealed no neoplastic disease. Such evidence reassures the treating specialists to follow up patients with repeat urinalysis and urine cytology on an annual basis. If a patient develops gross haematuria, positive or atypical cytology, or irritative voiding symptoms without infection, then repeat urological evaluation including imaging and cystoscopy is advised [12].

Nephrological

The role of renal biopsy in patients with isolated haematuria has not been defined. Although many such patients may have structural glomerular abnormalities, they appear to have a low risk for progressive renal disease. The natural history of patients diagnosed with IgA nephropathy and isolated microscopic haematuria is usually benign. In up to half, haematuria will disappear, 20 % will have intermittent haematuria and in the remainder haematuria will persist. Some of these patients may develop hypertension and proteinuria over 5–10 years. The presence of proteinuria is the single biggest risk factor for progression of renal disease. Without proteinuria the risk of renal impairment is low and that of end stage renal failure (ESRF) is extremely low. In the presence of significant proteinuria, hypertension, elevated serum creatinine and additional abnormalities on renal biopsy, the risk of ESRF at 20 years may be as high as 30 %. When the patient has persistent haematuria, either in the presence of a normal previous renal biopsy or where biopsy was not performed, follow up should be with yearly evaluation by the primary care physician to exclude the development of hypertension, proteinuria or renal insufficiency.

Haematospermia

Haematospermia is defined as the appearance of blood in the ejaculate. For haematospermia to occur, intact emission and ejaculation functions are necessary. Haematospermia is usually painless and self-limiting in most cases. Its exact incidence remains unknown as most ejaculates go unnoticed during intercourse. It is often self limiting in men younger than 40 years of age without risk factors such as bleeding disorders, urogenital malformation or history of cancer. Men less than 40 years who present with haematospermia associated with lower urinary tract symptoms usually have sexually transmitted infections or other urogenital infections. Workup in these patients can be limited to urinalysis and testing for sexually transmitted infections, with treatment as indicated. In men 40 years and older, blood in semen is caused most commonly by urogenital instrumentation or prostate biopsy. Recurrent or persistent hematospermia with associated symptoms (e.g., fever, chills, weight loss, bone pain) should prompt further investigation, starting with good clinical evaluation including a digital rectal examination of the prostate and prostate specific antigen testing to evaluate prostate cancer [29]. Hematospermia is rare (0.5 %) in a prostate cancer screening population but in men who present with hemospermia the reported incidence is 13.7 % [30].

Causes of Haematospermia

Hematospermia was not considered clinically significant, and it was mostly attributed to prolonged sexual abstinence or intense sexual experiences because a precise etiology could not be determined in as many as 70 % of patients who presented with it. Advancements in medical imaging and laboratory techniques have allowed physicians to determine a more precise cause in up to 85 % of hematospermia cases, many of which are benign [31]. Of specific etiologies, infectious conditions are the most common, accounting for approximately 40 % of hematospermia cases. Other etiologies include inflammatory, neoplastic (e.g., prostate cancer, testicular cancer), iatrogenic (e.g., prostate biopsy [most common], prostate surgery, urologic instrumentation, radiation therapy, haemorrhoid injections), structural, systemic, and vascular causes (Table 8.5).

Most common causes of haematospermia are attributed to iatrogenic, infective and behavioural aetiologies.

Clinical Evaluation

Good clinical evaluation is necessary for evaluation of haematospermia. Initially pseudo haematospermia should be ruled out wherever possible by a good history (haematuria, sexual partner source, melanospermia i.e. metastasis to prostate from malignant melanoma). It is important however, to make sure that the patient is actually describing haematospermia and not haematuria; in some cases both may co-exist. If haematuria is present in association with haematospermia, haematuria is also investigated. Fever and tachycardia may indicate a systemic cause, infection, or malignancy. Detailed abdominal and genitourinary examinations should be performed to assess for trauma, inflammation, discharge, and lymphadenopathy. Full scrotal examination is important to evaluate for inflammation, infection, masses of the testes, epididymis, and spermatic cords [33]. Rectal examination is needed to check the prostate for size, tenderness, fluctuation, symmetry, firmness, and nodularity [34].

Investigations

The aims of investigation are to exclude neoplasia or a specific pathology that is treatable thereby alleviating the patient's symptoms and to reassure the patient, if no causative factor is found. Urinalysis and urine culture should be performed and testing for genitourinary infections, including STIs should be considered.

- **Urinalysis and urine culture** will help to confirm the presence of urinary infection and haematuria, which if present will require further radiological investigations where indicated.

Table 8.5 Causes of haematospermia and their presentation

Etiology	Typical presentation
Behavioral	
Excessive sex or masturbation, Interrupted sex, prolonged sexual abstinence	Isolated hematospermia episode triggered by particular sexual behavior
Infectious	
Echinococcus (rare)	Irritative genitourinary symptoms; urinalysis positive for inflammation; positive microbiology findings
Gram-positive and gram-negative uropathogens	
Mycobacterium tuberculosis (rare)	
Schistosoma (rare)	
Sexually transmitted infections: *Chlamydia trachomatis; Neisseria gonorrhoeae;* herpes simplex virus types 1 and 2 urethritis; urethral human papillomavirus	
Inflammatory	
Chemical epididymitis	Irritative genitourinary symptoms; urinalysis positive for inflammation; negative microbiology findings
Interstitial, eosinophilic, proliferative cystitis	
Prostatitis	
Seminal vesiculitis	
Neoplastic	
Benign and malignant tumors of the bladder, urethra, prostate, seminal vesicles, spermatic cord, epididymis, and testes	Abnormal findings on examination or imaging
Structural	
Ectopic prostatic tissue or prostatic polyps	Voiding problems
Intraprostatic Müllerian duct remnants	
Prostatic stones, cysts, benign prostatic hyperplasia	
Urethral stricture, fistula, diverticula	
Systemic	
Amyloidosis	Hematospermia associated with systemic disease without other explanations
Bleeding disorders	
Chronic liver disease	
Severe uncontrolled hypertension	
Trauma (iatrogenic)	
Hemorrhoid injections	Temporary hematospermia related to trauma
Penile injections	
Prostate biopsy, radiation therapy, brachytherapy, microwave therapy, transurethral resection of the prostate	
Urethral instrumentation	
Urethral stent migration	
Vascular	
Arteriovenous malformations	Isolated hematospermia episode, or hematospermia associated with hematuria
Bladder neck and prostatic varices, submucosal bleeding, hemangiomas, telangiectasias	

Based on data from Ref. [32]

- **Semen analysis** may show pus cells which then warrant further investigation in search of an infectious aetiology; this includes semen culture, urethral swabs, mycobacterial cultures and viral serology.
- **Serum coagulation profile** may reveal underlying bleeding disorders attributable to haematospermia whilst the erythrocyte sedimentation rate (ESR) may be raised in tuberculosis.
- **Urethral cultures**: If sexually transmitted diseases are suspected, urethral cultures for gonorrhoea and chlymadia are obtained. In patients who have a suspicious nodule on rectal examination or who are at risk of prostate cancer, a PSA test is required.
- **Transrectal ultrasonography (TRUS)** may help in the diagnosis of prostatic and seminal vesicular pathology including calculi, cysts, mullerian duct remnants, varices and inflammatory changes within the prostate.
- **Scrotal ultrasound** is required if clinically a testicular pathology is suspected.
- **Magnetic Resonance Imaging (MRI)** both conventional and with endorectal coil, improves visualisation of the anatomy of the pelvic organs and can be performed when TRUS is unsatisfactory or non diagnostic.

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Chapter 9
Renal Failure, Dialysis and Transplantation: In the Management of Renal Cell Carcinoma (Solitary Kidney and Bilateral Renal Tumours)

Raj Thuraisingham

There are numerous scenarios where altered renal function is likely to be an issue or could be anticipated after surgery. In practice the commonest scenario is obstructive uropathy. Various causes of obstructive uropathy are outlined in Table 9.1:

1. Obstructive Uropathy: Obstruction to the urinary flow could occur at various levels of upper urinary tract; it could be bilateral or unilateral, supravesical (above vesico-ureteric junction) or infravesical (below vesico-ureteric junction) (Table 9.1).
2. Renal cell carcinoma (RCC) in solitary kidney
3. Pre-existing renal disease (Acquired cystic disease in patients who are on dialysis)
4. Nephrotoxicity induced by high-dose chemotherapy
5. Malignancies in Renal transplant patients
6. Other systemic diseases, which affect renal function like diabetes and hypertension
7. Effects of previous cancer treatment: Radiotherapy, chemotherapy
8. Renal damage as a result of nephrotoxicity due to analgesics and antibiotics
9. Paraneoplastic syndromes

Patient Assessment

When assessing such patients there are a few **key questions** which are essential in the overall decision-making process:

R. Thuraisingham, MD, FRCP
Department of Renal Medicine and Transplantation, Royal London Hospital,
London E1 1BB, UK
e-mail: raj.thuraisingham@bartshealth.nhs.uk

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Table 9.1 Cancers that cause unilateral or bilateral obstruction

Infravesical: Urothelial cancer of the bladder, prostate cancer, urethral carcinoma, carcinoma cervix/uterus/ovary and rectum
Supravesical: Urothelial cancer of ureter and renal pelvis, bladder, primary or secondary Retroperitoneal lymph node involvement, malignant retroperitoneal fibrosis

- What is the likely course and prognosis of the disease process?
- Are there co-morbid conditions which are likely to be more serious than the cancer process itself?
- What is the overall level of renal function? What is the differential renal function?
- Has the patient got one kidney only? How much function is likely to be lost following surgery? (Partial or total loss)
- Is the potential loss of function likely to render the patient dialysis-dependent.
- If so, is it short term or long-term.
- What would the prognosis of the patient be without treatment compared to dialysis.
- Is further treatment (e.g. Chemotherapy) likely to cause deterioration in the renal function.

In acute cases of bilateral obstruction, relief of obstruction by drainage or in selected cases dialysis followed by resuscitation and correcting fluid balance and metabolic acidosis is necessary prior to proper staging and deciding about the definitive management of the malignancy (Chap. 7).

1. **Overall course and prognosis of the disease process**.

This is most crucial question in planning the treatment as the clinicians try to work out how far they can push the boundaries of management.

2. **Co-morbid conditions**, which are likely to be more serious than the cancer process itself: The patient's comorbidity such as cardiovascular status, previous history of stroke will influence the prognosis of renal failure management.
3. **Overall level of renal function**

Methods of assessing renal function: Assessing the baseline renal function can be done in numerous ways. This basic information is required and forms the basis of the rest of the assessment.

Blood Tests

The simplest is measuring the serum concentrations of urea and creatinine. **Blood urea** is not generally felt to be a marker of renal function as urea clearance is 50–60 % of GFR [1]. Urea levels are influenced by age of the patient, dietary protein intake and protein metabolism. Similarly blood urea nitrogen (BUN), a product urea has similar limitations.

Serum creatinine (**SCr**) levels are more reliable than urea and reflect not only renal excretion, but also the generation, intake, and metabolism of creatine and phosphocreatine [2]. Factors other than renal function also influence SCr which include age, weight, nutritional status, gender and ethnicity. SCr levels may not rise above the normal range until the kidney function has become significantly impaired [3]. For example, an elderly malnourished patient may have SCr within the normal range but may well have a markedly impaired glomerular filtration rate (GFR). Conversely a young muscular male may have a SCr that is above the normal range but have a normal GFR. In most instances therefore the SCr is sufficient to assess renal function but is important to remember that serum creatinine levels are also influenced by extrarenal factors.

Creatinine Clearance

As creatinine is not metabolized in the kidney and freely filtered by the glomeruli, it is a simple way of measuring GFR. The urinary creatinine (U) excretion over 24 h when divided by the SCr (P) will provide a measured creatinine clearance ($[U] \times [urine\ volume]/[P]$). However, as creatinine is also secreted by proximal tubule, the creatinine clearance usually exceeds GFR [4]. This test was used frequently in clinical practice but is subject to error in that it is highly dependent on an accurate 24 h urine collection and the creatinine levels.

Glomerular Filtration Rate (GFR)

Although GFR gives fairly accurate assessment of functioning nephrons it is not frequently used in clinical practice [5]. It can be estimated using several validated formulae. The Cockcroft-Gault formula [6] requires the patient's weight, age and serum Creatinine (μmol/L). There are likely to be errors in measurements and it is difficult to ensure the quality of the variables [5].

Cockcroft-Gault Formula

$$\text{GFR} = K \times \text{weight} \times [140 - \text{age}] / \text{Serum Creatinine}$$
$$(Where\, K = 1.23\ for\ males\ and\ 1.03\ for\ females)$$

The MDRD (Modification of Diet in Renal Disease in US study) equation however does not require the weight [7]. Although it has been validated in many clinical situations, the adjustment for ethnicity is limited to African-American, which may affect other ethnic groups. However increasingly the MDRD formula is being used as the preferred method of estimating the GFR (eGFR).

MDRD Formula

$$\begin{aligned}\text{GFR} = 186 \times [\text{Serum Creatinine}] - 1.154 \times [\text{age}] \\ -0.203 \times [0.742 \text{ if female}] \times [1.212 \text{ if black}]\end{aligned}$$

As already mentioned these formulae have their strengths and weaknesses. Neither formula has been validated in the context of acute renal failure, which again limits their use. Their main strength is that finally we can estimate the GFR with some degree of accuracy without having to resort to expensive and time-consuming tests.

Radioisotopes/Radiocontrast Studies

(Chapter 6)– These techniques are the most accurate methods of measuring the GFR in clinical practice [8]. The success of these methods relies on the use of radiopharmaceticals that are freely filtered by the glomerulus and are neither reabsorbed nor secreted by the tubules. The principles of isotope renography are discussed in Chap. 5. These methods however are invasive and expensive and may not be available in all clinical settings. In a study of 122 cancer patients eGFR measured by the equations above was compared with Tc^{99m} DTPA clearance and the data suggested that there were significant limitations to using eGFR compared [8].

How Much Function Is Likely to Be Lost Following Surgery/Treatment?

In order to estimate the potential loss of function post operatively, it is clearly important to know the contribution each kidney makes to the total GFR. As mentioned earlier, this can be assessed using isotope renography. These techniques employ radio-pharmaceutical agent which are either glomerular filtration agents (diethylenetriaminepentaacetic acid -DTPA) or tubular secretion agents (mercaptoacetyltriglycine-MAG3, dimercaptosuccinic acid- DMSA). Following intravenous administration, it is possible to measure renal blood flow and renal cortical function by the isotope activity which is then computed using scintigraphic techniques [9].

By using this information combined with the knowledge of the overall GFR, the single kidney GFR can be determined. As an example, if a nephrectomy is being planned and the contribution of the problem kidney is 10 % for someone with an overall GFR of 80 ml/min (i.e. problem kidney GFR = 8 ml/min) then there should be more than sufficient residual renal function post operatively. If however the affected kidney contributes 50 % or more to overall function in someone with a total

GFR of 20 ml/min, the planned nephrectomy may render the patient dialysis dependent. The impact on renal function following nephron sparing surgery however is more difficult to predict but at least patients can be counselled regarding the "worst case scenario".

The information regarding the degree of residual renal function post surgery is extremely important as it enables clinicians to advise the patients on the potential need for dialysis post operatively either on a temporary or permanent basis. This will be discussed in more detail below.

Is the Potential Loss of Function Likely to Render the Patient Dialysis Dependent?

The threshold GFR at which renal support is required varies according the individual patient and also accepted practice in different renal units. Most though would agree that a GFR of 10 ml/min/1.73 m^2 or less is an indication for dialysis (National Kidney Foundation Kidney Disease Outcomes Quality Initiative- NKF-DOQI Clinical practice guideline) [10]. Based on the measurements discussed above one may be able to predict, with some degree of certainty, the likely need for dialysis support post operatively. This information should be relayed to the patient as it may inform their choice of treatment options. As mentioned above, in the case of nephron sparing surgery (or partial nephrectomy) it is more difficult to predict the impact of surgery on renal function.

There are several post-operative scenarios for renal support in GU cancer patients with compromised renal function (Fig. 9.1):

1. *Patients with sufficient residual function who do not require postoperative dialysis*. Their remaining nephron mass is sufficient for them not to need renal replacement therapy.
2. *Patients who need dialysis in the short term but then become dialysis independent*. In this scenario the patient is left with sufficient nephron mass not to require long-term dialysis but the operative procedure has caused acute tubular necrosis and temporary renal shut down. This usually recovers in time but may take up to 6 weeks.
3. *Patient regains independent renal function post-operatively but over subsequent months/years develops remnant nephropathy and end stage renal failure*. Once a critical nephron mass is lost a maladaptive response known as **hyperfiltration** ensues irrespective of original pathology [11, 12]. In simple terms the remaining glomeruli of the kidney(s) hypertrophy. In the short term this increases the GFR but in the long term leads to focal glomerulosclerosis and remnant nephropathy and ultimately to end stage renal failure.
4. *Patient will need dialysis thenceforth*. Sufficient renal mass has been removed such that the patient does not have independent kidney function and will thus require long term/permanent dialysis.

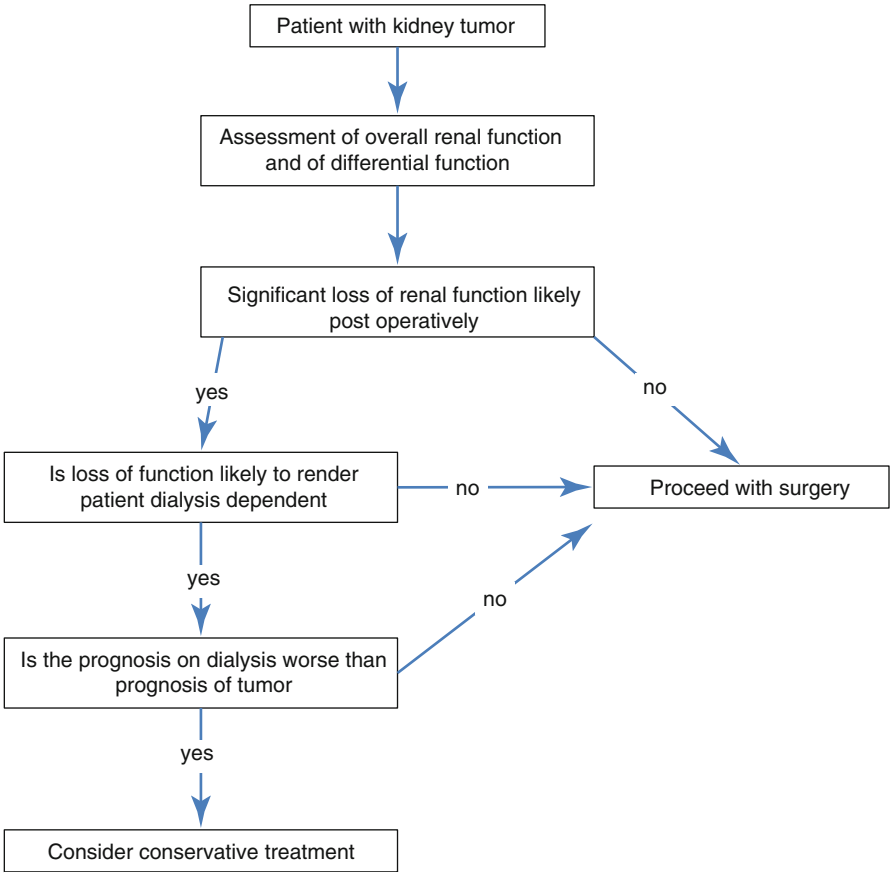

Fig. 9.1 Treatment decision flowchart

Based on the results garnered from the investigations outlined above (overall renal function and split renal function) it is possible, with a modest degree of certainty, to predict which of these scenarios is likely. This information should be passed on to the patient. It also extremely important for the physicians and surgeons to be aware of this as it may influence the decisions regarding surgery. This is especially true if the likely prognosis on dialysis is poor in which case surgery may not be in the patient's best interest.

Prognosis of Tumour vs. Dialysis

When deciding treatment options it is important to bear in mind the prognosis of the individual patient on long term dialysis if that is a likely scenario. The prognosis on dialysis of a young dialysis patient with no co-morbidity is very different from an elderly

patient with serious comorbidities such as heart disease and diabetes in relation to survival. These need to be borne in mind in that the prognosis of the underlying tumour may be significantly better with conservative management in certain individuals.

It is worth remembering that for a debilitated and dependant patient, quality of life on dialysis may be very poor often with multiple admissions to the hospital for initiation and maintenance of dialysis. These facts may also influence treatment decisions (Fig. 9.1).

Perioperative Management

The preoperative management of patient undergoing radical nephrectomy with a normally functioning contralateral kidney does not need any specific measures. Special precautions are however necessary in patients undergoing nephron-saving surgery. Fluid balance is the mainstay of maintaining renal function over the perioperative period.

Preoperative Management

Patients should be volume replete at the time of surgery, which often means they will require a continuous intravenous infusion during the 'nil by mouth' period. Although there are little data on preoperative fluid regimens, studies examining hydration prior to contrast examinations have shown crystalloid infusions (at 1 ml/kg/h for 12 h) to be very effective in preventing subsequent renal dysfunction [13]. This however must not be applied to patients who are anuric (i.e. on dialysis) as they run the danger of becoming volume overloaded.

During nephron-saving surgery temporary occlusion of renal artery is required to achieve a bloodless field. To prevent ischaemic injury to the kidney the patient should be well hydrated and intravenous mannitol is given 5–10 min prior to renal artery occlusion to prevent intracellular oedema [14]. Mannitol could be repeated after removal of the vascular clamp to induce diuresis. Cooling the kidney with ice slush to decrease the core temperature to 15–20 °C allows the surgeon with 2–3 h of "safe ischaemia" [15].

Postoperative Fluid Management

The principles of post operative fluid management very much depend on the patients' urine output and other fluid losses from drains and nasogastric tubes. Other important parameters include daily weights, blood pressure, pulse rate, central venous pressure and daily blood chemistry in the initial post operative phase. Central venous pressure (CVP) measurements should not replace the simple clinical parameters listed above.

Management in Patients with Good Urine Output

Patients need to remain on intravenous fluids until they are able to eat and drink without restriction. As a rough guide if there is renal impairment then all that the patient will require is 1–1.5 L/day of crystalloid adjusted according to input-output charts, serum biochemistry and daily weights.

Management in Patients with Poor Urine Output/Anuria

Intravenous fluid should not be prescribed unless required as judged by the parameters outlined above. If the oliguria is felt to be secondary to volume depletion then diuretics should be avoided but fluid prescribed instead. The signs of volume depletion include tachycardia, hypotension (especially postural hypotension), fall in weight, and non-visible jugular venous pulse and a low CVP. Signs such as dry mucus membranes and poor skin turgor are unreliable and should not be used. Urea and electrolytes will need to be checked immediately post operatively and daily thereafter. Dialysis will need to be started if there is hyperkalaemia, profound acidosis or fluid overload.

Management of Patients on Dialysis

Managing a dialysis patient post operatively requires special attention. Fluids should be administered using the guidelines above for the anuria/oliguric patient. In addition daily assessments of the chemistry should be carried out and dialysis recommenced when required. In the case of patients on peritoneal dialysis (PD) if the peritoneum has been breached then they will require temporary haemodialysis for a period prior to recommencing PD. For haemodialysis patients dialysis should be carried out with as little anticoagulation as possible.

The Transplant Patient

The fluid management of these patients post operatively is dependent on their urine output as discussed above but the key issues revolve around their medication. Where possible they should continue with their oral immunosuppressive medication, however most would need an increase in their steroid dose (if on steroids) during the immediate post operative period as these patients may have adrenal suppression. If the patient is unable to tolerate steroids orally then administration by intravenous route is necessary (e.g. Hydrocortisone can be used instead of prednisolone) ciclosporin and tacrolimus (immuno-suppressants) doses need adjusting to 1/3 their oral doses whereas the dose of intravenous azathioprine and mycophenalate mofetil is the same as the oral. Rapamicin is not available for intravenous use.

Dialysis Modality

In the acute post operative period most would advocate the use of haemodialysis as opposed to peritoneal dialysis for patients who were not previously on dialysis. If the patient is stable, intermittent haemodialysis via a central venous catheter would be the method of choice. The timing of initiation will depend on the patient's blood chemistry, pH and fluid status.

Because of the need for anticoagulation during the dialysis it maybe preferable to delay the treatment until absolutely necessary in order to minimise the risk of bleeding although dialysis can often be carried out with little or no anticoagulation. In the case of the hypotensive or haemodynamically unstable patient continuous veno-venous haemodialysis or diafiltration is usually employed but in these situations the patient is usually on the intensive care. The danger of these modalities is bleeding as patients need to be continuously anticoagulated. In patients who need long term renal replacement therapy peritoneal dialysis can be successful especially if their renal surgery has been carried out via retroperitoneal approach. For others haemodialysis can be carried out.

Transplantation

Patients rendered dialysis dependent post surgery could potentially be listed for transplantation following a detailed assessment. Most of the best practice guidelines suggested an observation period to ensure no recurrence. Although the current policy of waiting for patients with end-stage renal disease and localised prostate cancer is 5 years after primary therapy, it is reasonable to assess these patients for transplantation on individualized risk assessment [16]. For most patients with renal tumours a delay of 2 years or so is probably sufficient [17]. Those with urothelial tumours however are a different issue as recurrence may be late. In such patients waiting period of 5 years is prudent [17].

GU Cancers in Patients with Renal Failure

The incidence of GU tumours is increased in patients on dialysis [18, 19]. For kidney cancers the risk in increased roughly 3-fold compared to the normal population and more so in the younger age group [19]. The main reason for this is the increased incidence of acquired cystic disease of the kidney, which occurs in between 40 and 80 % of patients on dialysis.

Acquired cystic disease puts patients at increased risk of developing renal parenchymal cancers independent of the primary renal diagnosis. In conditions such as analgesic nephropathy however the kidney cancers are more often of urothelial ori-

gin. The risk of bladder cancer is also increased (50 % increase) in patients on dialysis but to a lesser extant compared to the normal population. The incidence of bladder cancer falls with increasing time on dialysis whereas that of kidney cancers increases with time on dialysis [19].

Renal transplant recipients are also at increased risk of developing renal and urinary tract cancers. Kidney tumours may appear in donor kidney or in the native kidneys. Renal carcinoma may develop in 0.5–3.9 % of transplant recipients which is a roughly 10–100 times higher than in the general population [20]. Those most at risk are patients with acquired cystic disease of the kidney (50-fold increase) [21] and those with a history of analgesic nephropathy or renal tract tumours [22]. Rarely renal tumours may occur in the transplant kidney. In this case the management is to stop the immunosuppression and remove the kidney.

Diagnosis of GU Tumours in End Stage Renal Failure

One cannot rely on urine screening to pick up GU tumours in anuric patients but they may occasionally present with the passage of blood per urethra. Polycythaemia is associated with renal tumours but in patients with end stage renal failure this may present as a steady unexplained decline in the need for erythropoietin. Conversely patients with any form of cancer often suffer from relative erythropoietin resistance and hence may present with unexplained anaemia in the context of erythropoietin therapy. All the other symptoms and signs are the same as in patients with normal renal function.

The diagnosis of prostatic cancer is also difficult in the anuric patient as the symptoms of prostatism cannot be relied upon. Total PSA measurements are as valid in these patients as they are in the general population though and hence may be of some help.

Treatment of GU Cancers in Dialysis Patients

The treatment principles are the same as in a non dialysis patient however assessment of split function, overall renal function etc discussed above is irrelevant. The surgical technique however does matter as any transperitoneal approach in a patient on CAPD is likely to require a permanent transfer to haemodialysis thereafter hence a retroperitoneal approach is preferred to transperitoneal approach.

Tumours in Solitary Kidney and Bilateral Renal Tumours

In a rare patient with solitary kidney and severe comorbid conditions the best option could be conservative management. Various surgical options include radical surgery (radical nephrectomy or nephroureterectomy) followed by dialysis, enucleation of the tumour, partial nephrectomy and rarely bench surgery (*ex-vivo*) with autotransplantation (Chap. 17). It is also possible to treat small tumours with cryosurgery, high intensity focused ultrasound (HIFU) or radiofrequency ablation (RFA) [23].

Table 9.2 Possible causes of acute Renal Failure in GU cancer patients

Pre-renal	Haemorrhage and shock
	Sepsis
	Dehydration
	Drugs: NSAIDs, ACE Inhibitors
	Acute tumour lysis syndrome
Renal	Renal ischaemia: Shock, sepsis
	Chemotherapeutic agents: Ifosamide, methotrexate, carboplatin and cisplatin
	Antimicrobial agents: Aminoglycosides, amphotericin, Rifampicin, quinolones
	Pyelonephritis
	NSAIDs
Post-renal	GU Malignancies: Bilateral ureteric and bladder carcinoma, prostate cancer, urethral carcinoma, retroperitoneal fibrosis, Pelvic malignancies (Uterine, ovarian, cervical, colo-rectal cancers)
	Benign Conditions: BPH, Uterine prolapse

As patients undergoing nephron-saving surgery may end up having total removal of the kidney depending on technical problems and findings at the time of surgery. It is therefore important to get preoperative nephrological assessment in these patients. As mentioned earlier postoperative dialysis support may be required for a limited period in patients who had nephron-saving surgery.

Acute Renal Failure (ARF)

In acute renal failure, there is rapid deterioration of renal function leading to a progressive rise in serum creatinine levels. This is further characterised by failure to excrete nitrogenous products from the blood and ensuing metabolic acidosis. ARF could be the first manifestation of GU cancers and later occur during the course of treatment or progression of the malignancy. ARF causes substantial morbidity and mortality in cancer patients [24]. The causes of ARF are prerenal, renal and postrenal (Table 9.2).

Pre-renal

Renal failure associated with renal hypoperfusion responds well to appropriate fluid replacement. Hypoperfusion leads to reduced GFR and drastic reduction in volume of urine.

Drug Toxicity

There are 2 broad mechanisms of renal drug toxicity: biochemical (direct and indirect) and immunological. The kidney is susceptible for drug toxicity due to its high blood flow, capacity to concentrate drugs and its ability to metabolize the

drugs. It is important to note that NSAIDs increase the risk of ARF through products of prostaglandin metabolism [25] and this is dose dependent. Concurrent medication with other nephrotoxic agents could enhance worsening of the renal function [26].

Acute Tumour Lysis Syndrome

It is a life-threatening complication of cancer chemotherapy in chemosensitive tumours due to rapid release of intracellular contents into extracellular space. This is generally seen in haematological cancers although it has been reported in germ cell tumours [27].

Renal

The majority of hospital-acquired acute renal failure are due to acute tubular necrosis (ATN) [28]. ATN is multifactorial in origin and being usually due to renal hypoperfusion, usage of nephrotoxic drugs and sepsis. Prolonged episodes of renal hypoperfusion lead to cortical necrosis. Patients who are likely to be vulnerable to ATN include elderly, diabetics, patients with pre-existing renal disease, congestive cardiac failure and those who have volume depletion.

Chemotherapy Agents

Two main drugs used in urological cancers are cisplatin and methotrexate. Cisplatin-induced renal toxicity: Most of cisplatin is cleared through the kidneys. It has a direct effect on proximal tubule and its nephrotoxic effect is exacerbated in low-chloride environment [29]. Doses of cisplatin >50 mg/m^2 have potential to cause renal insufficiency and doses in excess of 100 mg/m^2 can cause irreversible renal damage [30]. Hydration and avoidance of concomitant nephrotoxic agents (e.g. aminoglycosides) is essential to prevent cisplatin toxicity. Amifostine (inorganic thiophosphates) has been shown to prevent renal failure [24]. Cisplatin also causes nausea and vomiting which may exacerbate dehydration and electrolyte disturbances. **Monitoring renal function therefore is of utmost importance in cisplatin therapy**.

Methotrexate: It is excreted primarily by the kidney. High doses methotrexate are associated with renal failure due to precipitation of methotrexate or its metabolites in the tubular lumen [31]. Monitoring methotrexate levels is necessary to prevent nephrotoxicity. intravenous fluids are given during methotrexate administration to maintain high urine output. Alkalisation of urine to pH 7.5 is recommended [24]. Once the toxicity has caused ARF, methotrexate is removed through haemodialysis [24].

Anti-microbial Agents

Other drugs commonly used are anti-microbial agents.

Amphotericin is an effective antifungal agent which can cause acute renal failure by its toxic effects on renal tubular cells resulting in acute tubular necrosis [32].

Aminoglycosides such as gentamycin are commonly used in urological practice in the treatment of gram-negative bacterial infection. They are not metabolized in the body and are freely filtered through the glomeruli. A sizable amount accumulates in the renal cortex leading to cellular damage [33, 34].

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

These agents alter renal blood flow by their effects on prostaglandin metabolism but they can also cause acute renal failure via a hypersensitivity reaction in some individuals which results in a tubulointerstitial nephritis.

Obstructive Uropathy

Diagnosis and management of obstructive uropathy is discussed earlier in this chapter. The total renal mass needs to be obstructed in order for the renal function to deteriorate, hence a unilateral transitional cell carcinoma of the ureter will only cause acute renal failure if the contralateral kidney is diseased or absent.

The mainstay of management is to effectively diagnose outflow obstruction. A history of anuria is suggestive, but imaging is required. An ultrasound scan is probably the initial investigation of choice as it avoids the use of potentially nephrotoxic contrast agents. It is important to note however that obstruction cannot necessarily be ruled out on the basis of a non dilated renal pelvis nor can the diagnosis be made with complete certainty in cases with hydronephrotic kidneys. Improvement in renal function following drainage is occasionally the only way of being certain if obstruction was present. In acute cases of bilateral obstruction, drainage (nephrostomy or JJ-stenting) followed by resuscitation with correction of the fluid balance and metabolic acidosis is necessary prior to staging and deciding about the definitive management (Chap. 11). Once the obstruction is relieved there is a phase of diuresis leading to fluid loss, decreased urine concentrating ability and electrolyte imbalance. This needs careful correction of problems in high-risk patients.

Residual Renal Function After Partial or Radical Nephrectomy

Patients are usually worried about residual renal function and chances of getting another RCC in the healthy kidney after nephrectomy. The aspect of residual renal function after nephrectomy is relatively poorly defined in the medical literature. A

50 % removal in the renal mass is followed by a reduction in renal function to about half its pre-nephrectomy value decrease in renal function [35]. Within a short time the contralateral kidney starts compensating for the loss of opposite kidney. Partial nephrectomy or nephron-saving surgery on the other hand preserves significant renal mass after surgery. Even though the adaptation is full after radical nephrectomy, over a period of time chronic hyperfiltration, driven partly by an increase in glomerular pressure, will lead to renal damage or an accelerated deterioration of pre-existing renal damage [36]. Information on renal function after nephrectomy mainly comes from the studies done on healthy live kidney donors. Long-term assessment of healthy kidney donors indicate that there is a decrease in creatinine clearance by about 30 % (GFR), a low risk of proteinuria and a negligible risk of developing end-stage renal disease following kidney donation.

There are several implications of reduced renal function (particularly KDOQI stage III/IV) in patients with RCC. These include uremic thrombopathy, renal anemia, a tendency to become fluid overloaded, hyperkalemia and increased susceptibility for infection [37]. Patients with chronic kidney disease are prone for perioperative acute kidney injury. The CKD may also affect usage of tyrosine kinase or mTOR inhibitors used in the targeted therapy of RCC. To circumvent these problems wherever possible nephron-saving treatments should be considered.

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Chapter 10
Diet and GU Cancers

Ali Panah and Chandran Tanabalan

The Role of Diet in Cancer

Apart from hereditary cancers, most of the malignant tumours are related to the dietary and various environmental factors. Based on the statistical and epidemiological data, Doll and Peto [1] reported that 10–70 % (average 35 %) of human cancer mortality was attributable to the dietary factors. In another study, nearly 35 % of worldwide deaths were attributable to potentially modifiable risk factors with 31 % deaths in high-income countries and 69 % in low and middle-income nations [2]. In this study, the main risk factors for death in low and middle-income countries included smoking, alcohol use, low fruit and vegetable intake while in the high-income countries the main risk factors were smoking, excessive alcohol use, obesity and overweight.

From the initial observations that the oesophageal cancers were more common in people with a high consumption of smoked fish and the link between smoking and lung cancer, it has become obvious that there exists a link between the food we consume and our susceptibility to the development of certain types of cancers. Similarly there has been much written in the popular press about complementary and alternative medicine (CAM) for cancers, including the role of trace elements and anti-oxidants that may actually have a role in prevention of certain types of cancers. The reason as to why this may be the case is the subject of ongoing research. In this chapter we explore the pro and anti carcinogenic effects of food on reducing the risk of developing urological cancer. Cancer patients want to avoid any factors that might have caused their cancer and are also becoming increasingly keen in modulating their diet and embrace alternative/complementary health regimes. However, understanding the precise actions of dietary factors in cancer

A. Panah, MRCS (✉) • C. Tanabalan, MRCS
Department of Urology, Homerton University Hospital NHS Trust,
Homerton Row, London E9 6SR, UK
e-mail: ali.panah@doctos.org.uk

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prevention is not an easy science and any recommendation that is made has to be a qualified one.

Another important question is whether isolated vitamin, mineral and antioxidant supplements are as effective as those naturally present in fruits and vegetables. There are increasing reports that the interaction of the natural vitamins and antioxidants make them more effective than the isolated compounds. Thus there has been an increased public awareness of the benefits of eating fresh fruits and vegetables to prevent or hinder cancer progression rather than just taking proprietary makes of multivitamins and other trace elements. There is compelling evidence of a wide range of dietary factors stimulating or inhibiting the development, growth and spread of tumours in experimental animals.

As mentioned before, there is also a marked difference in the total cancer burden between developed (high income) and developing (low to middle income) countries. The main reason for this variation is probably related to the environmental and lifestyle factors rather than genetic factors [3]. Other factors such as obesity and physical activity have been extensively investigated. Dietary habits coupled with sedentary life style influence the proportion of body fat present in an individual with excessive fat leading to obesity. Its relationship with cancer is being currently investigated in several studies. Renal carcinoma seems to be associated with excess weight (see below) [4].

Prostate Cancer (PCa)

Prostate cancer is the most commonly diagnosed malignancy in men in industrialised countries and the second leading cause of male cancer-related death. It is thus of great importance that any factor that may lead us to decrease the risk of developing or progressing of prostate cancer be explored.

Fat Intake

A close correlation exists between the average per capita fat intake and prostate cancer mortality in numerous countries around the world. Japanese and Chinese men who migrate to the USA experience dramatic increases in prostate cancer risk within one generation compared with their Caucasian neighbours and with the members of their racial group who have retained traditional diet in their homeland [5]. It is also noteworthy that there has been an increase in prostate cancer among Asians in Singapore and Hong Kong who have adopted a western lifestyle, including diet. Also, mortality rates for prostate cancer significantly increased by 3.2 % per year from 1958 to 1993 in Japan as a result of nutrition transition [6]. The Physician's Health Study by Gann et al. [7] found an association between red meat consumption and prostate cancer risk, but this association was not found to be statistically significant. Linoleic acid, which is the major polyunsaturated fat in most diets, has been associated with an increased risk of prostate carcinoma in some

studies. There was no obvious association between prostate cancer and alcohol consumption [8] even at higher doses [9]. In a large multicentre prospective study in Europe [10], there was no evidence of any association between high intake of dietary fat and increased risk of prostate cancer.

Calorie Intake

Few studies investigating the relationship between the risk of developing prostate cancer to calorie intake in rats, have indicated a reduction in tumour growth with energy restricted diet, regardless of the food contents. Thus a reduction in energy intake not just fat seems to be needed to reduce prostate cancer growth in experimental models [11–13]. Overall the emphasis is on control of weight, regular physical activity and avoiding excessive calories.

Meat Mutagenicity in PCa

Meats cooked at high temperatures release carcinogenic heterocyclic amines and polycyclic aromatic hydrocarbons. Koutras et al. [14] observed in their study among 23,080 men with complete dietary data that there was no association between meat type or specific cooking method and risk of developing PCa. However, intake of very well cooked meat was associated with 1.26-fold increased risk of prostate cancer and 1.97-fold increased risk of advanced disease. Although the epidemiological evidence is not consistent, high meat consumption particularly red meat and processed meat has a higher association with increased prostate cancer risk [15].

Agents That May Protect Against PCa

A plethora of epidemiological and some molecular data supports the use of selenium, zinc, vitamin E, vitamin D, lycopene, and green tea as potential preventatives possibly by reducing the oxidative damage in prostatic tissue [16, 17]. Long-term supplementation with α-tocopherol, a form of vitamin E, significantly reduced prostate cancer incidence and mortality in smokers [18]. Some of these agents are being tested in a new large-scale phase III clinical trials.

Selenium: There is a considerable interest in the mineral selenium as a chemopreventative agent in PCa. Selenoproteins- glutathione peroxidase and theoredoxin have antioxidant activity and also affect on DNA methylation. A long term randomised study, known as SELECT (Selenium and Vitamin E Cancer Prevention Trial) evaluated vitamin E and Selenium [19]. It identified the dose for selenium as 200 mcg/day and Vitamin E (reduced dose to prevent the possible cardiovascular effects of higher doses) to 150 IU/day. However, the trial was recently discontinued due to no evidence of benefit from either agent [20].

Green tea: It is a commonly consumed beverage in Asia and its bioactive components include catechins, epigallocatechin-3-galate (EGCG) and theaflavins with catechins being present in high concentration [21]. *In vitro* investigations have shown that EGCG has protective effects against hormone–related cancers (such as breast and prostate). It is shown to induce apoptosis and affect expression of cell cycle regulatory proteins that are necessary for cell survival and apoptosis [22]. *In vitro* effects also include its key role in DNA methylation. The effects of polyphenon E (green tea) in prostate cancer patients are interesting [23]. The study was done in a small cohort of men undergoing radical prostatectomy. The findings indicated a significant reduction in serum levels of PSA, HGF, and VEGF after a brief treatment with polyphenon E with no elevation of liver enzymes. These findings support a potential role for polyphenon E in the treatment or prevention of prostate cancer nevertheless these findings have to be corroborated with clinical trials [23]. Although findings of low bioavailability and/or bioaccumulation of green tea polyphenols in prostate tissue and statistically insignificant changes in systemic and tissue biomarkers suggest that prostate cancer preventive activity of green tea polyphenols, if occurring, may be through indirect means and/or that the activity may need to be evaluated with longer intervention durations and repeated dosing [24].

Omega-3 fatty acids, obtained mainly from fatty fish, have been shown to inhibit prostate cancer cell lines in laboratory experiments. The Netherlands Cohort Study found a potential protective effect of omega-3 fatty acids but this was not statistically significant [25, 26].

Soy isoflavins and phytoestrogens: Various epidemiological studies have indicated that consumption of soy containing foods may be associated with a reduction in PCa risk in men. In a metanalysis of 15 epidemiological publications on soy consumption and prostate cancer risk, Yan and Spitznagel [27] concluded that consumption of soy food is associated with a reduction in prostate cancer risk in men. This protection depends on type and quantity of soy products consumed. The ability of soy isoflavins to combine with α and β oestrogen receptors and altering its metabolism is attributed to the isoflavin called genistein [28]. Again the effect seems to be on DNA methylation by moderating the activity of DNA methyl transferase (DNMT). A large-scale cross-national study in 59 countries showed that soy food products were significantly protective ($P<0.001$), with an effect size per kilocalorie at least four times as large as that of any other dietary factor [29].

Bladder Cancer

Pro-carcinogenic Factors in Diet

The evidence linking dietary factors and the development of bladder cancer is not quite strong. Environmental toxins (such as used in dye, rubber, and textile manufacturing) seem to predominate as the major factors affecting the incidence of bladder cancers and have been estimated to be responsible for up to 20 % of bladder

cancer cases. Aromatic amines from occupational exposures are activated and detoxified through the same reactions that aromatic amines in cigarette smoke are activated and detoxified.

It also means that exposures to occupational agents and cigarette smoke may be additive. In clinical practice, more than 80 % of patients with bladder cancer have a significant smoking history.

Some studies have indicated an increased risk of bladder cancer and coffee drinking [30–32], although this association remains controversial. The role of alcohol in increasing the risk of prostate, renal and bladder cancer is still uncertain, because of the confounding variables of smoking and dietary fat. The exact role of fat intake in bladder cancer is unclear [33]. The high levels of arachidonic acid and its derivatives in meat products, is postulated to have a promoting effect on prostate cancer in animals and the same mechanism may be true in human bladder cancer [34, 35]. Several studies have reported correlation between total fluid intake and the risk of developing bladder cancer [36] but no significant trend was observed [37–39].

Anticarcinogenic Factors in Diet

A reduction in the risk of bladder cancer was observed in nonsmokers with a high intake of cruciferous vegetables (Cabbage, Brussels sprouts, broccoli, and cauliflower) [33]. Protective effects of cruciferous vegetables may be due to their high concentration of the carotenoids, lutein and zeaxanthin. *In vitro* studies have shown isoflavonoids, found in soy to inhibit bladder cancer cells [33]. The trace element selenium does not possess a proven protection. However, it has been shown that persons with a high selenium plasma level have relatively lower incidence of bladder cancer. The preventive action of nonsteroidal anti-inflammatory drugs (NSAIDs) is controversial. Surprisingly, analgesic users have a lower incidence of bladder cancer [40].

There are no significant data supportive of an independent relationship between the intake of milk or dairy products and the risk of bladder cancer [41], but there are studies suggestive that milk may be related to reduction of bladder cancer risk [42]. The role of various micronutrients including vitamin E, carotenoids, vitamin D, thiamin and niacin in relation to the risk of developing bladder cancer warrants further large scale studies particularly in relation to high risk groups such as heavy smokers and older individuals [43].

Renal Cancer

Investigations have shown an increase in RCC among men and women with high-energy intake [44]. There seems to be he increased risk of RCC with high-energy intake, especially when derived from increased fried meat consumption [44, 45].

Polycyclic aromatic hydrocarbons (PAHs) in barbecued meat, is associated with a higher risk of RCC [46]. Chow et al. [47] reported that high protein consumption was associated with noncancerous chronic renal diseases that may predispose to RCC while other studies did not. Increased consumption of chlorination by-products also appears to increase the risk [48, 49]. Ljungberg et al. [50] showed smoking, overweight and obesity to be established risk factors for RCC. Their study also reported that hypertension and advanced kidney disease, which makes dialysis necessary, also increase RCC risk.

Alcohol consumption seems to have a protective effect for reasons yet unknown. There are not enough data available for many other factors such as salt that may have an important role in the causation of RCC. Recurrent urinary tract infections, increased intake protein and fried foods as well as female sex appear to increase the risk of renal cancer. Thus, dietary modification and other public health measures directed at environmental carcinogens have a potential to reduce the incidence of urological malignancies [51]. In a large prospective diet and health study conducted in the US on nearly half million participants on dietary intake and food sources of fibre in relation to RCC risk over a mean period of 9 years, Daniel et al. found a 15–20 % reduced risk of RCC [52]. Their findings suggested an inverses association between fibre intake and RCC and this was consistent among participants who never smoked, had no history of diabetes or hypertension and had a body mass index of <30 [52].

Nutritional Effects of Anticancer Treatments

Radiotherapy

Most of the side effects of radiotherapy are felt around the second or third week of the treatment and subside 3–4 weeks after the completion of radiotherapy. Chronic side effects appear after a period of long duration of many years [53].

Nearly 70 % of patients receiving radiotherapy to the pelvis experience acute gastro-intestinal symptoms as healthy bowels are inevitably included in the radiation field. Fifty percent of these patients go on to develop chronic bowel symptoms subsequently, which may severely affect the quality of life [54]. It is, therefore, important to give this information to the patients before and after the treatment. There is no evidence base for the use of nutritional interventions to prevent or manage bowel symptoms attributable to radiotherapy. Diarrhoea is treated by high liquid intake and reduction in fibre content of the diet. It is also important to take diet rich in potassium. Low-fat diets, probiotic supplementation and elemental diet merit further investigation. One year after pelvic radiotherapy, dietary manipulation was found to be generally unhelpful for gastrointestinal symptoms, although the role of eliminating raw vegetables is questionable and may benefit from further evaluation. With regard to late effects patients with abnormal body mass index and current smokers are more likely to experience worse symptoms at 1 year [55].

Chemotherapy

Systemic chemotherapy leads to more severe side effects than radiation or surgical treatment. Most side effects are of short duration and subside once the treatment has been discontinued. The main areas that are affected by chemotherapy are those where cell division and growth is rapid, such as oral mucosa, the gastro-intestinal tract, skin, hair and bone marrow. Anorexia, altered taste sensation, nausea, vomiting, stomatitis, mucositis/oesophagitis, diarrhoea and constipation are some well-known side effects. Patients tend to seek for 'complementary' therapy to alleviate the side effects of chemotherapy so further research in this direction is necessary. One of the interesting topics is the role of anti-oxidant therapy and its impact on short and long term benefits of chemotherapy and their side effects. This again needs further elucidation [56].

Nutritional Needs of Cancer Patients Who Are Undergoing Active Treatment

The nutritional needs of cancer patients are likely to differ from healthy population in many ways due to hypermetabolism, impaired organ function, increased loss of nutrients, chemotherapy side effects and complications of cancer therapy (surgery, radiotherapy or chemotherapy) [57]. In addition they may also have pre-existing conditions (e.g. chronic renal failure with RCC). Malnutrition in cancer patients is associated with a poor prognosis, history of weight loss being an important predictor of mortality. Malignant disease and its treatments have a major impact on the nutritional status. By improving the nutritional status, there is possibility of improving the prognosis, quality of life and functional status, thereby facilitating improved tolerance to treatment [58]. Dietary counselling is recommended for patients who are at the risk of malnutrition. It should be introduced early in close collaboration with the patient. Administering oral nutritional supplements to malnourished patients has been shown to affect mortality, complications and the length of hospital stay. Supplementation with enteral nutrition has shown to increase appetite, energy intake, nutritional status and, above all, reduced gastrointestinal toxicity from cancer treatments due to a better response to therapy. Supplementation with home parenteral nutrition in terminally ill patients has shown improved quality of life, energy balance, body composition and prolonged survival. These patients usually have less side effects, better wound healing, fewer infections, and are able to be more active. In order to prevent malnutrition from the cancer itself and chemotherapy it is essential that patients are educated about nutritional needs.

Malnutrition and weight loss lead to poor immunity and weakness, which subsequently affect a patient's ability to regain health and acceptable blood counts between chemotherapy cycles. The antigen presenting cell – regulatory T cell – CD4+ lymphocyte axis might be affected by calorie and nutritional disturbances

[59]. This alteration could affect treatment regimes and ability of the patient to stay on treatment schedules, which is important in achieving a successful outcome in chemotherapy.

Neutropenic diets were once thought to be important in giving the patients' immune system a boost and also in protecting them from having to succumb to infection from neutropenia while undergoing chemotherapy/radiotherapy [60]. The rationale behind the neutropenic diet was to limit the introduction of harmful bacteria into the gut by restricting the food that might contain those bacteria [61]. Although food may contain harmful organisms and research has shown that bacterial translocation is possible, recent studies have been unable to obtain significant differences between placebo and intervention groups. However, neutropenic diets remain in place in many institutions even though their usefulness is controversial. Without scientific evidence, the best advice for neutropenic patients is to follow food safety guidelines as indicated by government entities. Patients need to be educated about neutropenic diets. A neutropenic diet includes all well-cooked foods and elimination of foods that may contain potential disease-causing microorganisms. However, this needs further elucidation by more specific studies. Yogurt, which contains live active cultures of *lactobacillus bulgaricus* and *streptococcus thermophilus*, garlic, foods high in zinc such as oysters, pot roast, dark meat turkey, pumpkin, squash seeds and shitake mushrooms are common ingredients of a neutropenic diet.

Cancer patients may have lower concentrations of −3 fatty acids due to metabolic disturbances. Supplementation with omega-3 fatty acids appears to offer benefits that are verifiable at a biochemical, clinical and functional level although there have been some conflicting results. Supplementation with glutamine appears to support the efficacy of chemo-radiotherapy treatment while reducing toxicity of the tissues and improving outcomes. Oral supplementation with branched amino acid appears to reduce the length of hospital stay, decrease morbidity and improve the quality of life, without any changes in mortality. Perioperative supplementation with arginine has shown a reduced incidence of complications and a significant increase in long-term survival [58].

Maintaining nutrition is an integral part of patient care and when it is possible enteral nutrition is regarded as superior to parenteral nutrition. However when it is not possible to eat or ingest high calorie drinks then enteral nutrition via nasogastric route is preferable. Post-pyloric feeding may enable enteral feeding to be maintained in patients who cannot tolerate nasogastric feeding Post-pyloric feeding can be successfully used to maintain enteral nutrition in patients who would otherwise require parenteral nutrition.

Parenteral nutrition is the last step and reserved for patients in whom it is not possible to feed enterally especially as there may be some worry about the tumour boosting activity of parenteral feeding and the invasiveness of this approach along with risk of infection and the morbidity associated in inserting a line. Anorexia is present in 15–25 % of cancer patients and is nearly present in patients with metastasis [62]. It is further aggravated by depression, loss of personal interests and hope-anxiety resulting in protein-calorie malnutrition [63].

Immunotherapy

Despite recent advances in local therapy with curative intent, chemotherapeutic treatments for metastatic disease often remain unsatisfying due to severe side effects and incomplete long-term remission. Therefore, the evaluation of novel therapeutic options is of great interest [64]. Conventional, along with newer treatment strategies target the immune system that suppresses genitourinary (GU) malignancies. Metastatic renal cell carcinoma and non-muscle-invasive bladder caner represent the most immune-responsive types of all human cancers. Monoclonal antibodies are used to block cancer-cell receptors for growth-stimulating factors, which also cause the side effect from this form of treatment. Interferon (non-specific immunotherapy agent) along with other immune therapy agents affects the nutritional status of the patients. They cause fever, nausea, vomiting, diarrhoea and fatigue. Similar side-effects are also experienced by patients who receive interleukin-2 for metastatic RCC; although some patients have reported weight gain with interleukin-2 therapy [65].

Granulocyte-macrophage colony-stimulating factor (GMCSF), a very commonly used agent to increase the production of white blood cells, may also cause fever, nausea, vomiting, and diarrhoea. These symptoms can lead to gradual or drastic weight loss causing malnutrition and complicate the expected healing and recovery process. These side-effects can be avoided by screening and assessing the patient which should be done before starting the anti-cancer treatment and continue during and after treatment. Screening is useful in identifying patients at risk of developing malnutrition during the course of illness and treatment.

Surgery

Radical or salvage surgery is another option for cancer treatment. Poorly nourished patients are at increased risk of post-operative morbidity and mortality. Every attempt should be made to correct nutritional deficiencies prior to surgery [66]. Preoperative assessment and correction of the nutritional deficiencies with oral supplements, enteral or parental nutrition and /or use of pharmacological therapies to suppress nausea should be actively practiced.

Surgery, depending on the procedure (ileal conduit, transperitoneal nephrectomy, retro-pubic prostatectomy, retroperitoneal lymph node dissection-RPLND) may cause mechanical or physiological obstruction leading to inadequate nutrition [66]. Surgery causes an immediate metabolic demand that increases nutritional requirements essential for wound healing and recovery. Many patients are unable to eat normal diet and experience loss of appetite, fatigue and pain as result of surgery. Malnutrition leads to prolonged recovery time and problems with wound healing and other wound-related complications.

Aims of Nutritional Therapy in Cancer Patients

Nutritional management of GU cancer patient is a team effort and should include physician/surgeon, specialist nurse and registered dietician. The main goal of the nutrition therapy in cancer patients is to help with uninterrupted active treatment and achieving rapid recovery by restoring healthy nutrition. It aims at correcting malnutrition, preventing muscle wasting, catabolic state and immunodeficiency.

The benefit of optimal caloric and nutritional intake is well documented in patients undergoing treatment or recovering from therapy and also who are in remission and normal individuals who are aiming to avoid cancer [67–69]. Nutritional evaluation should be included in the patient management by taking into consideration patients' needs, quality of life and expectations and this will help in tailoring the forms of nutritional support for them [70]. In individuals who have advanced cancer, the goal of nutrition therapy should not be weight gain or reversal of malnutrition, but rather centred towards comfort and symptom relief. Nutrition continues to play an integral role for individuals whose cancer has been cured or who are in remission [71]. Many patients undergoing cancer treatment use dietary supplements, particularly antioxidants, in the hope of reducing the toxicity of chemotherapy and radiotherapy. Preclinical data are inconclusive and it is advisable to not to use any agent, that is not beneficial [72].

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Chapter 11
The Anaesthetic Management of Patients with Genitourinary Cancer

Rajesh Mehta and Ravishankar Rao Baikady

Introduction

A consideration of the anaesthetic management of patients with urologic cancer undergoing surgery reveals a diverse range of anaesthetic skills is necessary to manage these patients successfully. This reflects the fact that the patient population with genitourinary cancer is not a homogenous one. Patients vary from the young to the elderly undergoing anything from a routine surveillance cystoscopy to major surgical extirpation and reconstructive procedures. In addition patients may be suffering from co-morbidities and the side effects of chemo and radiotherapy. Additionally the therapeutic goal of surgery will vary from palliation to cure. All these factors impact on the anaesthetic management of the patient. Despite these different variables patients must be assessed in a consistent and systematic manner at the anaesthesia pre-assessment clinic. During this clinic a history, clinical examination and investigations ranging from the routine to specialist tests such as cardio-pulmonary exercise testing are obtained. A plan can then be formulated for the pre, intra and post-operative care including pain management. This ensures patients can undergo surgery safely with pre-existing conditions identified and optimised. Provision can be made for any anticipated blood loss and plans made for analgesia, antibiotics and post-operative anticoagulation. Finally a decision can be made about the appropriate level of care that is required post operatively. All this must be done in a time critical manner in the knowledge that when warranted, early surgical intervention improves survival in patients with cancer. It is vital that surgical and anaesthetic teams work together for

R. Mehta, MBBS, BSc, FRCA (✉)
Department of Anesthesia, The Royal London Hospital, Barts Health NHS Trust, Whitechapel Road, Whitechapel, London EC1A 7BE, UK
e-mail: Rajesh.Mehta@bartshealth.nhs.uk

R.R. Baikady, FRCA
Department of Anaesthesia, The Royal Marsden Hospital, London, UK

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smooth recovery of the patient. In this direction urological team should provide details of the aims of the surgical treatment, peri-operative complications, amount of likely blood loss and the surgical approach to their anaesthetic colleagues

In this chapter we hope to give an insight into how patients with genitourinary cancer are prepared and managed by anaesthetists before, during and after surgery based on our experience of working in busy oncology units. We aim to provide a rationale and review some of the evidence behind our current practice

Pre-operative Management

Patient Pre-assessment

All patients undergoing urological surgery require routine pre-operative assessment in a clinic. The aim should be to ensure patients are in the best medical condition thus reducing the risk of intraoperative complications and minimize delays in scheduling surgery. The clinic is usually nurse-led [1] with input from a senior anaesthetist to assess all patients undergoing major surgery. As a large proportion of patients are elderly there is an increased possibility of associated medical co-morbidity. Table 11.1 summarises the clinicopathological variables and challenges associated with uro-oncological patients.

The objectives of the Pre-assessment clinic are to:

- Identify acutely deteriorating conditions that need intervention from a specialist to stabilise airway, breathing, and cardio-vascular function.
- Document all stable chronic medical diseases e.g. hypertension.
- Arrange appropriate pre-operative investigations.
- Formulate a plan for patient analgesia.
- Educate the patient and family about the anaesthesia and analgesia planned.
- Identify those patients who require critical care post-operatively.

Table 11.1 Challenges associated with uro-oncological patients

1. Obesity, cachexia
2. Varying degrees of impairment of renal function
3. Previous anaesthetic problems
4. Dehydration, acidosis/alkalosis, electrolyte imbalance
5. Paraneoplastic syndromes
6. Diabetes mellitus
7. Cardiac and vascular (including hypertension)
8. Bleeding diathesis
9. Abnormal liver function
10. Elderly patients
11. Impaired lung function (e.g. bleomycin, smoking)
12. Jehovah's witness
13. Dementia, cerebral palsy
14. Multisystem problems not related to cancer (pre-existing)

In meeting these objectives we can ensure patients are in an optimum condition minimising the risk of intra-operative complications and cancellation on the day of surgery. All assessments should consist of a history, clinical examination and investigations.

History

The following information should be sought:

Anaesthetic History

Patients should be asked about all previous general and local anaesthetic episodes and where possible independent verification sought by obtaining previous anaesthetic records. Specific information of interest is a history of a difficult airway or allergy to any medication used e.g. muscle relaxants. Hyperthermic reactions under anaesthesia raise the possibility of malignant hyperthermia. This is a rare (1:20,000) but life threatening inherited disorder, which must be identified pre-operatively (by obtaining a muscle biopsy and testing the tissue) [2]. Special precaution must be taken in patients with medical history to avoid a variety of drugs in particular the volatile inhalational anaesthetics that trigger a catastrophic hypermetabolic reaction within skeletal muscles. Another rare genetic disease with anaesthetic implication is a suxamethonium apnoea. Patients have an abnormal variant of the enzyme pseudocholinesterase and metabolise the muscle relaxant suxamethonium very slowly. As a result they have prolonged motor block and require intubation and ventilation until the drug is slowly metabolised and excreted (upto 5 h). The incidence of significant suxamethonium apnoea is estimated at 1:2,800 [3].

Medical and Surgical History

All existing medical conditions must be identified and stabilised. A detailed history of the cancer together with any metastatic disease must also be identified.

Drug History

Polypharmacy is common amongst elderly patients. A record must be made of medication taken including dosage and frequency. The majority of medication can be continued preoperatively. Special care must be taken with the drugs listed in Table 11.1, which are relevant to urology patients. Patients in addition may have received treatment with chemotherapy, the implication of which is discussed below. Drugs such as warfarin, clopidogrel and ticlopidine can have impact on surgery and should only be discontinued with in consultation with an anaesthetist and/or cardiologist (in patients with coronary stents).

Allergies

All drug allergies needs to be documented and a red allergy bracelet allocated. Patients with urological disease frequently require repeated medical/surgical procedures involving the use latex. As a result they can become sensitised and develop a latex allergy. A history of allergies to contrast, dressings and tape should also be sought.

Smoking History

Smoking history should be recorded including all past episodes of smoking. Smoking is a risk factor for both cardiorespiratory disease and urological cancer. Cigarette consumption is classified in pack years; that is the product of number packs per day (20 cigarettes per pack) smoked by the number of years.

Alcohol Intake

Consumption of alcohol is widespread in western society and a common co-factor in many diseases. Anaesthetists consider the acute and chronic effects of alcohol at all stages of the patient pathway. The alcohol intake is recorded in units and the Royal College of Physicians (U.K.) recommends no more then 21 units of alcohol for men and 14 units for women per week. In addition all patients must have 2 to 3 days of non alcohol consumption in order for the liver to recover.

Recreational Drug Use and Herbal Remedies

Opioid and cocaine use both have an impact on anaesthesia and need to be documented. Herbal remedies can also have impact on postoperative course (e.g. garlic pills and bleeding tendency).

Functional Enquiry

Functional status and exercise tolerance are important and can be measured in metabolic equivalent of task (MET) levels. The term MET is a physiological measure of the energy cost of physical activity based on population studies. The range is from 1 to 18 MET's with 1 MET being the oxygen consumed at rest whilst 18 that whilst running flat out. Four MET's is associated with climbing one flight of stairs whilst 7 with a light jog [4]. Patients with >7 MET's usually have a lower risk of complications following major surgery. Those with <4 MET's have a high risk of perioperative cardiovascular complications. MET's have now been superseded by formal cardio-pulmonary exercise testing (CPET) which gives a more accurate assessment of cardiorespiratory status (see below).

A history of breathlessness on minimal exertion or at rest is a symptom of cardiorespiratory disease and requires further investigation. Nocturnal awakening with

dyspnoea and complaints of swollen ankles suggest cardiac failure that requires an urgent cardiology referral. Similarly any patient complaining of exertional chest pain or syncopal episodes must also be referred to a cardiologist for review prior to undergoing general anaesthesia for major surgery.

Examination

The following systems must be examined:

Airway: Some Characteristics of Difficult Intubation Include.

- Limited mouth opening <2 cm
- Short neck
- Immobile cervical spine
- Retrognathia (malocclusion of maxilla and mandible) with large overbite
- Mallampati score > III (the ease with intubation is done)ref
- Radiotherapy scarring to neck/Thyroid Surgery
- Obesity
- Craniofacial anomalies e.g. Turner's Syndrome

It is important to ensure a fully equipped difficult airway trolley is present for difficult airway cases including a fibre-optic bronchoscope.

Cardiovascular Assessment: The Following Are Assessed

- Heart rate and rhythm
- Blood Pressure (BP): Patients frequently have elevated blood pressure as a consequence of age or renal disease. Such patients if found to be hypertensive with Diastolic BP >90 mmHg require treatment with B blockers, calcium channel antagonists and/or ACE inhibitors and expert help should be sought [5]. Anaesthetising uncontrolled BP place patients at risk of a perioperative myocardial infarction (MI) or stroke. Invasive monitoring is recommended in patients whose hypertension has recently been corrected (<6 Weeks).
- Heart sounds – The presence of murmurs should prompt a request for echocardiography to exclude valvular heart disease.
- Heart failure – Signs include pitting oedema of lower limbs, congested liver and elevated jugular venous pressure

Respiratory Assessment: Lungs

Lungs should be examined for evidence of wheeze (asthma/COPD), crackles (pulmonary fibrosis) and heart failure.

Table 11.2 American Society of Anaesthesiologists (ASA) physical status classification

ASA 1	A normal healthy patient
ASA 2	A patient with mild systemic disease
ASA 3	A patient with severe systemic disease
ASA 4	A patient with severe systemic disease that is a constant threat to life
ASA 5	A moribund patient who is not expected to survive without the operation
ASA 6	A declared brain-dead patient whose organs are being removed for donor purposes

Reprinted from Ref. [7]

Musculoskeletal

- The presence of kyphoscoliosis or metastatic disease affecting the spine in the elderly may make central neuraxial blockade more challenging.
- Care must also be taken when positioning the patients with kyphoscoliosis on the operating table.
- Care must be taken in those patients with hip replacements when placed in lithotomy position.
- Patients unable to lie flat during the examination (due to breathlessness, cough, pain etc.) may be unsuitable for a regional anaesthesia only.

Body Mass Index (BMI)

Those with a BMI >35 are likely to have underlying medical conditions including hypertension, diabetes, hypercholesterolaemia and ischaemic heart disease [6]. They are a greater challenge both anaesthetically and surgically. Heavy patients need special arrangements in the operating room to ensure that the operating table can support extra weight. An intensive therapy unit/high dependency bed may be required for obese patients, particularly those with symptoms of obstructive sleep apnoea, such as daytime somnolence, headache on waking (CO_2 retention), or loud snoring. Anaesthetists grade the patient's overall condition according to the American Society of Anaesthesiologists (ASA) scheme shown in Table 11.2 [7]. Although the ASA scale does not correlate linearly with mortality, it is simple to apply.

Investigations

A list of potential investigations in patients undergoing surgery is listed below together with some specific indications for performing the test. The list is not exhaustive and is based on the United Kingdom's National Institute of Clinical Excellence (NICE) guidelines [8]. All Urology patients should at the minimum have a preoperative full blood count (FBC), urea and electrolytes (U&Es).

Full Blood Count

Anaemia, polycythaemia, thrombocytopaenia, leucopenia and leukocytosis should be identified.

Pre-operative anaemia (Hb <13 g/dl in men; Hb <12 g/dl in women) should be investigated and corrected as this can further increase transfusion requirements during major surgery.

Clotting Profile

Necessary in those patients who are taking anti-coagulants or have liver disease. Also to be considered in patients undergoing central neuraxial block and prior to major surgery.

Creatinine, Urea and Electrolytes

Patients taking digoxin, diuretics, steroids, and those with diabetes, hypertension and renal disease must have venous electrolytes measured and any anomalies corrected pre-operatively.

Arterial Blood Gas

It is considered in all patients with chronic respiratory disease. An arterial PaO_2 <8.0 KPa on room air has been associated with an increased risk of perioperative respiratory complications and the need for postoperative ventilatory support [9].

Liver Function Tests (LFT)

Patient with a history of hepatic disease, high alcohol intake (>50 units/week), metastatic disease, or evidence of malnutrition must have LFT's checked.

Sickle Cell Test

Sickledex® kit (Diagnostic Solutions NZ) detects the presence of Haemoglobin S. Sickledex testing should be carried out in those whose ancestry is African, Afro-Caribbean, Asian, Middle-Eastern, east Mediterranean or those who cannot provide evidence of their sickle status.

Chest X-Ray

Chest imaging is considered in those patients with a history of cardio-respiratory symptoms or diseases and those suspected of having lung metastases/lymphoma. It is not necessary to obtain chest X-ray routinely in every patient.

Electrocardiogram

It is safer to do electrocardiogram in all males >50 and females >60 years of age. It is also indicated in patients who have irregular pulse and known cardio-respiratory disease or symptoms.

Pulmonary Function Tests

Pulmonary function is assessed by spirometry, flow & volume loops and bronchodilator testing. There is no single test that predicts intra or postoperative pulmonary complications. Data from patients undergoing lung resection suggest perioperative complications increase when FEV1 <40 % predicted or <0.8 l [9–11]. Reversible airways disease is defined as 12 % improvement or increase of 0.2 l of FEV1 following bronchodilator treatment. All such patients must be optimised pre-operatively [12].

Cardiopulmonary Exercise Testing (CPET)

Cardiovascular and respiratory systems are assessed by non-invasive methods prior to major surgery. CPET is more objective and accurate in the assessment of patients than MET values. Older and colleagues demonstrated patients undergoing major surgery with an anaerobic threshold (AT) of less than 11 ml/kg/min had an increased mortality (18 %) versus those with greater than 11 ml/kg/min (0.8 %) [13, 14].

Other Cardiac Investigations

Some of the cardiac investigations including exercise and pharmacological stress testing, angiography and cardiac MRI's are better performed under the guidance of a cardiologist.

It is important to review previous anaesthetic charts and operative notes for all patients to identify any problems on previous occasions and plan the appropriate care.

Specific Pre-operative Considerations

1. *Patients who are on anticoagulants:* Patients who are on anticoagulants need appropriate perioperative management of their condition. The following issues need addressing and their management planned:

a. What is the indication for anticoagulation? What investigations are required to assess its extent?
b. How soon before surgery should the anticoagulation be discontinued? This will require liaison between surgeons and haematologists. Patients with a mechanical heart valve may need their anticoagulation changed to a heparin infusion or its low-molecular-weight heparin (LMWH) equivalent.
c. How soon after surgery should anticoagulation be reintroduced?

It is customary to discontinue Warfarin generally 3–5 days before surgery; clotting studies (international normalized ratio, INR) should be repeated preoperatively at periodic intervals. A multidisciplinary approach of the surgeon, haematologist, and anaesthetist should be adopted. Low-dose aspirin is not in itself an anaesthesia risk, although it may be stopped for surgical reasons. Newer oral anticoagulants are direct thrombin inhibitors (Dabigatran, Rivoroxaban) and should be discontinued 2–5 days before surgery.

Antiplatelet agents (Clopidogrel and Ticlopidine): Clopidogrel is, a thienopyridine derivative, that inhibits platelet aggregation by blocking ADP receptor on platelets. They are used to reduce the risk of cerebrovascular accidents, myocardial infarction, acute coronary syndrome and in patients with peripheral vascular disease. Patients with coronary stents in situ (bare metal and drug eluting stents) are placed on dual antiplatelet therapy (DAPT) for upto a year following insertion. Cardiology advice is crucial during the peri-operative period as stopping these drugs may increase the risk of in stent thrombosis and further myocardial infarction.

2. *Patients with Pacemaker*: It is important to know the indication for pacemaker insertion, the underlying cardiac condition and the type of device inserted. Pacemakers are checked anually but this should be confirmed with the patient and their cardiologist. If the testing has not been done it should be arranged. Much of this information is present on the pacemaker identification card which patients are advised to carry at all times and this too must be checked.
3. *Patients Undergoing Periodic transurethral resections of bladder Tumours/ Check Cystoscopy:* This group of patients often undergo endoscopic surgical procedures on a frequent basis. They are often aged over 60 with chronic illnesses with multi-system involvement. It is important to review all previous anaesthetic charts and perform routine tests such as FBC, creatinine, Urea and electrolytes and electrocardiogram as outlined above. Unless there has been a specific change in signs and symptoms these should only be checked on a six monthly basis, as it is inappropriate to subject patients to costly complex investigations on each occasion they require anaesthesia.
4. *Diabetes mellitus:* Globally an estimated 285 million people suffer from diabetes expected to rise to 438 million by 2030 [15]. It is a chronic disease with multi-system involvement affecting the renal, cardiovascular, nervous, respiratory and musculoskeletal systems. The purpose of anaesthetic assessment is to evaluate the extent of end-organ damage and devise a plan for diabetic control through the perioperative period. Good diabetic control is important in reducing the length of stay and the risk of wound infections.

- Minor Surgical Procedures & Day Cases
  - Omit hypoglycaemic drugs on the day of surgery
  - Continue diet and medications post-operatively
- Major Surgery & Insulin Dependent Diabetics
  - Admitted pre-operatively, perhaps a day earlier
  - Intravenous dextrose, insulin and potassium regime commenced (sliding scale)
  - Continued into the early post-operative period until the resumption of normal diet.
- Intensive Care
  - Good glycaemic control has been shown to reduce morbidity and mortality [15, 16].
  - Safety however remains an issue outside of ICU with the risk of hypoglycaemia.

5. *Renal failure*: It is not uncommon for patients with urological malignancy to have a deranged renal function due to the cancer or multi-system diseases with an effect on the kidney e.g. diabetes or hypertension. Another scenario is in patients who need removal of solitary kidney or bilateral nephrectomy. The aetiology of the renal dysfunction may be classified in to prerenal, intrarenal or postrenal (obstructive uropathy) causes.

   The signs and symptoms of renal failure may be due to:

   - **Deranged electrolytes** – especially potassium, sodium and calcium
   - **Rising creatinine**
   - **Uraemia** – to understand the severity of renal function and fluid imbalance.
   - **Acidosis** – metabolic acidosis due to acute or chronic renal failure.
   - **Fluid imbalance** – dehydration or overload
   - **Impaired drug clearance and metabolism**
   - **Anaemia** – can be acute (due to bleeding) or chronic (Reduced production of erythropoietin).

   Renal function may improve or deteriorate following surgery depending on the extent of renal dysfunction pre-operatively and the nature of the surgery. The recovery of renal function is usually delayed. In patients undergoing nephrectomy it is important to assess the function of both kidneys prior to surgery by means of radioisotope renography in order to help determine. This is discussed in length in the chapter on renal medicine and urological cancers (Chap. 9).

6. *Paraneoplastic Syndrome*: The paraneoplastic syndrome is a collection of symptoms and signs that arise from the production of hormones by cancerous cells remote from the primary tumour. They can also be triggered by an abnormal immune reaction to neoplasia. The type of ectopic hormones/cytokines potentially released by cancerous cells includes erythropoietin, parathyroid hormones, adrenocorticotropin, renin and insulin. It is estimated between 10 and 40 % of renal cell carcinoma patients have the paraneoplastic syndrome [17]. Symptoms

and signs may be generalised (e.g. fever, malaise, cachexia) or related to a specific metabolic or biochemical abnormality. The effects can be wide-ranging for example hypertension, polycythaemia, hypercalcemia, liver dysfunction and amyloidosis. It is important to identify such syndromes pre-operatively and correct any biochemical and physiological anomalies.

7. *Chemotherapy and radiotherapy*: There are a number of different chemotherapy agents that may have been employed prior to surgery as a primary or neoadjuvant treatment. The aim of this treatment is to reduce the tumour size in order to improve the chance of a curative resection. The chemotherapy agents can cause long-term side effects as a result of damage to healthy cells of respiratory, cardiovascular, renal, hepatic, nervous, gastrointestinal (GI), and haemopoietic systems. For example Bleomycin used in the treatment of testicular cancer may lead to pulmonary fibrosis, which can potentially be aggravated by administration of high concentration oxygen.

Radiotherapy may have been administered externally or in the case of prostate cancer internally through brachytherapy. This may cause localised fibrosis leading to difficult and lengthy surgery with increased blood loss.

Intra-operative Management

Options for Anaesthesia

There are four options for the provision of anaesthesia in patients with genitourinary cancer undergoing surgery. These include local, general, regional and a combination of general and regional techniques. The exact choice depends on both patient and surgical factors.

Local Anaesthesia

Some procedures for example preputial biopsy or circumcision can be carried out under local anaesthesia with tissue infiltration. It is desirable to use plain anaesthetic agent in the region of testis and penis. This is useful in those selected patients incapable of having a general anaesthetic for medical reasons. All require intravenous access, routine monitoring and a fully equipped resuscitation trolley (including defibrillator) in the event of accidental intravenous injection. Knowledge is also required of the following:

- Maximum safe dose of local anaesthetic with and without adrenaline:
  - Lignocaine: 3 mg/kg (7 mg/kg with adrenaline)
  - Bupivacaine 2 mg/kg with or without adrenaline
- Signs and symptoms of local anaesthetic toxicity
  - CNS: Dizziness, confusion, circumoral tingling, seizures & coma
  - CVS: Tachy and bradyarrhythmias and cardiac arrest

Table 11.3 Peripheral regional anaesthetic techniques

Nerve block	Comments
Paravertebral blocks (PVB):	Useful for renal and ureteric surgery
Genito-femoral nerve block (L1, L2)	Useful for surgery on the scrotum and testis
Ilio-inguinal & ilio-hypogastric nerve block (L1)	Suitable for testicular, scrotal and hydrocoele surgery
Transversus abdominal plane (TAP) block	The anterior rami of the spinal nerves T10-L1. The technique is performed under ultrasound guidance to improve efficacy. Bilateral blocks are useful for providing analgesia during and after laparoscopic surgery

General Anaesthesia

For a great majority of cases general anaesthesia is the technique of choice. Examples include intra-abdominal or pelvic surgery, any procedures greater than 2 h duration or patients needing to be placed in uncomfortable positions on the operating table such as steep Trendelenburg or the lateral table break position for nephrectomy. Anaesthesia can be maintained using either inhalational or intravenous agents. An important consideration during general anaesthesia is management of the airway. In general two options exist:

- Laryngeal Mask Airway (LMA)
  This supraglottic airway device is useful for endoscopic procedures or body surface surgery (for example scrotal surgery) when there is no history of gastric reflux and duration of surgery is less than 2 h. The patient can be spontaneously breathing or mechanically ventilated.
- Endotracheal Tube (ET)
  Suitable for cases greater than 2 h duration, in patients with a history of reflux and intra-abdominal or pelvic surgery where muscle relaxation is required to facilitate surgical access to the genitourinary tract.

Regional Anaesthesia

Surgeons and anaesthetists can perform a variety of blocks. Most are done in order to provide analgesia intra and postoperatively rather than as a sole anaesthetic technique (Table 11.3).

Because of the risk of rare but potentially debilitating side effects all patients must be consented in full by an anaesthetist trained in performing these techniques during pre-assessment. Epidurals tend to be commonly used during major abdominal and pelvic surgery as it provides analgesia that can be extended into the post-operative period through the placement of an indwelling epidural catheter. They are discussed in more detail below under post-operative care.

The "single shot" spinal anaesthetic involves inserting a small ($\leq$24 G) atraumatic spinal needle under sterile conditions into the intrathecal space. To minimise the risk of spinal cord injury spinal anaesthesia is never performed above the L2/L3

level in the adult. Rostral spread of local anaesthesia above T4 can result in "high spinal anaesthesia". This requires immediate management with mechanical ventilation, support of the cardiovascular system and sedation for a few hours until the effects wear off. Spinal anaesthesia has a 5–10 % failure rate. In the event this occurs it can be re-attempted or converted to general anaesthesia.

General and Regional Anaesthesia

Most patients undergoing major surgery will have a combination of the above general and regional anaesthetic techniques.

General Principles of Management for Patients Undergoing Anaesthesia

Regardless which anaesthetic technique is chosen the following factors must be considered:

Fasting

All patients should be given oral and written fasting instructions during pre-assessment clinic. There should be nothing consumed up to 6 h prior to surgery and clear fluids up to 2 h prior to surgery. Fasting patients before surgery minimises the risk of aspiration pneumonia. Clear fluid is defined as fluid through which newspaper print can be read. Chewing gum appears to have a variable effect on gastric secretions and pH, but to prevent confusion and complications it should be avoided for 6 h before surgery.

Most routine medications including anti-hypertensives can be continued. Some anaesthetists prefer stopping ACE inhibitors prior to major surgery however this depends on the underlying left ventricular function. All anti-rejection transplant medications should be continued. Anti-coagulants such as warfarin need to be stopped 5 days prior to surgery with low molecular weight heparins being used as a bridge prior to surgery (LMWH). Mention has already been made on anti-platelet drugs such as aspirin and Clopidogrel, which require up to 7 days to stop exerting their clinical effects.

Monitoring

In accordance with Association of Anaesthetists of Great Britain and Ireland (AAGBI) guidelines patients undergoing anaesthesia must have the minimum standard of monitoring consisting of ECG, pulse oximetry, carbon dioxide and non-invasive blood pressure [18]. The reasons for this are a variety of factors both anaesthetic and surgical can cause profound physiological de-arrangement affecting

the respiratory and cardiovascular systems. These need monitoring and correcting from induction of anaesthesia until the patient is fully recovered.

Patients undergoing major urological surgery such as radical nephrectomy or retroperitoneal lymph node dissection will additionally require invasive monitoring including arterial and central venous pressure monitoring (with an internal jugular multilumen central venous catheter). Recently NICE (UK) has recommended non-invasive cardiac output monitoring using the oesophageal Doppler for major surgery [19]. These devices contain a piezoelectric crystal that emits ultrasound and relies on the Doppler principle to measure the velocity of red cells in the descending aorta. Making certain assumptions based on patient height and weight the cardiac output, stroke volume and flow time can be calculated. It can be used intra-operatively in order to guide fluid and inotrope therapy in a real time dynamic manner. Core body temperature should also be monitored in elderly patients and those undergoing procedures for greater than 2 h. Bi spectral index (BIS) should be used for major cases in order to titrate the amount of anaesthesia needed and reduce the risk of patient awareness.

Positioning

A variety of different positions are employed in genito-urinary surgery to facilitate surgical access. Most patients are positioned on the operating table whilst anaesthetised. Great care must be taken to prevent injury (limbs, nerves, joints) and displacement of lines and the airway during this process. Patients with limited physiological reserve must be discussed with an anaesthetist as some of the positions employed have adverse physiological effects and in the event a patient becomes unstable surgery may need to be abandoned.

Trendelenburg Position

This position is mostly used for procedures in the pelvis such as robotically assisted laparoscopic prostatectomy. It is a steep head down position (15–45°) with knees flexed over the broken end of the table. The abdominal viscera move upward compressing the lungs reducing functional residual capacity (FRC) and increasing atelectasis and hypoxaemia. Venous engorgement of the head and neck may result in a raised intracranial, intraocular pressure and laryngeal oedema. Retinal detachment with loss of vision can also occur. The risk of regurgitation is increased and brachial plexus injury can occur if shoulder supports are used.

Lithotomy

The lithotomy position is widely used for endoscopic procedures of the prostate and bladder. In addition to the effects described above injuries can occur to the lower back, hips and knees. Hyperextension injury has been described to the sciatic nerve whilst common peroneal and saphenous nerves can become compressed against lithotomy poles.

Lateral

This is the position used for renal surgery. The dependent lungs receive a preferential supply of blood flow whilst the lungs upper most are better ventilated. This results in a V/Q mismatch and potential for hypoxaemia. Care must be taken with lower most limbs to reduce the risk of compression and damage.

Maintenance of Normal Body Temperature

Peri-operative hypothermia (core temperature <36 °C) is associated with a multitude of adverse effects. These include coagulopathy, increased rates of wound infections, arrhythmias and heightened pain/anxiety [20]. The human body loses heat by means of conduction, convection, evaporation and radiation. These effects are more pronounced under anaesthesia as the normal thermoregulatory control centre and its responses (for example shivering) become depressed. The elderly and very young are particularly prone to heat loss. Methods used to minimise hypothermia include using warmed intravenous and irrigation fluid, forced warm air blankets, warming mattresses and raising the ambient temperature/humidity. Core temperature can be measured at the ear, nose or rectum.

Antibiotic Prophylaxis

Appropriate anti-microbial prophylaxis should be commenced prior to skin incision. The agents given will vary according to nature of the surgery, renal function, previous positive cultures and known local pathogens together with knowledge of their antibiotic resistance.

Management of Major Haemorrhage

Major resection of urological cancer has the potential for significant haemorrhage. Severity of blood loss is variable and is related to the tumour size, its proximity to major blood vessels and overall general condition of the patient. Small to moderate volume blood losses (<1L) may not need any active intervention in presence of normal haemoglobin levels. The Association of Anaesthetists of Great Britain and Ireland (2010) has published a guideline entitled “Blood Transfusion and the Anaesthetist: Management of Massive Hemorrhage” [21] [Table 11.4].

The guideline addresses the management of blood loss exceeding 1.0L. In this situation a coordinated response to massive blood loss is required including surgical control of the haemorrhage while the anaesthetist resuscitates the patient with fluid and blood products. Prompt and preplanned clinical, laboratory and logistical approach is key to a successful outcome.

For optimal management of anticipated major haemorrhage, two large bore venous access sites together with central venous catheterisation and invasive arterial blood pressure monitoring are needed. A Rapid infuser kit should be readily available.

Table 11.4 Outlines the principles involved in the management of massive haemorrhage as described in the guidelines

1. Hospitals must have a major haemorrhage protocol in place and this should include clinical, laboratory and logistic responses
2. Immediate control of obvious bleeding is of paramount importance (pressure, tourniquet, haemostatic dressings)
3. The major haemorrhage protocol must be mobilised immediately when a massive haemorrhage situation is declared
4. A fibrinogen <1 $g \cdot l^{-1}$ or a prothrombin time (PT) and activated partial thromboplastin time (aPTT) of >1.5 times normal represents established haemostatic failure and is predictive of microvascular bleeding. Early infusion of fresh frozen plasma (FFP; 15 $ml \cdot kg^{-1}$) should be used to prevent this occurring if a senior clinician anticipates a massive haemorrhage
5. Established coagulopathy will require more than 15 $ml \cdot kg^{-1}$ of FFP to correct. The most effective way to achieve fibrinogen replacement rapidly is by giving fibrinogen concentrate or cryoprecipitate if fibrinogen is unavailable
6. 1:1:1 red cell:FFP:platelet regimens, as used by the military, are reserved for the most severely traumatised patients
7. A minimum target platelet count of $75 \times 10^9 \cdot l^{-1}$ is appropriate in this clinical situation
8. Group-specific blood can be issued without performing an antibody screen because patients will have minimal circulating antibodies. O negative blood should only be used if blood is needed immediately
9. In hospitals where the need to treat massive haemorrhage is frequent, the use of locally developed shock packs may be helpful
10. Standard venous thromboprophylaxis should be commenced as soon as possible after haemostasis has been secured as patients develop a prothrombotic state following massive haemorrhage

Modified from Thomas et al. [21]. With permission from John Wiley & Sons, Inc

Hypothermia, hypocalcaemia and academia should be avoided. In 2008 National Institute for Health and Clinical Excellence (NICE, UK) approved the use of intraoperative cell salvage during radical prostatectomy and radical cystectomy [22]. The leukofilters must be used to prevent cancer recurrence. According to NICE there is no reported evidence of the potential theoretical risk of re-infusing viable malignant cells leading to metastases.

Intraoperative Pain Management

The regional anaesthetic techniques described above can provide good analgesia intraoperatively. In the event that such techniques are contra-indicated or not technically possible then a variety of other options including opioid and non-opioid analgesia are available. These are discussed in more detail below under post-operative pain relief.

Remifentanil is a potent, ultrashort acting synthetic opioid that has become extremely popular for major surgical cases due to its short half life (3–8 min) that is independent of the duration of infusion. Unlike other opiates, remifentanil is metabolised by plasma esterase that is present in abundant supply and does not exhibit saturation kinetics. It is administered using a specialised target controlled infusion

Table 11.5 Physiological effects and complications of pneumoperitoneum in the Trendelenburg position

Cardiovascular system	Increased systemic vascular resistance
	Increased mean arterial pressure
	Increased O_2 consumption of myocardium
	Reduced splanchnic, portal and renal blood flow
	Reduced venous return due to IVC compression
	Arrhythmias due to hypercarbia
Respiratory system	Diaphragmatic splinting
	Reduced vital and functional residual capacity
	Reduced compliance
	Increased ventilation-perfusion mismatch
	Increased peak airway pressure – possibility of pneumothorax
	Hypercarbia & respiratory acidosis
	Pulmonary congestion & oedema; atelectasis and hypoxaemia
Central and peripheral nervous system	Increased intracranial pressure
	Increased cerebral blood flow
	Increased intraocular pressure
	Neuropraxia
Endocrine system	Increased catecholamine release
	Renin activation
Miscellaneous	Increased intragastric pressures & regurgitation
	CO_2 and gas embolism

Modified from Irvine and Patil [23]. With permission from Oxford University Press

(TCI) pump that requires knowledge of the patient's height, weight, gender and age to calculate the effect site concentration of the drug. Analgesia can be rapidly titrated according to the degree of surgical stimulation intra-operatively. One disadvantage however is that once discontinued the analgesic effect rapidly wears off. Thus alternate analgesia must be commenced at least 30 min prior to the end of surgery so patients can awake in comfort.

Surgery Specific Considerations

Laparoscopic and Robotic Surgery

Laparoscopic techniques are increasingly common with improved technology, faster recovery and less demand on high dependency care. Insufflation of carbon dioxide into the peritoneum allows visualisation of abdominal viscera; however it can have profound physiological effects outlined below. The effects are exacerbated by the steep Trendelenburg position, a position used for the most commonly performed procedure of radical prostatectomy [23]. The effects are summarised in Table 11.5.

Where possible the insufflation pressures should be minimised and kept below 20 cm H_20. Patients with poor exercise tolerance and cardiorespiratory disease may not tolerate these physiological changes and alternate surgical options must be considered.

Renal Surgery

Nephrectomy (radical and simple) and partial nephrectomy can be performed using an open or laparoscopic technique. The laparoscopic technique is preferred as it is associated with less pain, blood loss and faster postoperative recovery. In either case general anaesthesia with endotracheal intubation is performed. These tumours tend to be very vascular making the potential for blood loss high. The majority patients will therefore require multiple large bore IV access with invasive monitoring including arterial and central venous monitoring. The presence of a large thrombus within the renal vein and vena cava greatly complicates surgery. Large number of packed cell transfusions maybe required together with platelets and clotting products in these cases. Cardiopulmonary bypass may be required if the thrombus extends up to the right atrium. Embolisation of the tumour can have catastrophic consequences with arrhythmias, hypoxaemia and hypotension.

The patient is positioned according to which surgical approach is taken however the lateral decubitus with lateral table break is often performed. Care is taken in order to support pressure points and to avoid brachial plexus and other nerve injuries.

The options for peri-operative analgesia depend on whether an open or laparoscopic approach is employed. For the open approach an epidural should be considered. Other techniques include intra-pleural block, paravertebral block, transversus abdominis plane (TAP) blocks and local anaesthetic infiltration within the surgical wound. Opiate patient controlled analgesia (PCA) can also be used.

Cystoscopies and Check Cystoscopies for Bladder (Urothelial) Cancer

Bladder carcinoma most commonly occurs in fifth and sixth decades of life and is associated with a history of smoking [24]. As a consequence patients will often have significant co-morbidity such as ischaemic heart disease and chronic obstructive airways disease. Renal failure is present in patients who have obstruction of the urinary tract or part of chronic diseases with systemic involvement. All tumours are resected transurethrally (TURBT) for diagnostic purposes under general or regional anaesthesia. Patients with low grade disease periodically attend for surveillance (check cystoscopies). They are placed in the lithotomy position that can result in injury and cause adverse physiological changes discussed above. In addition the absorption of irrigation fluid during the resection may induce fluid overload, hyponatremia and other electrolyte imbalance collectively known as the transurethral resection (TUR) syndrome. Regional anaesthesia is advantageous in that it allows early detection and this condition that manifests itself initially as headache, restlessness, confusion and dyspnoea. Other procedures for urothelial cancer include ureteroscopy, laser ablation and stenting.

Cystectomy or radical cystectomy is required for more invasive bladder tumours or as part of treatment or palliative surgery to alleviate distressing symptoms like bleeding, pain, dysuria, or bowel obstruction. Again this could be a robot-assisted laparoscopic technique, or by stand-alone laparoscopy or by open method. These are extensive major surgical procedures that often involve pelvic lymph node dissection, removal of other pelvic organs (e.g. uterus, ovaries or rectum) and establishing urine drainage by conduit or by reservoir reconstruction. The procedure may require more than 4–6 h of operating time and involve large blood loss, significant fluid shifts, hypothermia and cause significant postoperative pain. In addition to cystectomy urinary diversion procedures like conduit or reservoir reconstruction are done in the second part of the operation. These procedures are carried out under general anaesthesia with an endotracheal tube and profound muscle relaxation. Central neuraxial blockade (CNB) is useful in providing intra and postoperative analgesia. One disadvantage of CNB however is that the unopposed parasympathetic activity (as a consequence of sympathetic blockade) can result in a contracted, hyperactive bowel that makes construction of a continent ileal reservoir more challenging. Intravenous papaverine or the anticholinergic drug glycopyrrolate may help alleviate this issue. All patients should have wide bore intravenous access and consideration must be given to invasive pressure monitoring. Cardiac output monitoring with oesophageal Doppler is also advised. Post-operative care should be in an intensive care unit for the first 24 h.

Prostate Cancer

Prostate cancer is the commonest urological cancer in men whose incidence increases with age. Due to the spectrum in clinical behaviour of the disease a broad range of treatment options are available both surgical and non surgical. Surgical management can be divided into open versus laparoscopic prostatectomy.

Laparoscopic and Robotic Prostatectomy

Robotically assisted laparoscopic prostatectomy (RALP) is increasingly the preferred option for prostate surgery. The procedure requires a prolonged period of Trendelenburg together with pneumoperitoneum, which has been discussed earlier in this chapter. This precludes patients with significant cardiorespiratory pathology in whom a standard open procedure or non-surgical treatment should be considered (Table 11.5). It is conducted under general anaesthesia with endotracheal intubation. The patients head must be kept in neutral alignment and the endotracheal tube taped not tied around the neck. Large bore intravenous access is obtained whilst invasive monitoring is not mandatory unless patients have a history of cardiorespiratory disease. The patient must be carefully positioned in order to reduce the risk of undue amounts of pressure on the elbows, back, axilla and shoulders. The arms are wrapped alongside the patient whom must remain completely stationary once in position until the robot is undocked at the end of the procedure. Care must be taken

to protect the face and eyes due to the risk of regurgitation of gastric contents. A remifentanil infusion is a useful method of providing intra-operative analgesia. Patients are usually kept euvolaemic until the urethra is anastomosed to the bladder neck at which point liberal use of intravenous fluid is recommended in order to minimise clot retention and urinary obstruction. Post-operatively useful methods of analgesia include TAP blocks, PCA and non opioid analgesics such as paracetamol. The majority of patients can be managed on a surgical ward and can be discharged home 24 h after the surgery [25].

Retropubic (Open) Radical (RRP) and Perineal Radical Prostatectomy (PRP)

RRP is becoming less frequent due to the advancement in prostate cancer treatment and the use of less invasive surgical techniques. The procedure may involve performing the procedure in the extended lithotomy position. The preparation and monitoring are similar to major cystectomy surgery but the approach is retropubic and preperitoneal. All cases are conducted under general anaesthesia with endotracheal intubation. Invasive arterial monitoring is recommended as it allows controlled hypotension during surgery to minimise blood loss. Major haemorrhage is a possibility and up to 2,000 ml of blood could be lost. Patients should be kept normothermic. Post-operative care involves good analgesia using an epidural and the need for intensive care. Another procedure worth mentioning is perineal radical prostatectomy, which is still carried out in some centres [26]. There are reports of perineal prostatectomy being done under spinal/epidural anaesthetic for minimising the cost and morbidity reasons [27].

Testicular Cancer

Orchidectomy

Radical inguinal orchidectomy is a relatively straightforward procedure and can be performed under regional (spinal/epidural) or general anaesthesia with peripheral analgesic nerve block (ilio-inguinal/ilio-hypogastric block). The surgery is increasingly performed as a day case procedure. Most of these patients opt for insertion of prosthesis so antibiotic prophylaxis is necessary.

Retroperitoneal Lymph Node Dissection (RPLND)

These procedures can be done using an open abdominal technique with a mid-line incision or rarely by thoraco-abdominal approach. Alternately for less bulky lymph node disease a laparoscopic or robotic approach can be considered. All cases are done under general anaesthesia with endotracheal intubation. Multiple large bore intravenous access must be obtained together with invasive arterial and central venous monitoring due to the risk of major haemorrhage. Patients are positioned either supine or in the lateral table break position. Chemotherapeutic agents

Table 11.6 Levels of care

Level	Criteria	Examples
Level 0	Normal ward care in an acute hospital	Intravenous therapy, 4 h observations
Level 1	Patients recently discharged from a higher level of care	4 h Observations, O_2 therapy, Epidural, risk of pneumonia, diabetics with IV insulin, bolus IV drugs, Controlled analgesia, intermittent renal support
Level 2	Care for a single organ failure or step down from a highest level of care or needing extended care	Immediate care, unstable patients, risk of deterioration, respiratory support;
Level 3	Advanced respiratory support of two organ systems and including all complex patients with multiorgan failure	Invasive mechanical ventilator support, Bi-level positive airway pressure Extracorporeal respiratory support

Modified from Intensive Care Society [28]

commonly used pre-operatively include cisplatin and bleomycin. The latter can cause pulmonary fibrosis and care must be taken not to use high-inspired oxygen contraction or excessive amount of fluids intra-operatively as this can result in post-operative pulmonary insufficiency. Postoperative pain can be severe and the options for pain management include epidural analgesia, opioid PCA or bilateral TAP blocks. Damage to the intercostals arteries during left sided dissections can rarely compromise the blood supply to the lower half of the spinal cord (artery of Adamkiewicz). It is important to document normal motor and sensory function following central neuraxial blocks for this procedure.

Post-operative Care

Prior to surgery an important decision must be made regarding the requirement for high dependency care (level 2) or intensive care (level 3) post operatively (Table 11.6) [28]. Some factors that may influence this important decision include the magnitude of surgery, anticipated blood loss and patient co-morbidities. A close discussion is required between the operating surgeon, anaesthetist and intensive care unit

In the United Kingdom it is estimated that there are a total of 1,486 level 2 and 3 beds for both medical and surgical patients [29]. Given there is an estimated four million surgical procedures carried out in the UK per annum it is not unsurprising there is an immense pressure on intensive care resources [30]. All patients with medical co-morbidity and patients undergoing high-risk surgery (e.g. major resection with a large anticipated blood loss) must be discussed with the intensive care at the earliest opportunity to ensure a bed can be booked electively.

Where patients are cared for in a ward environment the surgical team need to closely monitor patients recording heart rate, blood pressure, respiratory rate, temperature, oxygen saturation and conscious level regularly following surgery. Collectively these can be used to determine the patient at risk score (PAR). Any physiological derangements must be reported early in order to identify critically ill patients.

Critical care outreach teams consisting of specialist intensive care nurses play an invaluable role in patient management and education/training of ward-based staff in identifying critically ill patients. When the PAR score exceeds 5 or any variable is greater than 3 the critical care outreach team should be consulted. Where such a service does not exist in an institution good communication between surgical, anaesthetic and nursing staff is essential to ensure patient safety and high quality care [31].

Analgesia

Excellent pain control is essential in enhancing patient experience and minimising the psychological distress associated with surgery. It allows early ambulation thereby reducing the risk of thrombo-embolic and pulmonary complications. These in turn have economic benefits resulting in shorter inpatient stay and reducing re-admission rates due to pain. Under treatment of acute postoperative pain is also a risk factor in the development chronic pain syndromes that can have a negative impact on long-term patient well-being. On the other hand pain management techniques are not devoid of side effects including cardio-respiratory depression, sedation, pruritus, nausea, vomiting and impaired bowel function.

Successful pain management begins in the pre-assessment clinic where a directed pain history and physical examination is performed. Here patient and surgical factors are identified that will impact on the pain management techniques used. Patient factors include age, co-existing cardio-respiratory, renal and hepatic disease. It is important to take a history of medications patients are taking for example patients on anticoagulants may be precluded from central neuraxial blockade. A note must be made of any drug allergies in particular to local anaesthetics or any analgesia. Important surgical factors include the site and magnitude of surgery together with expected severity of pain. These are then used to calculate a risk/benefit ratio for the different techniques available and combined with patient's own experience a pain management plan is formulated. The pre-assessment clinic presents a unique opportunity to educate both patient and family regarding the importance of their role in achieving comfort and reporting pain. Sophisticated techniques such as patient controlled analgesia (PCA) or Epidural analgesia can be explained.

As part of the preparation any existing analgesia that is being taken should be continued in order to reduce the risk of abstinence syndrome. A consideration must be also be given to administering analgesia pre-emptively as pre-medication in order to better control post-operative pain.

A multitude of options exist for the provision of analgesia. Broadly they can be categorised as follows:

1. Non-Opioid Analgesics
2. Opioid Analgesics
3. Central Neural Blockade
4. Peripheral Regional Analgesic Techniques
5. Non-Pharmacological Techniques

Multimodal techniques involve administering two or more drugs that act by different mechanisms in order to provide analgesia. Unless contraindicated patients should receive combinations of the above analgesic techniques in order to maximise efficacy and reduce the possibility of side effects.

Non-opioid Analgesia

These should be considered for patients with mild to moderate pain and as part of a multimodal regime in those with severe pain. It includes a wide range of drugs with differing mechanisms. Unless contra-indicated all patients should receive around the clock regime of Acetaminophen. Non-steroidal anti-inflammatory drugs (NSAID's) and selective cyclooxygenase (COX) inhibitors should be considered in those patients with no contra-indications and in short courses only due to their potential to cause renal impairment, gastro-intestinal and anti-platelet effect. The calcium channel antagonists (Gabapentin, Pregabalin) and Ketamine can be considered in those patients in whose pain control maybe more challenging to manage.

Opioid Analgesics

Opioids are powerful analgesic drugs used in the management of moderate to severe post-operative pain. Caution must be used in those with renal impairment as most are metabolised in the liver and excreted by the kidney. They can be administered by a variety of routes. Oral administration is reserved for a day case setting (Table 11.7).

Intramuscular and sub-cutaneous administration is avoided due to erratic absorption leading to unpredictable plasma concentrations (leading to patient dissatisfaction and side effects). Inpatients can be given opiates intravenously by means of patient controlled analgesia (PCA) (Table 11.8). The dose, interval between doses

Table 11.7 Oral opioids

Opioid	Half life (h)	Duration (h)	Dose interval (h)	Dose (mg)
Codeine	3	3–4	4	30–60
Oxycodone	2–3	3–6	6	5–10
Tramadol	6–7	3–6	4–6	50–100
Dihydrocodeine	4	6	6	30–60

Table 11.8 Opioids commonly used in patient controlled analgesia (PCA)

Opioid	Bolus dose	Lockout (min)	Infusion rate – (not recommended unless on ITU)
Morphine sulphate	1–3 mg	5–15	0–3 mg/h
Fentanyl	10–20 mcg	10–20	0–50 mcg/h
Oxycodone	1–2 mg	5–10	0–2 mg/h

(lock-out period) and maximum dose in a given timeframe are programmed. When first initiated a loading dose is typically given in order to reach the minimum effective analgesic concentration (MEAC).

Patients can thereafter administer their own analgesia by means of a button they press. They are therefore unsuitable with those with physical handicap e.g. the patient with rheumatoid affecting the hands or those with limited comprehension on how to self-administer the analgesia. Studies however have shown superior analgesia, patient satisfaction and lower side effects when opiates are given via PCA. If the patient is in a monitored environment such as the post-anaesthesia recovery unit or intensive care a background infusion can be considered following major surgery. Opiates can also be given in the epidural or sub-arachnoid space and this is considered further below. In general it is good practice to avoid administering opioids by different routes simultaneously as it can lead to side effects associated with unpredictable plasma concentrations.

Central Neural Blockade

The contraindications to performing epidural anaesthesia have already been described. All patients must have informed consent prior to conducting these procedures. Under aseptic conditions a small catheter can be inserted into the epidural space in order to allow the continuous administration of local anaesthetic/opioid mixture. This can provide analgesia for up to 5 days following surgery. As the dura is not breached epidurals can be sited at any vertebral level although the site of insertion must coincide with the operative site. Thus for a mid-line incision from T6 to the pubis, a thoracic epidural between the seventh and eighth thoracic vertebrae is the most appropriate. All epidurals must be clearly labelled to minimise the risk of accidental injection of intravenous drugs into the epidural space. Patients with epidurals must be closely monitored on wards by suitably trained staff with daily review by the acute pain team to detect any complication and assess efficacy of analgesia.

The most serious complications associated with epidurals include dural punctures (0.01 %) and spinal cord/nerve root injuries (0.03–0.1 %) [32]. Dural punctures are characterised by fronto-occipital headaches with a postural element being worse on sitting. Patients may display the signs of meningism and it is important to contact the duty anaesthetist so that infection can be excluded. Most are managed with bed rest, hydration, stool softener and analgesia. Occasionally the tear in the dura may need to be closed by means of an epidural blood patch done by an experienced anaesthetist. Other complications include incomplete/unilateral or patchy sensory block and the anaesthetist can manage these by manipulating the position of the catheter under aseptic conditions. If this fails analgesia can be changed to a PCA. Puritis is also common.

Vertebral canal haematomas (VCH) are a rare but serious complication associated with neuraxial blocks. In Europe the incidence is estimated to be 1 in 2.5 million blocks, associated with DVT prophylaxis, disordered coagulation and technical difficulty in needle or catheter placement [33]. In relation to DVT prophylaxis clear policy must exist within hospitals regarding timing of insertion and removal of epidural catheters. In Europe, guidelines are no catheter must be inserted or removed

within 12 h of DVT prophylaxis [33]. NSAIDs such as aspirin, sodium diclofenac and ibuprofen do not increase the risk of VCH however patients on dual anti-platelet therapy for coronary stents must be referred to an anaesthetist for further assessment. Any patients with de-arranged coagulation or requiring anti-coagulation must also be discussed and management plan formulated.

Meta-analysis of randomised controlled trials demonstrates improved pain scores and patient satisfaction when epidural local anaesthetic/opioid is used for major surgery [34, 35]. Other benefits include improved circulation to the lower limbs, reduced risk of DVT and fewer pulmonary complications. Analysis of retrospective clinical studies suggests another possible potentially important benefit of neuraxial block is a reduction in the recurrence of several types of cancer. In one study it was found patients undergoing open prostatectomy with epidural analgesia had a substantially less risk of biochemical cancer recurrence then those managed using other analgesic techniques [36]. The mechanism behind this is unclear however has been related to the fact that epidurals can alter the neuroendocrine stress response in patients undergoing major surgery. This is the subject of intense scientific debate and a large randomised controlled clinical investigation is required that will prove or disprove this hypothesis.

Peripheral Regional Analgesic Techniques

This encompasses a broad range of blocks discussed above. They are usually performed as a single procedure pre-operatively however catheters can be left in situ to allow prolonged blockade in the post-operative period. Meta-analysis of RCTs reveals reduced analgesic consumption and reduced reported pain scores when used as part of a multi-modal pain management strategy [37]. They are particularly useful when central neuraxial block is be contraindicated.

Non-pharmacological Techniques

Patient education involves providing patients and family both oral and written information about pain, pain assessment and different methods used to treat pain following major surgery. It can help reduce patient anxiety, address any misconceptions regarding potential addiction to pain killers and generally improve compliance to treatment. Acupuncture, transcutaneous electrical nerve stimulation (TENS) and cognitive behavioural therapy such as cognitive distraction and relaxation therapy are also useful tools in the management of pain.

Other Considerations for Effective Patient Analgesia

In order for any pain management therapy to be successful it is important patients are continually assessed by means or regularly recorded pain scores. In this manner the efficacy of therapy can be evaluated and other options for pain relief considered if necessary. Hospital personnel need to be knowledgeable and skilled with regard to

the effective and safe use of all the treatment options available within an institution. A dedicated 24-h acute pain service must exist within all institutions as part of which anaesthetists play a key role. The acute pain service should be involved in assessing all patients following major surgery and addressing any pain issues. The pain service also plays an integral role in the training and education of all hospital staff.

Venous Thrombo-Embolism (VTE) and Pulmonary Embolism (PE) Prophylaxis

Patients with genito-urinary cancer having undergone surgery are at a high risk (15–30 %) of venous thromboembolism (VTE) and pulmonary embolism [38]. VTE and PE are associated with considerable morbidity and mortality. A recent US survey showed urology patients are less likely to receive VTE prophylaxis compared with patients undergoing general surgery [39]. All patients must be assessed and considered for VTE prophylaxis. Simple measures in the pre-operative period include appropriately sized graduated compression stockings (GCS) and administration of unfractionated heparin (UH) or a low molecular weight heparin (LMWH). Caution must be taken in those in whom central neuraxial block is planned allowing at least 12 h after administration of LMWH before the block. Intra-operatively both GCS and intermittent pneumatic compression (IPC) stockings applied to the calves should be used. Post-operatively a combination of mechanical and pharmacological thromboprophylaxis should be continued. At least 12 h must be allowed to pass and patients must have demonstrable normal clotting profile before epidural catheters are removed.

Antibiotics

Anti-microbial prophylaxis commenced within 60 min of skin incision should usually be discontinued within 24 h in clean uncontaminated wounds.

Oxygen

Following general anaesthesia all patients require oxygen until conscious and fully awake. In the case of patients undergoing major abdomino-pelvic surgery up to 40 % can become hypoxaemic on the second and third post operative night [40, 41]. By this time most have returned to the ward. Certain groups of patients are particularly venerable to hypoxaemia. These include those with ischaemic heart disease, those on PCA's or epidurals, smokers and the elderly. Hypoxaemia can result in myocardial ischaemia and peri-operative myocardial infarction. It is therefore recommended all patients undergoing major surgery receive humidified oxygen administered using a facemask or nasal cannulae for up to 3 days post-operatively. This

Table 11.9 Management of patient medication in the peri-operative period

Medication	Indication for use	Perioperative management
Angiotensin converting enzyme inhibitors	Hypertension	Check serum electrolytes
	Heart failure	Omit 24 h pre-op if good underlying left ventricular function
Warfarin	Many e.g. atrial fibrillation (AF), prosthetic heart valve	Check INR; fresh frozen platelets if INR >1.6: may need bridging
		Anticoagulation
Anti-platelet drugs	Many e.g. AF, TIA, CVA	If stents present seek advice from cardiologist/ anaesthetist
	Post coronary stent	7 days needed to reverse effects
Beta blockers	Many e.g. hypertension	Continue in patients with long term use
		Do not start new therapy unless patient high risk
		In high risk patients, treat for 2–4 weeks & titrate heart rate 60–80 bpm
Alpha blockers	Hypertension; benign prostatic hypertrophy	Consider omitting 24 h pre-operatively if regional planned
Diuretics	Many e.g. hypertension, heart failure, renal impairment	Identify reason for use
		Check electrolytes & correct imbalance

should be combined with deep breathing exercises and chest physiotherapy to prevent lung atelectasis and pneumonia.

Management of Drugs Regularly Taken by the Patients

As most of the patients take medications for a variety of associated conditions it important to start these medications as soon as patients are stabilized postoperatively. A summary of such medications is given in Table 11.9.

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Chapter 12
Laparoscopy and Robotic-Assisted Laparoscopy in Uro-oncological Surgery

Lukas Lusuardi and Günter Janetschek

The use of laparoscopic surgery has rapidly progressed over the past several years and with newer innovations such as single port techniques and robotics the oncological surgery is becoming more sophisticated with generally better outcomes and faster recovery rates for patients. The surgeons have to be well trained simultaneously in surgical skills and laparoscopic techniques in order to safely perform a multitude of laparoscopic urological procedures. In addition to the state-of-the-art equipment and surgical expertise, laparoscopic procedures are technically demanding and require coordination between well-trained operating anesthetic and perioperative care teams. In the debate of laparoscopic versus open abdominal surgery, there is a clear advantage in terms of quality of life outcomes, of laparoscopy demonstrated in comparable cases when validated with 'health-status instrument' [1]. However open procedures are still required in selected urological cases so therefore both techniques go hand in hand for achieving good oncological results.

It is our goal in this chapter to summarize the role of laparoscopic surgery in the management urologic malignancies and to analyze the oncological outcomes.

Prostate Cancer

In 1992, Bill Schüssler, reported a case of first laparoscopic radical prostatectomy (LRP) assisted by two endourologists who were experienced in laparoscopic renal surgery [2, 3]. Subsequently, these pioneers successfully performed 9 LRP-procedures and concluded that LRP had no benefit over traditional open retropubic

L. Lusuardi, MD, FEBU • G. Janetschek, MD (✉)
Department of Urology and Andrology, Paracelsus Medical University,
Hullner Hauptstrabe 48-50, Salzburg, Austria
e-mail: g.jamestschek@sack.at

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prostatectomy [3, 4]. Many French surgeons including Gaston [4, 5], Guillonneau and Vallancien contributed to the techniques of LRP mainly based on the principles of open radical prostatectomy [5, 6]. Since then several European and American centers followed the suit [7–11]. Perhaps more importantly, with the introduction of the da Vinci® Robotic Surgical System (Intuitive Surgical, Inc., Sunnyvale, CA, USA) endoscopic surgery has advanced further as even a non-laparoscopic surgeon could accomplish minimally invasive radical prostatectomy (RALP) with a shorter learning curve. Another factor is the cost issue but this could be compensated by shorter stay of the patients in the hospital.

The popularity of LRP has risen considerably in the European countries in the first decade of the new millennium. In 2002, a survey of laparoscopic procedures in Germany and Switzerland revealed that 15 % of the urology units performed LRP, and only 5 % did more than 15 cases *per annum* [12]. In 2004, a survey of German urology departments showed that, 19.2 % of them offered LRP, 26.9 % perineal, and 60.6 % open retropubic radical prostatectomy [13]. By 2006, more than 5,800 patients underwent LRP as observed in a multi-center study in Germany [14]. Despite the wide acceptance of LRP and RALP over the past 5 years in Europe and the United States, there are still no large-scale comparison studies between the results of the new approaches to the traditional open retropubic technique [15]. Performing a randomized controlled trial is clearly a very difficult task because patients are unwilling to accept the idea of randomization to a particular surgical treatment and are usually quite fascinated by the most modern surgical procedure. In addition the centers, which perform RALP, are usually focused on one approach thereby limiting or lacking their experience in open or laparoscopic techniques [16].

Any patient who is suitable for open radical retropubic prostatectomy is a candidate for laparoscopic and robotic assisted procedures. In other words LRP or RALP is indicated for a localized prostate cancer with no evidence of spread outside the prostate.

Principles of the Surgical Technique (LRP)

The laparoscopic removal of prostate can be accomplished either by intraperitoneal route or through extraperitoneal approach as done with open retropubic radical prostatectomy (RRP). The extraperitoneal technique may have shorter learning curve [17] as reflected by the shorter operating times reported from various centers [14, 18]. Main advantages of the extraperitoneal approach include: (i) a lower risk of bleeding due to early control of the lateral prostatic pedicles and (ii) the elimination of the initial step of retrovesical dissection of the seminal vesicles. As all key operative steps of LRP (i.e. dissection of seminal vesicles, division of urethra and bladder neck) have to be performed independently of the approach used, one would not expect the operating times to differ substantially in experienced hands. However, certain patient characteristics and technical problems may make one approach more favored than the other. For example, exposure of pouch of Douglas in the transperitoneal descending technique may be comparatively difficult in patients who had

previous extensive pelvic surgery, in men with redundant sigmoid colon or obesity. Similarly, early division of the dorsal vein complex with the ascending technique in patients with a very large prostate may become more difficult. These facts therefore support the parallel use of both techniques at centers with LRP-expertise.

Retrograde dissection technique is more popular in the open route [19], whereas most laparoscopic urologists favor the antegrade or descending approach [14, 20] starting from the bladder neck. The practical reason for this is the early control of prostatic pedicles and late division of the dorsal vein plexus in comparison with the retrograde dissection. The control of lateral pedicles ensures minimal bleeding and a clear working field, both being critical for the dissection and preservation of the cavernosal nerves. LRP has generated a renewed interest in the periprostatic neuroanatomy because of the superior image and magnification. It is also possible to be able to appreciate the fascial anatomy as described by Walsh [21]. Guillonneau [6] has described a technique of complete antegrade dissection for preservation of the neurovascular bundles (NVB). A potential drawback of this approach is that the precise course of the NVB is not easily visualized during antegrade dissection without having initially incised the levator fascia and developed a lateral NVB groove [22]. Gill et al. have proposed intraoperative transrectal ultrasound monitoring to identify the course of the NVB [23]. Tewari et al. [24] have given a detailed anatomic description of neurovascular anatomy in cadavers. Both pelvic and Denonvilliers fasciae hide the NVBs and location of pelvic plexus ganglia close to the seminal vesicles, therefore are vulnerable to thermal injuries. They also demonstrated the presence of additional neural plexus (accessory neural pathways) along the posterior and antero-lateral surface of prostate [24, 25].

We use five ports for both approaches: a 10-mm port for the camera through a periumbilical incision, a 12-mm port midway between the umbilicus and pubic symphysis, two 5-mm ports at the right and left iliac fossa midway between umbilicus and anterior superior iliac spine, and the last 5-mm port on the right side superolateral to the previous port. Either a transperitoneal or extraperitoneal laparoscopic approach could be employed. We chose the former if there is a possibility or indication to perform a lymphadenectomy.

In the transperitoneal access, the pre-vesical space is explored through an incision in the peritoneum and subsequently by blunt dissection between the bladder and the anterior abdominal wall. In extraperitoneal approach, a balloon trocar is used to create the working space following finger-dissection of the cave of Retzius.

The bladder neck is dissected with blunt and sharp dissection in a gradual manner aiming to define the angle between bladder and urethra with sharp dissection. The bladder neck is divided and the catheter becomes visible (Fig. 12.1). To facilitate this step, a special stay suture is inserted with a straight needle is passed transcutaneously and passed ventrally between prostate and dorsal vein complex to get a better exposure of the bladder neck region.

The longitudinal musculature at the prostate-vesical junction is then divided with scissors. This opens the space, which contains the vasa deferentia. The vasa are dissected, clamped and divided, followed by mobilization of the seminal vesicles bilaterally.

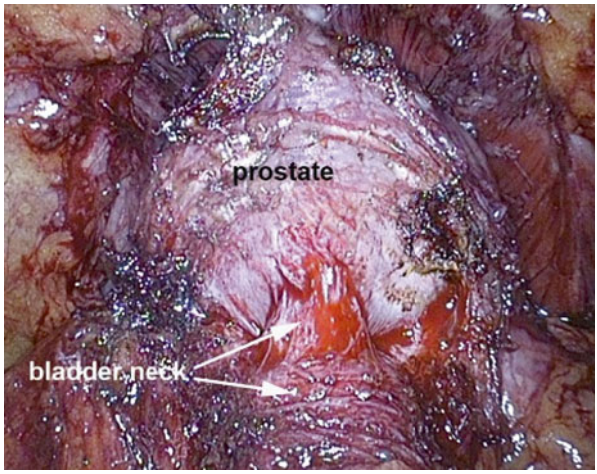

Fig. 12.1 Incision at the bladder neck

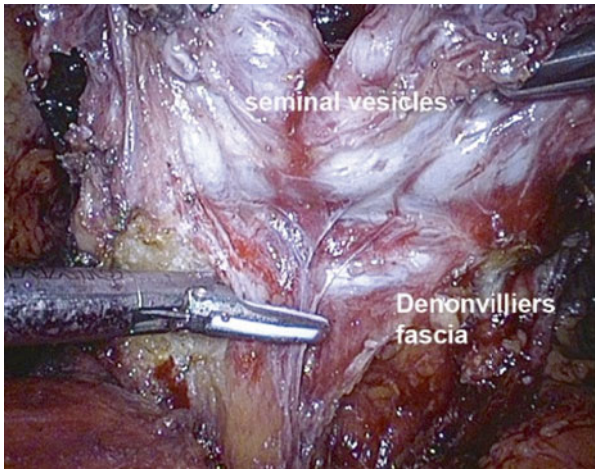

Fig. 12.2 Horizontal incision of Denonvilliers' fascia

Care must be taken not to employ any source of energy along the tip and lateral surface of the seminal vesicle due to its proximity to the NVBs. A Hem-o-lok clip (Weck Closure Systems, Research Triangle Park, North Carolina) is placed to control the artery to the seminal vesicle, which is then transected with cold scissors. Denonvilliers' fascia is incised horizontally close to the base of the prostate, entering the pre-rectal space along the posterior surface of the prostate (Fig. 12.2).

Both seminal vesicles and vas deferens, grasped by an Ellis clamp introduced through the 5 mm assistant port, are retracted antero-laterally to the left or right side, placing the respective lateral pedicle of the prostate on a gentle stretch.

Nerve sparing can be performed by intrafascial, interfascial or extrafascial techniques depending on patient selection and their individual pelvic characteristics.

The dorsal vein complex is divided with UltraCision (Ethicon), but not ligated at this stage. Next the prostate apex is mobilized and both NVBs are gently dissected away from it. The urethra is sharply transected with cold endoshears and the specimen is entrapped in an endobag.

In order to improve continence, we reconstruct the posterior aspect of the rhabdosphincter, which mainly consists of connective tissue, using a Vicryl 1-0 stitch [26]. Then urethro-vesical anastomosis is completed with a 3-0 V-Loc (Covidien North Haven, CT, USA) running suture [27]. The anterior bladder neck is finally fixed to the puboprostatic ligaments and dorsal vein complex with a Vicryl 1-0 suture in order to reconstruct the anatomy and for haemostasis.

Oncological and Functional Results

Open RRP vs. LRP

Various reasons sited in support of LRP over open RRP include: faster recovery due to absence of larger surgical incision, less blood loss, better preservation of NVB and a better vesico-urethral anastomosis because of clarity of vision. The disadvantages of LRP according to the proponents of RRP include postoperative ileus, lack of proprioception leading to higher positive surgical margins, increased theatre space, increased cost of equipment, special surgical expertise, increased learning curve and use of electrocautery [28]. There is no clinical evidence to the commonly made assumptions that LRP is associated with less pain, better visualization during surgery and recover quicker than RRP [29]. As mentioned before there are no systematic clinical studies comparing the results of LRP and RALRP with open RP [30]. However various authors have made efforts to combine the data to get comparative information on all three procedures (Open vs. LRP vs. RALRP).

The outcomes after RP can be ranked as shown in the Table 12.1

Table 12.1 Outcomes of RP based on clinical importance

1. Oncological results: cancer control
2. Periperative complications
3. Postoperative complications: Early and late
4. Urinary incontinence
5. Erectile dysfunction
6. Cost
7. Blood loss
8. Timing of catheter removal
9. Length of hospital stay
10. Postoperative pain
11. Further operative treatments due to complications

Based on data from Ref. [29]

Oncologic Outcomes

The main parameter to assess the oncological outcome in RP is surgical margin positivity. A surgical margin is considered positive if tumour tissue or cells reach the 'inked' boundaries of excised prostate specimen. The risk of recurrence increases with positive margins, which in itself is a prognostic marker independent of grade, PSA, clinical staging and DNA ploidy. The long term follow up for LRP on its own is still unavailable, as it has been regularly performed only since late 90s. And also the data that are available tend to be mostly a combined data from different centers.

Margin Positivity

There appears to be not much difference in margin positivity rates between open and laparoscopic prostatectomy procedures [31]; however the results might be better with open procedure in pT2 disease [29]. Similar results have been reported by most of the non-randomized prospective studies, with the exception of a study by Roumeguere et al. [32], which reported a significantly higher positive surgical margin rates in patients undergoing RRP. However, when the data were stratified by the pathologic stage, no differences were found between the two procedures.

In studies comparing RRP and RALP, no significant differences were reported in the study evaluating the early phase of the RALP learning curve [33]. However, the largest prospective study demonstrated lower positive surgical margin rates in those patients treated by RALP, compared with RRP [34].

No differences were found between the results of LRP and RALP, considering both early phases [35] and more advanced phases [36] of the RALP learning curve. With regard to the comparison between LRP and RALP, no statistically significant difference was found in the positive surgical margin rates (RR: 0.97; 95 % CI of RR: 0.65–1.46; $p = 0.9$), even in a sensitivity analysis limited to pT2 cancers.

Blood Transfusion

Pure LRP allowed a significant reduction in blood loss and, consequently, lower perioperative transfusion rates compared with RRP. Similarly, transfusion rates were significantly lower in the patients having RALP compared with RRP. The results of LRP and RALP were similar with regard to blood loss and transfusion rates on a cumulative analysis [35].

Continence

Functional results seem to overlap between RRP and LRP, with 12-month continence rates ranging from 60 to 93 % after RRP and from 66 to 95 % after LRP in one study [35]. In a study by Hu et al. [37] the diagnosis for incontinence was lower

for RRP patients than for RALP and LRP patients—12.2 versus 15.9 per 100 person-years, even after adjusting for baseline rates.

Sexual Function

In relation to sexual function no study, has shown any significant advantage of LRP over RRP in terms of erectile function recovery. The 12- and 18-month potency rates were similar, ranging from 10 to 93 % after RRP and from 42 to 76 % after LRP [35].

Tewari et al. [34] observed a faster recovery of continence and potency in patients who had RALP than in patients who underwent RRP. In another study on comparison of endoscopic techniques, there was no significant difference in outcomes of both RALP with LRP [36].

In summary LRP and RALP are followed by significantly lower blood loss and transfusion rates, but the available data are not sufficient to prove the superiority of any surgical approach in terms of functional and oncologic outcomes. Data concerning overall complication rates highlight that, once the learning curve is completed, LRP and RALP can be performed without a significant risk of major complications. Interestingly, our cumulative analysis showed a significant advantage in terms of overall complication rates in patients who underwent LRP in comparison with those treated by RRP. There were no significant differences between RRP and RALP. Like many others, we conclude that the critical issue in determining the risk of complications is the level of expertise of the surgeon and volume of work, regardless of the surgical approach. Further high-quality, prospective, multicentre, comparative studies are needed. It is important to compare the outcomes of endoscopic procedures with one of the oldest minimally invasive prostate procedure – perineal radical prostatectomy.

Cost

The overall service cost is an important factor in delivering any medical care. Both LRP and RALRP need continuing investment in expertise and advanced equipment. Consequently the two procedures cost much more than RRP. The robotic equipment cost about $1-2-1.5 million plus a yearly bill of more than $100,000 for maintenance. The cost of instruments per patient is estimated at $1,500 with an average total cost of $5,500. This is in comparison with the cost of LRP $3,870 and RRP $1,870 [38].

Kidney Cancer

Laparoscopic nephrectomy for T1-2 tumors has become a standard procedure within a short period of time. It should therefore be made available to the patients with kidney cancer. With the advent and widespread use of ultrasound and CT, there

is an increase in the detection of small incidental renal tumors (incidentalomas). Nephron-saving surgery or partial nephrectomy would be more appropriate than radical procedure in these patients particularly those with T1 tumors. In patients with small tumors in addition to the size, other parameters such as the location of the tumor in the kidney and the patient's general condition should be taken into account.

The principles of open surgery unequivocally apply to laparoscopic approach [39]. The decision making process for nephron saving treatments including surgery is discussed in the chapter on kidney cancer.

Radical Nephrectomy

The laparoscopic approach to radical nephrectomy (LRN) is considered a standard procedure for most patients with renal malignancy that are not eligible for a nephron-sparing procedure. The major advantages of LRN over open radical nephrectomy include decreased perioperative morbidity, lower blood loss, shorter length of hospital stay, and quicker convalescence.

Principles of the Technique

Retroperitoneal Radical Nephrectomy

Once the blunt dissection of loose hilar areolar tissue is performed, renal arterial pulsations are identified. The renal artery is circumferentially mobilized, clipped and divided. The renal vein is mobilized and controlled with a vascular stapler. A suprahilar dissection along the medial border of the kidney is performed up to the upper pole of the kidney. Adrenal vessels, including the main adrenal vein, are clipped and divided. Dissection is next redirected towards the superolateral aspect of the specimen, including *en bloc* adrenal gland, which is readily mobilized from the underside of the diaphragm. In the areolar tissue in this location inferior phrenic vessels to the adrenal gland are often encountered and need to be controlled. Care of the undersurface of the liver is taken on the right side.

The anterior aspect of the specimen is mobilized from the undersurface of the peritoneal envelope. The ureter and gonadal vein are secured, and the specimen is completely freed by mobilizing the lower pole of the kidney. The entire dissection is performed outside Gerota's fascia, in keeping with standard oncological principles. An Endocatch bag (USSC, Norwalk, CT, USA) is introduced through the right-hand port incision, and the specimen is entrapped. Intact specimen extraction is performed through an appropriate muscle-splitting incision. Hemostasis is confirmed under lowered pneumoretroperitoneal pressure and ports are removed under direct vision. Fascial closure is performed for all 10 mm or larger port sites using a 2-0-vicryl suture.

Transperitoneal

The transperitoneal approach utilizes a 4-port technique. Overlying bowel is reflected, the colo-renal attachments are released, as well as the ligaments attached to spleen and liver, on the left and right side respectively. After exposing the Gerota's fascia retracting the lower pole of the kidney helps to stretch the renal hilum. The major hilar vessels are then exposed, individually, clipped and divided, initially the artery and later the vein. The Endocatch bag is used, and the entrapped specimen is extracted intact through a muscle-splitting, low Pfannenstiel incision without morcellation.

Partial Nephrectomy/Nephron-Saving Surgery

Due to the increased usage of abdominal imaging techniques there seems to be increased detection of small renal tumors, which in turn has led to a greater utilization of nephron-saving surgical (NSS) techniques. In addition, NSS helps in preserving the overall renal function; the choice of treatment has to be individualized without compromising oncologic principles and outcome [40]. Various nephron-saving technique have been outlined in detail in the chapter on renal cancer.

The technique of laparoscopic partial nephrectomy for RCC has been in vogue for more than 15 years [41]. Initially, the resections were performed without ischemia, for small peripheral tumors. The introduction of warm ischemia has become a major concept in resecting more difficult lesions [42]. Subsequently it has become possible to excise the tumor accurately by laparoscopic procedures without massive hemorrhage, to close potential defects in the pelvicalyceal system, and to ensure hemostasis by suturing the cortical defect. The laparoscopic techniques of partial resection thus duplicate the open technique [43]. Improvements in suturing also include using absorbable clips, with marked reduction in warm ischemia time [44]. Shortening of warm ischaemic time could further be achieved by the "early declamping" technique [45]. Good hemostasis and closure of the pelvicalyceal system could also be achieved by running suture in the renal interstitial tissue. Bleeding vessels are selectively treated after release of clamps enhancing the reliability of hemostasis. The mean duration of ischemia could be reduced from 27 to 14 min. The principal outcome of these modifications is that ischemia time for laparoscopy is no longer than that for open surgery. We now routinely end warm ischemia after a maximum period of 20 min; any hemorrhage still present at this time can be easily controlled.

Cooling of the kidney permits longer periods of ischemia with no or minimal damage to the kidney. In open surgery cooling is achieved by encasing the kidney in crushed ice.

Similar technique could be employed in laparoscopic procedures also; however because of practical difficulties, it is not widely used [46]. However, a new type of soft ice (Gelice®, Fresenius Company, Germany) has been tested successfully in

animal experiments [47]. Gelice® is easy to apply because of its consistency although it is currently not approved for use in humans.

Another option is to cool the kidney via a catheter in the pelvicalyceal system in a retrograde fashion via the ureter [48]. This type of cooling is not very effective because the small capacity of the renal cavity as the cooling fluid is lost easily if the renal cavity is opened for tumor excision.

Cooling the kidney by means of arterial perfusion through the clamped renal artery although effective is quite a laborious approach [49]. With this technique, the renal parenchyma is protected from toxic substances that accumulate during the clamping as they are washed out.

Cooling of the kidney is required when one anticipates a longer period of ischemia during excision of a complex tumor. Gill et al. [50] have modified his technique recently and now perform all laparoscopic partial resections with induced hypotension and without ischemia. Arterial blood supply to the kidney is visualized as much as possible, especially in cases of hilar tumors. Bleeding vessels are selectively coagulated. The results published so far have been promising. The technique is employed when using the conventional laparoscopic and robotic assisted approach.

In our unit we do carry out partial resections without ischemia wherever possible. Currently we are conducting at a prospective study using a new laser (Eraser 1,318 nm Rolle, Austria), which is not particularly effective in terms of cutting, but effective in achieving hemostasis.

Principles of Surgical Technique

The patient is placed in the standard lateral decubitus position as for nephrectomy. The assistant operates the camera and an additional instrument. The ports for lower-pole tumors are similar to those used for nephrectomy. The camera trocar is placed in the umbilical port. A 12-mm working port helps to rapidly insert and remove the tourniquets and suture materials. In obese patients the position of the umbilicus is likely to be displaced, which is taken into consideration while using umbilicus as a port. In obese patients the port for the optics is moved laterally to the border of the rectus muscle with other ports positioned accordingly. On the other hand, for upper pole tumors, the camera is placed on lateral border of rectus, above the umbilicus, and the working ports just below the costal arch. We use vascular 'tourniquets' to control blood vessels during partial nephrectomy. The sling is folded and passed through 10 mm silicon tube and then introduced through a 12-mm port. The looped end of the sling is passed around the vessel, and back into the end and tube (like attaching a luggage tag). The free ends of the vessel loops are then fixed with a large (purple) Hem-o-lock clip so that they cannot fall apart. Traction on the end of the vessel loop, with application of a second XL (gold) Hem-o-lock firmly against the end of the tube, causes vessel occlusion. The slings are colour coded-red for artery (Web sil loop maxi + 10-mm silicone tube) and blue for the vein (vascular silicone ties mini + 6-mm silicone tube).

Following the mobilization, the lower pole of the kidney is elevated (by the assistant via a lateral port). The pedicle is freed from surrounding structures, without skeletonization. The artery is left *in situ* within the surrounding connective tissue to reduce

the risk of injury. A window is made between the pedicle and adrenal gland, through which a right-angle clamp (deflectable Snowden-Pencer, CareFusion, San Diego, CA, USA) is passed around the pedicle. With the help of this clamp, a self-made tourniquet folded over once to form a U-loop (vessel loop through 10-F silicon tube) is brought around the dorsal aspect of the pedicle. Next, the Gerota fascia is dissected from the kidney, so that adequate adjacent renal parenchyma is exposed. Intravenous mannitol (15 %w/v, 250 ml) is administered just before to the clamping. This is done by tightening the arterial tourniquet with a large Hem-o-lok clip (Fig. 12.3).

This clip is removed later to terminate ischaemia. The venous tourniquet can be used if there is a venous backflow. The renal capsule is incised about 5 mm away from the edge of the tumour by diathermy. The tumour is excised in a bloodless field, using cold Metzenbaum scissors to achieve a perpendicular cut through the parenchyma (Fig. 12.4). A close inspection of the cut surface while cutting helps to distinguish normal parenchyma from the tumour. If tumour tissue becomes visible or the surface is suspicious, excision of the specimen is continued within healthy

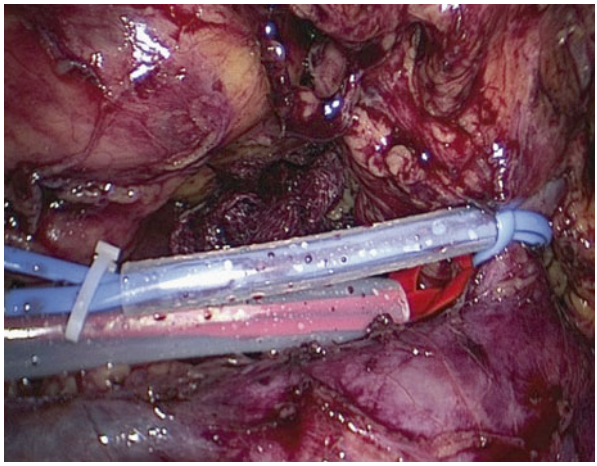

Fig. 12.3 Red tourniquet around the artery and the blue one around the vein

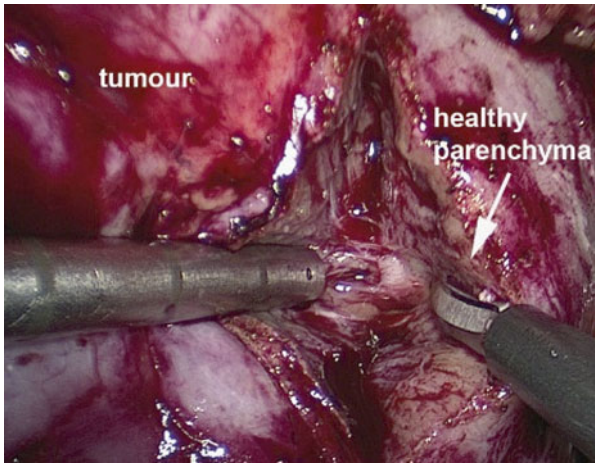

Fig. 12.4 The tumour is excised in a bloodless field

tissue. Strict observation of this technique makes random biopsies of the excision bed unnecessary. As excision proceeds, vessels may be identified and clipped.

Reconstruction of the cut surface is performed in two layers. The inner part is closed in the region of collecting system by approximating the interstitial tissue using a running suture (2×3/0 Vicryl 15 cm Lapra-Ty with a knot at the end of the suture with a 26.4 mm 5/8 needle). This suture, which is secured on both sides with a resorbable Lapra-Ty clip to avoid time-consuming knotting, is started at the opposite edge of the resection bed. It includes arteries and veins, thereby providing a secure haemostasis. Care must be taken to avoid injury to large central vessels. The second layer running suture (Vicryl 1, M04 needle, 15 cm + 20 cm) is used through the whole thickness of the renal parenchyma. This running suture is secured with a large Hem-o-lock clip at the end of the suture.

A knot behind the clip prevents it from displacement or slipping through. The suture overruns a bolster of oxidized regenerated cellulose (Tabotamp/Surgicel, Ethicon 360, USA). The bolster is haemostatic by itself and provides haemostasis by tamponade with pressure on the vessels underneath in the interstitial layer. This suture is secured after each stitch with a large Hem-olock clip (Teleflex Medical) (Fig. 12.5). The ischaemia is terminated after the first stitch and placement of the collagen (Tabotamp-Ethicon) roll by releasing the tourniquet (although it remains in position). The Hem-o-lock clip is cut by means of an ultrasonic scalpel. This early declamping reduces ischaemia time is by about 10 min. It is never a problem to continue the parenchymal suture without ischaemia. The end of the running suture is secured with a Lapra-Ty clip in addition to the Hem-o-lock clip so that the suture cannot loosen. Fibrin glue (Tissucol Duo S Immuno, Baxter, Deerfield, IL, USA) is applied over the suture line and between the approximated edges of the parenchyma to avoid delayed bleeding.

Finally, the remnants of the Gerota fascia are re-approximated over the repair. The kidney is brought back into its normal position and attached to the lateral abdominal wall with one suture to avoid torsion. A drain is placed through the most lateral port. The specimen is removed through an extension of the lower abdominal port site incision.

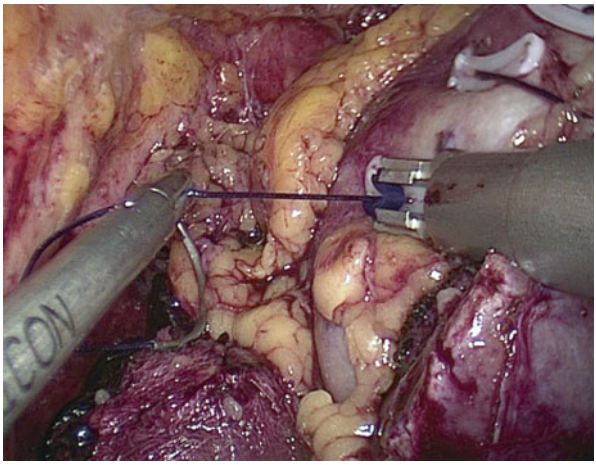

Fig. 12.5 The running suture is secured after each stitch with a large Hem-o-lock clip

Oncological Results

An important parameter is the rate of positive resection margin. This tends to vary between 1.8 and 2.4 % [51, 52]. The complication rates do not differ from those that are seen with open surgery. As the method is still quite new, published long-term data are scarce. Identical survival rates have been reported in a direct comparison with open surgery, spanning a follow-up period of 7 years. Tumor-free survival rates were 97.5 % (laparoscopy) and 97.3 % (open surgery), respectively [53].

Complications

In early publications, laparoscopy was reported to be associated with a higher rate of complications. Comparison of three clearly delineated time periods concerning a single surgeon showed that complication rates have fallen from initial 23.9 to 10.6 % [54]. This marked reduction is definitely not attributable to the learning curve of the surgeon alone, but also due to the evolution of the technique. In 18 patients with a complex hilar tumor, the rate of postoperative complications as well as the transfusion rate was 5.6 % [55]. It may be concluded that once the learning curve has been overcome, complication rates become similar to those for open surgery [56].

Comparison of Conventional Laparoscopy and the da Vinci® Robot

Very few studies published to date have directly compared two laparoscopic techniques (robot assisted and laparoscopic). Cho et al. [57] compared the data of the last ten patients operated on purely by the laparoscopic approach with the first ten patients operated on with the assistance of da Vinci® robot. The only difference is a longer period of ischemia in conventional laparoscopy (40 versus 31 min). However, certain aspects of this study have been criticized. The number of investigated patients was small. Although the size of the tumours was identical, no information was provided about the degree of complexity (location in the kidney, score). Furthermore, the period of ischemia in both techniques was markedly longer than that reported in the recent literature.

A direct comparison of partial resection by open surgery, conventional laparoscopy, and laparoscopy using the da Vinci robot was done in the USA and findings are interesting; a large number of parameters were considered in great detail [58]. There were minor variations in costs: conventional laparoscopy (10,311 $), open surgery occupied a mid-position (11,427 $), while the da Vinci® robot was very expensive (11,962 $).

Nephroureterectomy

Retroperitoneal approach: After the creation of the retroperitoneal workspace, the kidney is then retracted anterolaterally with a forceps, placing the renal hilum on traction. Gerota's fascia is incised longitudinally in the general area of the renal hilum, parallel and 1–2 cm anterior to the psoas muscle. Blunt dissection in this avascular area of loose areolar fatty tissue is performed to identify renal arterial pulsations. The renal artery is circumferentially mobilized, clip occluded, and divided. The renal vein is mobilized and controlled with a gastrointestinal anastomosis vascular stapler. Suprahilar dissection is performed along the medial aspect of the upper pole of the kidney, and the adrenal vessels, including the main adrenal vein, are precisely controlled.

Dissection is next redirected toward the superolateral aspect of the specimen, including the *en bloc* adrenal gland if decided, which is readily mobilized from the under surface of the diaphragm. In this location, inferior phrenic vessels to the adrenal gland are often encountered and controlled. Once the whole kidney is mobilized, the ureter and gonadal vein are the only attachments of the kidney. The ureter is now dissected down to the bladder level including the cuff of the bladder with the distal ureter – this can be accomplished by the open technique with a pfannenstiel incision and. Another approach is to resect the distal ureter using a resectoscope before the commencement of radical nephrectomy part of the procedure. The specimen is extracted intact groin incision. Wounds are closed in a standard manner.

Transperitoneal: The transperitoneal approach utilizes a four-port technique. Overlying bowel is reflected, the colon-renal ligaments are released, as well as the ligaments with the spleen and liver, in the left and right side, respectively, after exposing the Gerota's fascia and retracting the lower pole of the kidney to stretch the renal hilum. The major hilar vessels are then exposed, ligated individually, and divided, initially the artery and posteriorly the vein. The ureteral dissection, bladder cuff removal, and specimen extraction are similar to the retroperitoneal approach described above.

Adrenalectomy

Retroperitoneal: Patient is placed in a full flank position with the flank directly over the table break. A 3-port approach for the left side and 4-port approach for the right side is employed. The posterior aspect of Gerota's fascia is incised transversely at the level of the upper pole of the kidney. The aim of the ensuing dissection is to circumferentially mobilize the upper pole and mid-region of the kidney and the covering Gerota's fascia. The upper pole is now dropped posteriorly onto the psoas muscle away from the adrenal gland. This dissection proceeds immediately adjacent to the parenchyma of the upper pole of the kidney. Care must be taken not to injure any accessory vessel entering the upper pole of the kidney. At this juncture, the adrenal gland is still located in its normal position, attached anteriorly to the parietal peritoneum.

During the left adrenalectomy, careful blunt and sharp dissection is performed toward the renal hilum, between the upper pole of the kidney posterolaterally and the adrenal gland anteromedially. The caudal limit of this dissection is the renal hilar vessels, usually the superior branch of the renal artery. Multiple small renal hilar vessels supplying the adrenal gland are encountered in this location, which are securely clipped and divided. Dissection is now transversely continued medially along the renal vein or artery, and the main left adrenal vein may be identified at this juncture and clipped (5-mm clips) and transected. If the main left adrenal vein cannot be identified at this stage, dissection is redirected toward the undersurface of the diaphragm. The adrenal gland is mobilized cranially, controlling the inferior phrenic branches. Multiple aortic branches to the adrenal gland may need to be controlled in this area. Continued dissection along the medial and inferomedial aspect of the adrenal gland will identify the main left adrenal vein as its sole remaining attachment. The left adrenal vein is longer than the right, arises from the inferomedial aspect of the left adrenal gland, and courses obliquely to drain into the proximal left renal vein. The vein is then clipped and transected.

On the right side, the main adrenal vein is shorter, horizontally located along the superomedial edge of the adrenal gland, and drains directly into the inferior vena cava. Dissection is carried cephalad along the lateral aspect of the inferior vena cava, between it and the adrenal gland, until the right adrenal vein is seen, circumferentially mobilized, clipped, and divided. The adrenal gland is then mobilized from the undersurface of the diaphragm. The main right adrenal vein usually arises from the superomedial aspect of the right adrenal gland. Although multiple small renal hilar arteries and veins enter the adrenal gland along its inferior and inferomedial edge, the larger, more well-defined main right adrenal vein usually resides in a more cephalad location, beneath and along the posterior edge of the right lobe of the liver.

After control of the adrenal vasculature has been secured, combination of blunt and sharp dissection of the remaining attachments frees up the adrenal gland. Inferior phrenic vessels are often encountered along the undersurface of the diaphragm. During specimen mobilization, one should be careful not to create an unintentional breach in peritoneum (peritoneotomy). Although a peritoneotomy does not significantly compromise operative exposure during a retroperitoneoscopic radical nephrectomy, a peritoneotomy during retroperitoneoscopic adrenalectomy may decrease the operative field in the vicinity of the undersurface of the diaphragm. In this circumstance, placement of a fourth port may be necessary for anterior retraction. A 2-mm port suffices for this purpose.

The Endocatch bag is introduced through the right-hand port, and the excised specimen is entrapped and extracted intact through the primary port site. Hemostasis is confirmed and the ports are removed under laparoscopic vision. The larger (10–12 mm) port site(s) is (are) closed in fascial layers, and the smaller (5-mm) ports are closed with subcuticular sutures.

Transperitoneal: Usually four ports are required. On the right side the liver is retracted anteriorly and the posterior peritoneum is transversely incised high along the under surface of the liver. This extends from the line of Toldt laterally up to the inferior vena cava on the medial side. Visualized without any need for mobilizing

the hepatic flexure, the adrenal gland, which is surrounded by periadrenal fat, is retracted laterally. The main adrenal vein is dissected, clipped and divided.

In contrast, on the left side of the spleen, the splenic flexure, the descending colon, and the tail of the pancreas require extensive mobilization to visualize the left adrenal gland. Recently a supragastric transperitoneal approach to the left adrenal gland was described, in which dissection is performed along the greater curvature of the stomach, cephalad to the body of the pancreas. This maneuver avoids mobilization of the descending colon and spleen, which is the primary advantage of this technique.

Radical Cystectomy

The radical cystectomy and pelvic lymphadenectomy is a standard operation for muscle invasive bladder cancer and for non-muscle invasive bladder cancer (NMIBC) where intravesical therapy has failed. It is also indicated in squamous cell carcinoma and sarcoma of the bladder. It is one of the major procedures in genitourinary oncology, which is associated with a high morbidity and mortality even in high volume centres due to the complexity of the operation, which involves removing pelvic structures and bowel resection coupled with patients who might have considerable co-morbidities [59, 60]. The procedure can be carried out by an open laparotomy, laparoscopic technique with or without robot assistance.

Again like other laparoscopic urologic procedures no systematic randomized studies have been done and data collected from different studies have a short term follow up. Similarly robotic assisted laparoscopic radical cystectomy (RALRC) needs prospective, long-term controlled studies to evaluate its role and place in radical bladder cancer surgery [61]. Short-term results suggest that results are better with laparoscopic radical cystectomy (LRC) and robotic assisted radical cystectomy (RALRC) in experienced hands in terms of lymph node counts, morbidity and oncological outcomes [62]. Positive tissue margins are similar to open techniques for T2/T3 disease but inferior for bulky T4 disease [62].

Despite an increased cost RALRC cystectomy seems to be less expensive than open radical cystectomy if one considers the cost of complications [63]. The cost is less for RALRC assisted ileal conduit and continent cutaneous diversion compared to orthotopic neobladder.

All patients are assessed by CT Chest, abdomen and pelvis and bone scintigraphy to stage the disease correctly and rule out distant metastasis (see chapter on bladder cancer).

Principles of Surgical Technique

With the patient in the supine lithotomy position, a six-port transperitoneal approach is used. With the bladder retracted anteriorly and the sigmoid colon retracted posteriorly and cephalad, a wide horizontal incision is made in the posterior parietal

peritoneum covering the rectovesical pouch, starting in the midline and extending up to the common iliac artery on either side. Both vasa deferentia are divided, and dissection is performed along the posterior aspect of the seminal vesicles toward the bladder base. The Denonvilliers fascia is incised, and the plane between the prostate and the rectum is developed. Generous ureteral mobilization is performed bilaterally from the retroperitoneum up to their entry into the urinary bladder. This allowed definition of the lateral and posterior vascular pedicles of the bladder, which are controlled by serial applications of the Endo-GIA stapler (U.S. Surgical).

The bladder is distended with 200 mL, and an inverted-V incision is made in the anterior parietal peritoneum. The urachus is detached from the umbilicus, and the bladder is mobilized posteriorly. The retropubic space is developed, and the endopelvic fascia is divided bilaterally.

The puboprostatic ligaments are divided, and the dorsal vein complex is sutureligated. The urethra is transected distal to the apex of the prostate, the rectourethralis muscle is divided, and the remaining attachments are released to completely free the radical cystoprostatectomy specimen, which is immediately entrapped within an Endocatch bag. The pelvic lymphadenectomy is usually performed after the cystectomy in order not to compromise tissue planes and avoid blood-staining in the pelvis.

Ileal Conduit

A 15-cm segment of ileum is identified approximately 15 cm proximal to the ileocecal junction. The Endo-GIA stapler is used to isolate the ileal loop and its mesentery. Complete hemostasis at the cut end of the mesentery is obtained by the additional selective application of metallic clips. Intestinal continuity is reestablished by creating a generous side-to-side ileo-ileal anastomosis with two sequential firings of the Endo-GIA stapler. The open ends of the bowel are closed with two transverse applications of the Endo-GIA stapler.

The left ureter is delivered retroperitoneally to the right side of the abdomen under the sigmoid mesocolon. The distal end of the ileal loop is exteriorized through the preselected stoma site in the right rectus muscle, and an endo-ileal stoma is created in one patient and a loop-ileal stoma in the other. A 90-cm, 7 F single-J ileoureteral stent, grasped by a laparoscopic right-angle clamp, is inserted through the stoma into the conduit lumen, so as to tent the ileal loop within the abdomen at the desired site of ileoureteral anastomosis. Using a laparoscopic electrosurgical J-hook, a small ileotomy is created at that site, and the stent is delivered into the abdominal cavity.

The right ileoureteral anastomosis is performed initially. After spatulating the ureteral cut edge, the initial stitch is passed outside-in at the apex of the ureteral spatulation and anchored at the appropriate site (6-o'clock position) on the ileal conduit (4-0 Vicryl, RB-1 needle). After performing a continuous suture to approximate 80 % of the posterior (far) wall of the ileoureteral anastomosis, the J-stent is passed into the ureter up to the renal pelvis. The remainder of the posterior wall is then completed. The anterior (near) wall of the anastomosis is completed with a

separate running suture to preclude circumferential anastomotic narrowing. The left ileoureteral anastomosis is performed in a similar fashion. Laparoscopic freehand suturing and in situ knot-tying techniques are used exclusively.

The bilateral pelvic lymphadenectomy is completed. Two 10-mm Jackson-Pratt drains are inserted through different port sites, and a Foley catheter pelvic drain is inserted per urethra. The entrapped specimen is extracted intact through a 3.5-cm extension of a port-site incision. Hemostasis is confirmed and laparoscopic exit performed.

Orthotopic Neobladder

An additional 5-mm port is inserted in the midline, midway between the symphysis pubis and umbilicus. The laparoscope is now repositioned in the left lateral port, pointing toward the liver, with the surgeon working through the midline infraumbilical and right pararectal ports. The ileocecal junction is identified, and a 65-cm segment of ileum is selected 15–20 cm away from the ileocecal junction. Precise measurement of bowel length is obtained by inserting a malleable foot ruler into the abdomen through a 12-mm port. The distal end of the selected ileal segment is transected with an Endo-GIA stapler using the 3.5-mm blue cartridge. Division of the ileal mesentery at this location is performed by two sequential firings of the Endo-GIA stapler using the 2.5-mm gray vascular cartridge.

During mesenteric transection, care is taken to avoid the primary mesenteric vessels by close laparoscopic inspection. Additionally, the line of mesenteric division remained perpendicular to the mesenteric border of the ileum to avoid risking bowel ischemia by veering too close to the bowel. In a similar manner, the proximal end of the 65-cm ileal segment is transected and the proximal mesenteric division is performed with only one firing of the stapler.

The excluded ileal segment is dropped posteriorly, and side-to-side ileo-ileal continuity is restored by two sequential firings of the Endo-GIA stapler (3.5-mm blue cartridge) along the respective antimesenteric borders of the two adjacent loops of ileum. Two to three transverse firings of the Endo-GIA stapler are performed to secure both open ileal ends, thereby completing the side-to-side anastomosis. For added security, the transected ends of the ileum are oversewn with running 2-0 polyglactin suture. The window in the ileal mesentery is closed with two to three interrupted stitches.

The proximal 10-cm length of the isolated ileal segment is maintained intact for the Studer limb. The remaining distal 55-cm length of the ileal segment is detubularized along its antimesenteric border using a combination of electro-surgical Endoshears and the harmonic scalpel. Before detubularization, the ileal segment is gently irrigated with the suction irrigator device inserted in the bowel lumen through a small ileotomy incision to preclude peritoneal soiling. The posterior plate of the neobladder is created by continuous intracorporeal suturing of the corresponding edges of the detubularized ileum using 2-0 poly-glactin suture on a CT-1 needle. The ileal plate is delivered into the pelvis toward the urethral stump. Care is taken to ensure that the ileum is not under any undue tension and that the mesenteric pedicle

is not twisted. The most dependent site along the apex of the ileal plate is selected for performing the running circum-ferential urethro-ileal anastomosis using 2-0 polyglactin suture on a UR-6 needle. A 22 F silicone Foley catheter is inserted per urethra before completing the urethro-ileal anastomosis. In female patients a 90-cm single ileo-ureteral J-stent is inserted via the external urethral meatus alongside the Foley catheter and delivered into the neobladder. In the male patient the two ileo-ureteral stents are inserted through the right lateral port, which is then removed and reinserted alongside the stents. In this manner, although the ileo-ureteral stents are inserted through the port-site incision, they are not occupying the port itself. The anterior wall of the orthotopic neobladder is folded over and suture-approximated to achieve globular configuration of the neobladder. Before completion of the anterior wall, both ileo-ureteral stents are delivered into the Studer limb and retrieved into the peritoneal cavity through two separate, small (1–1.5 cm) ileotomy incisions, which are precisely created at the proposed site of the ileo-ureteral anastomoses. Bilateral ureteroileal anastomoses are performed sequentially, with the right ureteral anastomosis performed initially on the more distal ileotomy incision.

Each ureteroileal anastomosis is done in a continuous manner using two separate 3-0 polyglactin sutures on an RB-1 needle, with one suture each for the anterior and the posterior ureteral wall, respectively. Before completion of the anastomosis, the single ileo-ureteral J-stent is advanced up to the renal pelvis. The left ureteroileal anastomosis is completed in similar manner. All suturing and knot tying is performed intracorporeally using free-hand laparoscopic techniques exclusively. The constructed orthotopic neobladder is irrigated through the Foley catheter, and any obvious leakage site is precisely repaired by a figure-of-8 stitch. A suprapubic catheter is inserted into the neobladder through the midline port-site incision. Two Jackson-Pratt drains are inserted, one through each lateral port site, and the specimen is extracted through a 2- to 3-cm circumumbilical extension of the umbilical port incision. The laparoscopic exit is completed. An Indiana pouch and continent catheterizable ileal limb can be created extracorporeally through a mini-laparotomy incision by standard open techniques, and the bowel is reinserted into the abdomen for the bilateral ureteroileal anastomoses to be created intracorporeally by free-hand laparoscopic techniques. A catheterizable, continent ileal stoma is then fashioned to the umbilicus.

Postoperatively, the urethral Foley catheter is irrigated every 4–6 h for the first 2–3 days and every 8 h thereafter. The Jackson-Pratt drains are removed sequentially as drainage decreased appropriately. A cystogram is obtained at 4–6 weeks to confirm complete healing of the neobladder before removing the Foley urethral catheter.

Oncological Results

In a small series of 41 patients (21 robotic and 20 open), Nix et al. [64] compared robotic with open cystectomy prospectively taking lymph node yield as a primary endpoint. They found no difference in results, which included perioperative outcomes, complications and narcotic usage. In a multi-institutional analysis of 227

patients (178 males and 49 females) operated by RALRC, Smith et al. [65] observed acceptable operative and pathological outcomes; however long-term follow up is still needed to confirm oncological outcomes.

Future of Laparoscopy and Robot-Assisted Surgery

Conventional laparoscopy has two major disadvantages: one has to dispense with spatial viewing and one has rigid instruments with marginal degrees of freedom. Therefore, currently we have two variants in laparoscopy – conventional laparoscopy, and the da Vinci® assisted laparoscopy which circumvents the above mentioned disadvantages of conventional laparoscopy. Although 3-D video has been available for a long time in conventional laparoscopy it has not been technically developed. As significant advances have been made in recent times, the systems are now ready for use in surgical procedures. There are excellent 3-D video systems (Viking Systems, Westborough, MA, USA) that are commercially available. In our unit we are currently looking a prototype (Karl Storz, Tuttlingen, Germany) and surprised to note that the 3-D video system is useful for beginners and experts alike. Instruments that offer nearly the same degree of freedom as the da Vinci® device were introduced in the market in 2010 (Kymerax®, Terumo Corporation, Tokyo, Japan). These hand-held instruments are driven by an electric motor and steered by the handle. In partial kidney resections, additional freedom of the needle holder enables the surgeon to introduce the needle at an ideal angle through the parenchyma. Previously this could be achieved only by full mobilization of the kidney. The combination of 3-D video and these steered instruments with extended degrees of freedom offer previously unforeseen options in a cost-effective way. We are convinced that the two worlds of laparoscopy, separate until now will be coming much closer in the future and 1 day may even fuse with each other.

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Chapter 13
Principles of Chemotherapy for Genitourinary Cancer

Gary Frenette and Derek Raghavan

Introduction

Systemic anticancer therapy evolved from the concepts of Lissauer and Ehrlich early in the twentieth century. The initial protocols focused on cytotoxic chemotherapy were characterized by a lack of specificity, often with significant normal-tissue toxicity. This has improved somewhat due to a better understanding of tumor biology, the role of the cell cycle in normal tissue and tumor growth, the constituency and relevance of the human genome, and the biochemical basis of response and resistance to chemotherapy regimens. Our improved understanding of the mechanisms of regulation of carcinogenesis, cellular growth and turnover has presented new therapeutic targets. This has also been associated with significant refinement of our technology, leading to more effective and less toxic systemic therapies. This brief review addresses progress in this domain, with a focus on practitioners and students with a focus on urological malignancy.

Tumor Cell Kinetics

The biological behavior and heterogeneity of tumors is explained by several factors: heterogeneity of constituent cell populations, variable function of cell regulatory functions, nutritional factors, tumor volume/cell number, and cytokinetics

G. Frenette, MD, PhD
Department of Solid Tumor Oncology, Levine Cancer Institute,
Carolinas HealthCare System, Charlotte, NC USA

D. Raghavan, MD, PhD, FRACP, FACP, FASCO (✉)
Levine Cancer Institute, Carolinas HealthCare System,
P.O. Box 32861, Charlotte, NC 28232, USA
e-mail: derek.raghavan@carolinashealthcare.org

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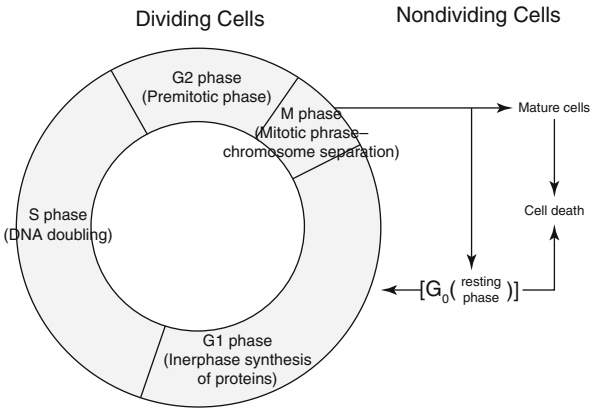

Fig. 13.1 Cell cycle (Reprinted from Kalmadi and Raghavan [43]. With permission from Springer Verlag)

[1]. This can lead to wide differences in cell cycle function between different tumors [2].

Cells grow and divide predominantly in an ordered sequence, consisting of the following steps (Fig. 13.1):

1. Cells remain quiescent in a resting phase (G0), which may be prolonged over years;
2. Cells that are committed to replication enter the interphase (G1) that is characterized by synthesis of RNA and protein, preparing the cell to enter the next phase;
3. DNA synthetic (S) phase, in which the DNA content is doubled.
4. Second resting (G2) phase prior to the cell undergoing mitosis
5. Mitotic phase (M), in which the chromosomes separate and divide, forming two daughter cells

Mitosis results in cells which consist of (a) non-dividing, terminally differentiated cells; (b) resting cells (G0) which can be recruited into the cell cycle; and (c) continually dividing cells which enter into G1 phase again. Major checkpoints in the cell proliferation occur in G1 when cells must commit themselves to division and in G2 before undergoing mitosis. The cell cycle is under the control of numerous regulatory mechanisms, including cyclins (proteins that are positive regulators) and cyclin-dependent kinases (CDK). CDKs are present in all phases of the cell cycle and control the cascade of proliferative signals. The regulation of CDKs by the cyclin molecules causes their levels to fluctuate, leading to synchronization of the processes of cell division [3].

Chemotherapy and radiation are most effective in achieving cytotoxicity when the cells are in cycle. One approach to the categorization of cytotoxics is based on their activities relative to the cell cycle:

A. "Phase specific" drugs are effective only if present in the tumor cell during a specific phase of the cell division. Although an increase in the drug level or dose will not result in more tumor kill, exposure over a longer period of time may allow more cells to enter the specific lethal phase of the cycle, thus producing a greater level of cell kill. Examples of this process include the antimetabolites during the S phase, and taxanes and vinca alkaloids during G2 and M phases.

B. "Phase non-specific" agents have actions not restricted to a specific step in the cell cycle; these can be further divided into (a) cycle nonspecific drugs which can kill non-dividing cells (e.g. steroids, some antitumor antibiotics); and (b) cycle specific agents which can kill cells which enter into the cell cycle (e.g. alkylating agents). Phase nonspecific agents have a linear dose-response curve: the higher the dose administered, the greater the fraction of cells killed.

With improved understanding of the human genome, we have developed more knowledge of the level of molecular checks and balances involved in the regulation of the cell cycle. A detailed discussion of this topic is beyond the scope of this overview, apart from a brief focus that relates to targeted therapeutics (see below).

Tumor Kinetic Modeling

The growth of a tumor can be simplistically conceptualized as being dependent on several variables: the rate of cell loss, growth fraction (proportion of cells in proliferative phase) and cell doubling time. Several models have been devised to explain the impact of therapeutic regimens on the tumor cell cycle [4].

Skipper et al. originally proposed the log kill model, which was based on the behavior of L1210 leukemia cell lines in rodents [5]. They suggested that the benefit of chemotherapy was due to the cytocidal effects on the cancer cells and that tumor growth and tumor regression in response to chemotherapy were exponential in nature. This model proposed that a drug that would cause a reduction of tumor burden from 10^{12} to 10^{11}, if given in the same dose, would also decrease the burden from 10^6 to 10^5 (i.e. each reduction reflected a 90 % tumor cell kill). This formed the basis for the use of repeated cycles of chemotherapy to achieve maximal tumor eradication. However, it has become clear that exposure to the same regimen for more than 4–6 doses does not improve outcomes. We now understand the growth models of tumor have also a mixed nature with respect to different cancer cells in vivo [6]. The Gompertzian sigmoid growth curve is characteristic of many solid tumors. Tumors grow most rapidly at smaller sizes and then the growth rate slows, secondary to problems with vascularity, hypoxia and interaction with the other cells in their microenvironment [7–11].

Concepts initially derived from resistance in antibacterial therapy were applied to the study of antimetabolites in the treatment of murine cancer models and cell lines, and it was shown that resistance is acquired at various points during the growth of the tumor. This also occurs in human tumors. Goldie and Coldman suggested that larger tumors have more cells and thus have a greater chance of undergoing spontaneous mutation [12], which may, in turn, confer resistance to chemotherapy. It has thus been suggested that tumors are more effectively treated at a smaller size, before they have the ability to develop mutations and resistance. This has also led to the concept that non-cross resistant multiple agent chemotherapy would have a greater proportionate tumor kill and could thus prevent the development of resistance.

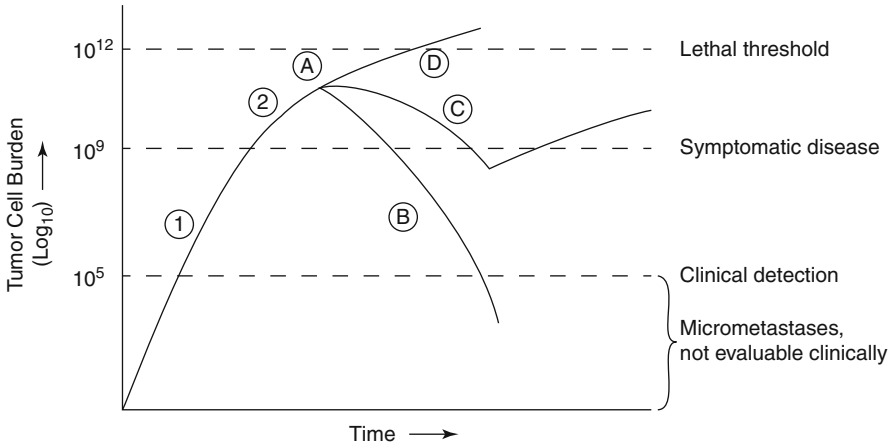

Fig. 13.2 Gompertizan model of tumor growth: Relation between tumor mass, diagnosis, and treatment regimens. Growth phases (*1*) Exponential growth (*2*) Plateau phase with slower growth due to cells outgrowing vascular supply and nutritional resources, and possible other regulatory mechanisms. Treatment responses (*A*) Initiation of treatment; (*B*) Curative therapy; (*C*) initial response with secondary resistance; (*D*) primary resistance (Reprinted from Kalmadi and Raghavan [43]. With permission from Springer Verlag)

Another fundamental concept of cell cycle kinetics is the so-called Norton-Simon regression hypothesis [13]. Their concept is that administration of chemotherapy at shorter time intervals (with greater dose-intensity) achieves greater proportionate tumor cell kill. As noted above (Fig. 13.2), some tumors do not grow in a simple exponential manner but rather follow a Gompterzian growth pattern [11, 13]. Norton and Simon have also proposed that less time available for tumor regrowth between treatments will improve the chance of cure, and that sequential, dose-dense, non-cross resistant regimens will minimize drug resistance. This approach destroys the dominant tumor population initially via the first component of treatment, with different agents addressing the residual resistant cells, without the potential for significant tumor regrowth.

The Goldie-Coldman and Norton-Simon hypotheses have also been applied to the design of adjuvant chemotherapy regimens, attempting to rationalize the prior empirical approach. This has resulted in improved cure rates, perhaps due to increased cytotoxicity and/or a reduced emergence of drug resistance [13–15].

Pharmacology of Antineoplastic Agents

The clinical pharmacology of antineoplastic agents has been an evolving field for the past century, with the most progress having been made in the past decade through the advent of analytical tools such as liquid chromatography and mass spectroscopy. Most cytotoxic agents offer a very narrow therapeutic index compared with most drugs [16].

Pharmacokinetic Principles

Pharmacokinetics involves the study of the fate of administered medications, including absorption, distribution, metabolism and excretion. Absorption has historically not been a major issue for oncologists, because for decades most drugs were administered intravenously. With the advances in drug delivery involving orally administered targeted agents and prodrugs, this has become an issue with oral and cutaneously absorbed drugs. The level of bioavailability is calculated by comparing the area under the curve (AUC) of an oral drug to the same dose given intravenously.

Clearance of the drug is the most critical aspect and can be conceptualized as being a function of drug distribution, metabolism and elimination. Although drug distribution can be viewed most simply as being two-compartmental (extracellular and intracellular), it is actually more complex. It should more properly by considered as a multi-compartment model with frequent redistribution within. The presence of sanctuary sites with poor penetration of the drug may result in apparent resistance of tumors that would otherwise be responsive to chemotherapy.

Distribution can also be affected by disease states such as cardiac failure, or by the impact of advanced cancer (e.g. with associated hypoalbuminemia), resulting in pleural effusions and ascites, thus creating pathological compartments.

When third spaces are present, such as pleural effusions or ascites, some agents (e.g. methotrexate) can cause excessive toxicity due to prolonged exposure, since methotrexate accumulates in these third spaces. Elimination is studied along two different models: (1) The linear kinetic model is based on the assumption that the half life of the drug will be constant. (2) Nonlinear kinetics assumes that the elimination of the drug is saturable resulting in different rates of excretion at different concentrations resulting in variable half-lives.

The metabolism of these agents is determined by the amount of resemblance that they show to physiologic substrate. Drugs (eg. purine and pyrimidine analogues) that are similar to normal metabolites are processed by the same mechanisms as the normal metabolites intracellularly. Those that differ from normal metabolites are degraded in the liver, in reactions involving oxidation (controlled by the cytochrome P450 enzymes) and conjugation. The ultimate excretion of the drug from the body is via the hepatobiliary system and/or the kidney. Creatinine clearance, often used as a surrogate marker of renal function, assesses the glomerular function rate. This index is subject to the influence of muscle mass, and may be misleading in the elderly patient with reduced muscle bulk. Tubular secretion and reabsorption may also play a role in drug excretion. Changes in the renal excretion of the drugs can alter their efficacy and toxicity profile.

Hepatic excretion involves a number of transport systems including P-glycoprotein and canalicular multispecific organic anion transporter (cMOAT). Enterohepatic recirculation also plays a major role, especially for the drugs metabolized by the glucuronide pathway. Changes in the regulation of the cytochrome system by other medications being used may cause changes in the bioavailable levels of chemotherapeutic agents metabolised by this system. The use of liver function

tests to modify the dosage of these drugs is thus fraught by numerous pitfalls, since it does not always accurately predict the toxicity risk due to the fact that they do not accurately estimate the level of dysfunction [17].

Another important component of the system is inter-patient pharmacokinetic variability [18]. Pharmacogenetic variation explains some of the variability in the response and toxicity of patient groups to agents like 5-FU and irinotecan [18, 19].

Deficiency of dihydropyrimidine dehydrogenase, reflecting different polymorphisms of the DPD gene, which inactivates 5-FU, will lead to increased toxicity from this cytotoxic. The active form of irinotecan, SN38, is inactivated via glucuronidation. Reduced activity of UGT1A1, which is involved in this glucuronidation, and which is a sine qua non of Gilbert's syndrome, leads to dose limiting diarrhea and neutropenia.

Other factors may also cause inter-patient variation in pharmacokinetics. The variability in absorption of oral drugs secondary to chemotherapy induced damage to the mucosa can alter efficacy and toxicity of these agents. Most chemotherapy regimens are dosed based on body surface area, which is calculated by using body weight and height. Obesity, which causes increase in the lipophilic compartment, is not well addressed by this calculation of drug dosing. The amount of lipid solubility of a drug can cause changes in the drug levels in the obese. Hypoalbuminemia causing decreased binding and increased free concentration of the drug can increase side effects. This may be quite important in a pretreated patient with advanced cancer and cachexia, which is commonly associated with hypoalbuminemia.

Pharmacodynamics

The fundamental objective of pharmacodynamics is to understand dose-response relationships, usually predicated on the assessment of drug levels in different tissues [19, 20], as well as the pharmacogenomic considerations noted above. Initial pharmacodynamic principles were based on the concept that all drugs will have a sigmoidal shape in their drug effect, based on the theory that drugs require a receptor interaction for their effect. However, this rule is not valid for phase specific antineoplastic agents. When cells are not in the specific phase, increasing the dose will not increase the sensitivity, although increasing the time of exposure may have the desired effect.

The prediction of toxicity and response in an individual patient should be based on both pharmacokinetic and pharmacodynamic principles. Reducing drug dose for excessive toxicities may seem to be logical in the case of altered excretory function, but may not be effective in the case of reduced hematological reserve after prior treatment, resulting simply in under-dosing.

Monitoring of drugs with a narrow therapeutic index is usually done by monitoring drug levels in the body, in most other areas of medicine. This is more complicated in cancer treatment because of the frequent use of combination chemotherapy. Techniques such as low-dose weekly scheduling (e.g. taxanes) and AUC dosing based on creatinine clearance (e.g. carboplatin) are being used to limit toxicity without compromising efficacy.

Patterns of Drug Response and Resistance

Response of tumors can be divided into three broad groups [21, 22]: (a) drug sensitive tumors, with treatment resulting in cure; (b) highly responsive tumors, but with eventual refractoriness to cytotoxic treatment; and (c) tumors with little responsiveness to chemotherapy (Table 13.1).

Drug resistance has been studied in both in vivo and in vitro in a range of models. Multiple reasons involving anatomical, pharmacological and biochemical mechanisms explain various aspects of tumor resistance to cytotoxic chemotherapy:

- Reduced intracellular levels secondary to transport system inhibition (e.g. the folate transport mechanism leading to methotrexate resistance), reduced diffusion across the cell membrane or increased efflux (P-glycoprotein MDR1 drug efflux pump). Classical multidrug resistance (MDR) is associated with the overexpression of P-glycoprotein (MDR1, P-170) [23, 24]. This causes increased efflux of various antineoplastic agents from the cell leading to decreased accumulation intracellularly. This has been implicated in the cross-resistance patterns between anthracyclines (e.g. doxorubicin), taxanes (e.g. paclitaxel), vinca alkaloids (e.g. vincristine) and the topoisomerase inhibitors (e.g. etoposide). Tumors, which over-express this gene, have sometimes demonstrated increased resistance and poor response to chemotherapy;
- Defects in cellular death mechanisms. Alkylating agents cause cell death by intrastrand DNA linkages. This results in defective cell repair systems that should lead to cell death. However, if this system does not recognize the DNA defects, this will prevent tumor cell death, resulting in resistance [15, 25]. Defects in the apoptotic pathway can also involve the Bcl-2 family of proteins and other regulatory mechanisms, such as p-53. Bcl-2 family proteins include both up- and

Table 13.1 Responsiveness of genitourinary tumors to chemotherapy

1. **Highly sensitive**
A. Childhood cancers, such as Wilms tumor, Ewings tumor, and rhabdomyosarcoma
B. Germ cell tumors – e.g. of testis, retroperitoneum
C. Lymphoma (extranodal) – Hodgkin's disease; Burkitt's lymphoma
2. **Moderately sensitive**
A. Adenocarcinoma of the prostate
B. Transitional cell carcinoma of bladder and urothelial tract
C. Squamous cell carcinoma of penis or urethra
D. Some non-Hodgkin's lymphomas involving genitourinary tract
E. Small cell anaplastic carcinoma – prostate, bladder
F. Sarcomas of bladder or prostate in adults
3. **Less/Minimally sensitive**
A. Adrenal gland cancers
B. Renal carcinoma[a]
C. Adenocarcinoma of bladder

[a]Note: emerging changes with recent development of targeted therapies

down- regulators of apoptosis. Chemotherapy induced damage to cells is perceived by p53 which can then initiate either apoptosis or cell repair. Altered p53 is one of the most common genetic abnormalities seen in solid tumors. Expression of wild type p53 and changes in Bcl-2 family members can result in altered sensitivity of the tumor cell to chemotherapy agents [26, 27];
- Alteration of drug targets, including receptors or enzymes (e.g. thymidylate synthetase in 5-FU resistance) [27];
- increased levels of cell protective agents (e.g. glutathione in cisplatin resistance), which prevent oxidative damage and death of the cell via cell scavenging functions, have been implicated in preclinical models of bladder cancer [28];
- Modification of drug metabolism can be catastrophic to antineoplastic agents that are designed as prodrugs (e.g. cyclophosphamide must be activated in the liver; irinotecan must be converted to SN-38, its active moiety);
- Tumor cell heterogeneity with spontaneous genetic mutations occurs even before exposure to treatment [27, 29, 30]. After chemotherapy eliminates the sensitive cells, these resistant cells may grow to become the predominant cell population.

Approaches to circumvent drug resistance have involved the use of multidrug combinations, dose escalation, agents that reverse increased efflux, cofactors that amplify drug efficacy, and inhibition of drug inactivation. Recently liposomal and nanoparticle albumin- stabilized formulations have been applied to overcome drug resistance, but with limited success in genitourinary malignancy [31]. These increase the delivery of chemotherapy to the tumor cell while minimizing toxicity.

Combination Chemotherapy Principles

Single agent regimens, with few exceptions (e.g. gestational choriocarcinoma), are rarely able to achieve cure. In view of this and the observations above, combination chemotherapy regimens have been devised to accomplish the major objectives of attaining maximum tumor kill with minimal toxicity and to prevent drug resistance [16, 32]. The era began when numerous active drugs became available simultaneously and were applied to curative management of leukemias and lymphomas in the late 1970s. Fundamental principles used in the selection of the drugs for combination regimens include [32]:

- Use of drugs with defined activity against the tumor
- Known expression of different patterns of resistance
- Different mechanisms of action with potential synergy
- Non overlapping dose-limiting toxicities
- Optimal dosing and timing in combination to allow the shortest treatment-free interval
- Absence of negative interactions – e.g. adverse interactions between cytotoxics and targeted therapies, negative summation effects between two cytotoxics

The relationship between doses and combination of these agents is complex [32, 33]. The maintenance of dose intensity has proved to be important in the success of some of these regimens. Reduction of dose can result in significantly decreased cure rates, especially in the more responsive tumors such as germ cell cancer. Thus, although responses may occur despite dose reduction, residual tumor cells often persist, leading to eventual relapse and decreased survival. The concept of relative dose intensity (amount of drug delivered in a given time frame) has evolved over the past two decades, but it remains controversial as to whether this is a major factor in cure [33].

Ideally drugs should be used in their optimal schedule and dosage even when being combined with other agents. However, care must be exercised to avoid overdosage and excessive normal-tissue toxicity. In general, the interval of drug delivery also needs to be consistent, keeping the treatment free interval to be the shortest time necessary for resolution of any dose limiting toxicity (usually bone marrow toxicity) to maintain dose intensity [32–34].

The selection of patients to receive combination chemotherapy has also undergone refinement. In the present era, we are more cautious than in the past, and many oncologists believe that it may not be appropriate for a patient with a poor performance score (e.g. ECOG level 3–4) to be given a toxic regimen, unless there is substantial evidence that his disease is likely to be highly responsive to the treatment [35]. We believe that it is critically important to discuss the aims and expectations of chemotherapy with all patients, but of even greater importance in the elderly and infirm. By contrast, with better understanding of age-related changes in drug pharmacology and the importance of performance status, more venturesome approaches are now being explored in the chemotherapy of the fit elderly with advanced cancer [36].

High Dose Chemotherapy and Stem Cell Transplantation

High dose chemotherapy involves the use of potentially lethal doses of chemotherapy with or without radiation, followed by rescue with hematopoietic stem cells obtained from the blood or by marrow harvest and storage [37–40]. This is predicated on the concepts that (a) there is a dose response relationship for a specific regimen in certain tumors; (b) there is benefit to dosing at a higher level than can be survived by normal tissues (e.g. bone marrow), provided that re-infusion of bone marrow can avoid the death of the host. This modality, which is predominantly used in hematological malignancies, has been applied to the management of relapsed or poor-risk metastatic germ cell tumors [38]. To date, despite evidence of anti-cancer activity, prospective, randomized trial data have not shown an unequivocal survival benefit from this approach to the management of advanced germ cell tumors, compared to standard dose poor-risk or salvage regimens [38, 41]. There are still advocates of this procedure in the management of poor-risk or relapsed germ cell tumors, but the majority of evidence to support this contention comes from retrospective, historically controlled analyses [42].

Allogeneic Bone Marrow Transplantation

This process involves the acquisition of stem cells from a donor who has complete/partial HLA-compatibility with the patient [39, 40]. This can include matched related donor, matched unrelated donor (e.g. HLA matched donor from the Bone marrow registry), stored cord blood, syngeneic (identical twin), and haplo-identical transplantation (e.g. sibling/parent who is half matched to the patient). Complexities of allogeneic bone marrow transplantation involve immunosuppression after the transplant to prevent rejection of the donor cells by the host. This milieu of intense cytotoxic damage to the bone marrow and immunosuppression allows the donor graft cells to launch a response against the recipient termed as graft versus host disease (GVHD). GVHD can also have a positive effect on the tumor by having a graft versus tumor effect; which can be curative in some malignancies like Chronic Myelogenous Leukemia. Advantages of allogeneic bone marrow transplantation include the graft versus tumor effect, curative option in patients with tumor involvement of the bone marrow and no tumor contamination of the graft cells.

Disadvantages include graft versus host disease; higher acute treatment related mortality, higher infectious complications secondary to immunosuppression needed after transplant and the need to locate a suitable donor. In addition, increasing evidence is available regarding late complications, including the development of second malignancies [40].

Autologous Bone Marrow Transplantation

This variant of marrow transplantation uses the patient's own hematopoietic stem cells, which are harvested and cryopreserved prior to initiation of treatment [38]. After the completion of high dose chemotherapy and/or radiation the harvested marrow is reinfused. Advantages include the absence of requirement for immunosuppression after infusion of stem cells, no Graft Versus Host Disease, the potential for use in older patients; no requirement for a donor; and lower treatment related mortality of about 2–5 %.

Some of the disadvantages of this approach include the absence of graft versus tumor effect, and the risk of re-seeding tumor cells if there is marrow involvement by the malignancy.

Brief Overview of Cytotoxic Agents

Alkylating Agents

The alkylating agents are among the oldest cytotoxic agents, and form the backbone of numerous regimens. They impair cell function by transferring alkyl groups to amino, carboxyl, phosphate or sulfhydryl groups of nucleic acids (DNA & RNA).

The most actively alkylated site is the N-7 position of guanine. This results in cross-linked DNA strands that cannot replicate, impaired transcription of RNA and other damage to the genetic material. They are cell cycle specific, but not phase specific. They have traditionally been divided into five classes, although the platinum complexes (with similar, bifunctional alkylating action) have been included as a sixth class.

Nausea, vomiting, alopecia, and myelosuppression are common acute side effects. They can also cause secondary acute leukemia or other solid tumors several years after the initiation of treatment. This iatrogenic leukemia, typically preceded by a myelodysplastic phase of variable duration, is associated with abnormalities of chromosome 5, 7 or 8. The features of the common alkylating agents are summarized in Table 13.2 [43].

Table 13.2 Major alkylating agents in clinical genitourinary cancer practice

Drug	Pharmacology	Uses	Toxicity
Carboplatin	Second generation platinum compound similar to cisplatin with different toxicity. Half-life is shorter than cisplatin	Modest activity against germ cell tumors and perhaps prostate cancer	DLT = Myelosuppression especially thrombocytopenia. Dosage typically done by AUC calculation
Cisplatin	First heavy metal anti neoplastic. Long half-life, may remain in tissues for months or years. Poor CNS penetration. Primarily excreted in the urine. Clinical cross-resistance with Carboplatin	Active against germ cell tumors & bladder cancer; some activity against prostate and adrenal cancers	DLT = Cumulative nephropathy which can be reduced to <5 % with vigorous hydration. Cumulative peripheral sensory neuropathy. Ototoxicity with tinnitus and high frequency hearing loss
Cyclo-phosphamide	Both oral and IV forms. Requires activation in the liver to form acrolein and an alkylating metabolite. Drugs affecting microsomal enzymes will affect efficacy	Activity against prostate cancer; some activity against germ cell tumors; modest activity against UC	DLT = Myelosuppression. High dose as preparation for BMT can cause cardiac necrosis. Hemorrhagic cystitis is secondary to a metabolite and can be prevented by hydration and Mesna
Ifosfamide	IV formulation. Requires activation in the liver similar to cyclophosphamide	Bladder UC sarcomas, germ cell tumors	DLT = Myelosuppression. Hemorrhagic cystitis. High doses can lead to encephalopathy
Nitrosureas	Highly lipid soluble. Rapidly biotransformed	Minor activity in hormone refractory prostate cancer	DLT = Myelosuppression can be prolonged and cumulative. Nausea and vomiting can last upto 24 h
Temozolamide	Oral medication which is activated spontaneously to the same active metabolite as DTIC	Inactive in hormone refractory prostate cancer	DLT = Myelosuppression especially thrombocytopenia. Moderate Gastrointestinal side effects

DLT dose-limiting toxicity, *UC* urothelial cancer, *AUC* area under the curve

Antimetabolites

Antimetabolites have been used since 1948, when they first produced temporary remission in children with acute lymphatic leukemia (Table 13.3). Subsequently methotrexate proved that chemotherapy could cure cancer as a single agent in gestational trophoblastic neoplasia. These constitute a large group of drugs, which interfere with the building blocks of DNA/RNA synthesis. They can be structural analogues of normal molecules needed for cell growth or inhibit enzymes needed for the synthesis of essential compounds. Therefore, their activity is greatest in the S phase of the cell cycle. Pharmacokinetics is characterized by their nonlinear dose-response curve (an exception being 5-FU). After a certain dose, there is no more cell death, however increasing the length of time that the cells are exposed will increase the cell killing potential.

Antitumor Antibiotics

The antitumor antibiotics are generally derived from microorganisms (Table 13.4). They interfere with DNA by intercalation, where the drug inserts between DNA base pairs. This interferes with DNA replication and messenger RNA production.

Table 13.3 Antimetabolites in clinical genitourinary cancer practice

Drug	Pharmacology	Uses	Toxicity
Capecitabine	Prodrug of 5-FU which can be given orally	Possible activity against bladder adeno CA	DLT = Diarrhea. Hand-foot syndrome is common and can be dose limiting
5-Fluorouracil	Inhibition of Thymidylate synthetase by inhibits DNA synthesis. Other metabolites may interfere with RNA function. Differs from other antimetabolites in having a log linear cell kill. **Leucovorin** enhances the action by acting at thymidylate synthetase	Modest activity against bladder adeno CA and minor activity against prostate CA	DLT = Myelosuppression (more common with bolus regimens), mucositis and diarrhea (More common with infusion regimens). Other toxicities include cardiac, excessive lacrimation, nasal discharge, and cerebellar toxicity
Methotrexate	Synthetic analog of Folic acid, which blocks the enzyme Dihydrofolate reductase preventing formation of reduced folic acid that interferes with vital cellular enzymes	Active against germ cell tumors & bladder cancer; minor activity against prostate CA and penile CA	DLT = Myelosuppression, stomatitis, renal dysfunction, neurotoxicity, depending on dose and duration of use. Leucovorin rescues normal tissues from toxicity and is used in high dose regimens

DLT dose-limiting toxicity, *CA* carcinoma

Table 13.4 Antitumor antibiotics in clinical genitourinary cancer practice

Drug	Pharmacology	Uses	Toxicity
Actinomycin D (Dactinomycin)	Extensively tissue bound with long half life (36 h)	Active against Wilms tumor, sarcoma, germ cell tumor	DLT = Myelosuppression; may cause severe nausea and vomiting and allergic reactions
Bleomycin	Activated by microsomal reduction. Radiation sensitizer	Active against germ cell tumors; modest activity against penile cancer	Chills and febrile reactions that are infusion related. Pneumonitis can occur 4–10 weeks after initiation; skin pigmentation
Doxorubicin Epirubicin	Extensively plasma protein bound with long half-life. Liposomal formulation (**Doxil**) is undergoing trials in various tumors	Activity against small cell anaplastic cancers, prostate cancer, bladder cancer, Wilms tumor	DLT = Myelosuppression, commonly leukopenia. Cardiomyopathy with CHF is more frequent after a cumulative dose of 550 mg/m^2 (400 mg/m^2 with previous mediastinal irradiation)
Mitomycin	Also functions as an alkylating agent	Active against bladder cancer; modest activity against prostate CA	DLT = Myelosuppression which can be cumulative and prolonged. Thrombocytopenia may occur up to 8 weeks. Cutaneous irritant

DLT dose-limiting toxicity

They also interfere with topoisomerase function. They are cell cycle non-specific drugs and are an important component against slowly growing tumors with a low growth fraction. As a class they tend to be vesicants, and extravasation may cause skin necrosis and ulceration. Common side effects include nausea, vomiting, alopecia and myelosuppression. Mitomycin and doxorubicin, both large molecular weight compounds, have been used extensively for intravesical treatment of superficial bladder cancer, and can be inserted into the bladder via urinary catheter. In this setting, mitomycin C can occasionally cause significant cutaneous eruptions if spilled onto the skin and not washed away.

Tubulin Targeting Agents

The class of anti-tubulin drugs includes the vinca alkaloids and taxanes (Table 13.5). The primary target of these drugs is the mitotic spindle. The vinca alkaloids bind to microtubular proteins inhibiting their assembly, leading to mitotic spindle dysfunction, mitotic arrest and eventually cell death from apoptosis. The taxanes bind to tubulin polymers, promoting their assembly but make them resistant to depolymerization resulting in nonfunctional microtubules. Each of this class of cytotoxics may be exported from the cancer cell by the function of p-glycoprotein. Recently vinflunine, a fluorinated vinca alkaloid, was shown to be superior to best supportive care

Table 13.5 Tubulin targeting agents in clinical genitourinary cancer practice

Drugs	Uses	Pharmacology	Toxicity
Docetaxel	Activity against hormone refractory prostate cancer, bladder cancer, germ cell tumors and squamous cancers	Semi-synthetic and thus more soluble; does not require Cremophor; triphasic decline; degradation via metabolism, rather than excretion	DLT = Myelosuppression. Fluid retention is dose dependent, secondary to increased capillary permeability and is reversible. Hypersensitivity reactions similar to Paclitaxel (despite not being formulated in Cremophor) can occur, but less common. Peripheral neuropathy
Paclitaxel, NAB-paclitaxel	Activity against hormone refractory prostate cancer, bladder cancer, germ cell tumors and squamous cancers	Requires cremophor for dissolution, adding toxicity. Recent nano-engineered preparation may improve cellular uptake and reduce toxicity; altered disposition with increasing age; biphasic or triphasic decline of levels; metabolic clearance. NAB-paclitaxel is a recent investigational, nano-engineered variant that allows tumor uptake without the need for cremophor as a diluent	DLT = Myelosuppression. Hypersensitivity (3 %) to Cremophor (Carrier vehicle) occurs usually within 20 min of initiating treatment, 90 % of which happen within the first two doses. Premedication with steroids and Histamine blockers is routinely recommended. Peripheral neuropathy is dose dependent
Cabazitaxel	Activity against hormone refractory prostate cancer	Binds less avidly to multi-drug resistance protein; degradation via metabolism	DLT = Myelosuppression. Other toxicities include nausea, vomiting, diarrhea, asthenia, fatigue, peripheral neuropathy. Toxic deaths from sepsis reported in European centers in TROPIC trial
Vincristine Vinblastine Vinflunine	Activity against bladder cancer and germ cell tumors	Hepatic clearance; triphasic decline; these agents are vesicants	DLT = Dose dependent peripheral neuropathy universally develops. It is reversible, however can take several months. Associated side effects may include cranial nerve palsies, abdominal pain, asthenia, obstipation, ataxia, foot-drop, cortical blindness, constipation

in a phase III trial after failure of initial chemotherapy for metastatic urothelial cancer, but the duration of survival in each arm was short.

Cabazitaxel, formerly known as XRP6258, a new generation semi-synthetic taxane with low affinity for multidrug resistance protein, has been demonstrated to show efficacy against docetaxel-treated castrate-resistant prostate cancer [44].

In the international "TROPIC" randomized trial, patients were allocated to treatment with mitoxantrone or cabazitaxel after prior failure of docetaxel, and a statistically significant median survival benefit of 3.4 months was noted with cabazitaxel [44]. In several eastern European centers, toxic deaths were experienced in patients treated with this novel agent, emphasizing the hazards of myelosuppression in an elderly population with potential renal dysfunction and bone marrow compromise. This agent was recently approved by the Food and Drug Administration for use in North America for castration-resistant prostate cancer.

Topoisomerase Inhibitors

Semisynthetic glycosides of the naturally occurring podophyllotoxins, the epipodophyllotoxins (etoposide and tenoposide), have been in clinical use for 30 years, because of anticancer efficacy and modest toxicity (Table 13.6). Etoposide has become a drug of choice for germ cell malignancies and for small cell cancers (including those derived from bladder and prostate).

The camptothecin derivatives (irinotecan and topotecan) have also been introduced into clinical practice because of their function against topoisomerases. Irinotecan has found particular application against gastrointestinal adenocarcinomas. DNA attachment to the nuclear matrix occurs at areas called "domains", and topoisomerases bind to these areas, forming a complex that allows DNA to unwind for cell division. Topoisomerase I aids in the relaxation of supercoiled DNA, while topoisomerase II catalyzes the breakage and repair of DNA. These enzymes are crucial in several critical steps of the cell cycle. The epipodophyllotoxins inhibit topoisomerase I and the camptothecins inhibit topoisomerase II. Anthracyclines also exhibit topoisomerase inhibition. Topoisomerase II inhibitors can cause secondary leukemia with a shorter latency period than with alkylating agents and not typically preceded by a myelodysplastic phase. These are associated with a balanced translocation involving chromosome 11 (11q23) or 21 (21q22).

Table 13.6 Topoisomerase inhibitors in clinical genitourinary cancer practice

Drugs	Pharmacology	Uses	Toxicities
Etoposide (VP-16)	Can be used orally and IV. Bioavailability is 50 %, however it is nonlinear and decreases with doses higher than 200 mg	Activity in germ cell tumors, Wilms tumor	DLT = Neutropenia. Gastrointestinal toxicities common with oral drug
Irinotecan (CPT-11, Camptosar)	Needs to be activated to SN-38. This conversion occurs primarily in the liver, but can also occur in the plasma and in the intestinal mucosa	Some activity in phase II trials in bladder cancer	Early diarrhea within 24 h of the infusion is cholinergic and is controlled with atropine. Late diarrhea is due to SN-38 and needs to be controlled with antibiotics and Loperamide

Principles of Targeted Therapies

Since Paul Ehrlich proposed the concept of the "magic bullet" to cure each infection with a specific targeted drug, there has been a search for similar applications in cancer. The discovery of drugs with targets that are variably expressed in neoplastic cells would theoretically result in increased anti-cancer effect and reduced toxicity. Recently, with the unraveling of the human genome and of the molecular pathways in cancer biology, functional targeted therapies have been discovered [45–49].

The prototype clinical compound has been imatinib mesylate ("Gleevec"), a signal transduction inhibitor that targets the BCR-ABL protein and related tyrosine kinases (the constitutive abnormality created by the Philadelphia chromosome in chronic myeloid leukemia). This agent has had application in chronic myeloid leukemia, gastro-intestinal stromal tumors and some sarcomas. The agent inhibits differentiation, proliferation and induces apoptosis in BCR-ABL positive cells.

Traditional cytotoxic chemotherapy has proven disappointing in the treatment of renal cell carcinoma (RCC) and prostate cancer but these malignancies have provided fertile ground for the development of targeted systemic treatment. This is perhaps most evident in the setting of metastatic clear cell renal carcinoma, with the discovery of frequent inactivation of the Von Hippel-Lindau (VHL) tumor suppressor gene in this disease [47, 49]. Given the role of the VHL gene in adaptation to hypoxia, trials were developed focusing on targeted inhibition of angiogenesis. Angiogenesis is crucial for tumor growth, and this is promoted by oncogene driven expression of vascular epithelial growth factor (VEGF) interleukins and other growth factors [45–48]. In tumors, VEGF is constitutively overexpressed as compared to normal tissue, and is further increased by hypoxia [47]. This has been targeted with monoclonal antibodies and tyrosine kinase inhibitors, and details are beyond the scope of this brief review.

Over the last 7 years, this strategy has resulted in approval by the Food and Drug Administration (FDA) of several targeted therapies in metastatic RCC. These agents are directed against VEGF, the VEGF receptor (VEGFR), or downstream events in angiogenesis and hypoxia.

Small Molecule Tyrosine Kinase Inhibitors

Four drugs—sorafenib, sunitinib, axitinib, and pazopanib—are multitarget tyrosine kinase inhibitors currently approved by the FDA for the treatment of metastatic RCC. They are designed to inhibit the intracellular activation of the VEGFR but differ in their potency and receptor specificity and therefore have unique toxicity profiles.

Sorafenib was the first multikinase inhibitor to obtain FDA approval in metastatic RCC in 2005. Sorafenib is an oral drug that inhibits signaling by the VEGFR

family, as well as RAS and platelet-derived growth factor receptor (PDGFR). This agent can cause rash, nausea and vomiting, hand-foot syndrome, diarrhea, myelosuppression, and hepatic dysfunction. Sorafenib was approved based on the results of the randomized, double-blind, placebo-controlled Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET) [50]. More than 900 patients with cytokine-refractory metastatic renal cell carcinoma were randomized to oral sorafenib versus placebo. Based on favorable results in the sorafenib-treated arm in a planned interim analysis, patients treated with placebo were allowed to cross over to the treatment arm. A preplanned second interim analysis that was designed to account for the variables introduced by the cross over revealed a significant increase in overall survival with sorafenib compared to placebo (17.8 versus 14.3 months, $p=0.0287$) [51].

Sunitinib is an oral multikinase inhibitor that targets the VEGFR family, PDGFR, and the c-kit oncogene. Side effects include rash, stomatitis, diarrhea, constipation, hepatic dysfunction, fatigue and neurological symptoms. Sunitinib received first-line approval from the FDA for the treatment of metastatic RCC on the basis of a randomized phase III trial published in 2007 [52]. Untreated patients with metastatic RCC were randomized to oral sunitinib vs. subcutaneous interferon-alfa. Progression-free survival (PFS), the primary endpoint of the study, was significantly improved with sunitinib compared to interferon (11 months versus 5 months, $p<0.001$). This improvement allowed patients on the interferon therapy to cross over to sunitinib treatment, which lessened the impact of sunitinib therapy at the final analysis. However, an exploratory analysis accounting for the confounding issues of cross over revealed a significantly improved overall survival that represented a secondary endpoint of this pivotal study [53].

Axitinib, a potent, selective second-generation inhibitor of VEGFR, was compared to sorafenib in second line use for patients with clear cell RCC who had been treated with sunitinib, bevacizumab plus interferon-alfa, temsirolimus or cytokines [54]. The most common adverse events were diarrhea, hypertension and fatigue in the axitinib arm, and diarrhea, palmar-plantar erythrodysesthesia (hand-foot syndrome) in the sorafenib arm. Axitinib resulted in a significantly longer progression free survival (PFS), and while the difference was modest (6.7 vs. 4.7 months), this led to FDA approval.

Pazopanib was the most recent small molecule tyrosine kinase inhibitor FDA-approved on the basis of a phase III trial in cytokine-resistant and treatment naïve metastatic RCC patients published in 2010 [55]. This study randomly compared oral pazopanib versus placebo using progression-free survival as a primary endpoint. The median PFS was more the doubled in the treatment arm compared to the entire placebo-controlled population (9.2 versus 4.2 months, $p<0.0001$) and was also statistically superior to the untreated and cytokine-refractory placebo-treated subgroups. The profile of side effects is similar, and includes, diarrhea, rash, constipation, hypertension, nausea and altered hepatic function. The COMPARZ trial, randomizing patients with metastatic RCC to sunitinib versus pazopanib has completed accrual, and showed that pazopanib and sunitinib have equal efficacy, but that safety and quality of life measures favour pazopanib [56].

VEGF Inhibition

Bevacizumab is an antibody directed against the VEGF ligand first approved in the treatment of metastatic colorectal cancer. In conjunction with interferon alfa, it was approved for use in metastatic RCC in 2009. The pivotal phase III studies resulting in approval included the AVOREN trial (Avastin and Roferon in Renal Cell Carcinoma) [57] and the Cancer and Leukemia Group (CALGB) 90,206 trials [58]. Both trials compared bevacizumab and interferon alfa to interferon alfa alone and both reported statistical improvement in PFS with combination therapy. Neither study revealed an improvement in overall survival; this is likely the result of cross over to bevacizumab (AVOREN) or subsequent therapy with small molecule tyrosine kinase inhibitors (CALGB).

Mammalian Target of Rapamycin (mTOR) Inhibitors

mTOR is a protein kinase with downstream activity in multiple signaling cascades including angiogenesis, protein synthesis and cellular migration. Current mTOR inhibitors mimic ATP and target the mTOR kinase domain. Two of these agents, temsirolimus and everolimus have been approved for the treatment of metastatic RCC.

Temsirolimus was the first of these agents to receive FDA approval for initial treatment of patients with poor-prognosis metastatic RCC. The Global Advanced Renal Cell Carcinoma trial compared temsirolimus, with or without interferon alfa to interferon alfa alone [59]. Enrolled patients on the study had to have at least three predictors of shortened survival. The primary endpoint of the study was overall survival and this was improved with temsirolimus compared to interferon alfa (10.9 versus 7.3 months $p = 0.008$) but not combination therapy versus interferon alfa (8.4 versus 7.3 months). In addition, fewer adverse events were observed with single-agent temsirolimus as compared to interferon alfa or combination therapy.

The FDA approved everolimus in 2009 based on the pivotal RECORD-1 trial (Renal Cell Cancer Treatment with Oral RAD-001 given Daily) [60]. This study randomized 410 patients with MCCRCC who had failed therapy with at least one small molecule TKI to everolimus versus placebo. The primary endpoint of PFS was met after the second interim analysis (4 months versus 1.9 months for placebo, $p < 0.001$) and the study was terminated early. Overall survival was not improved in the study, likely due to a high cross over rate of enrolled patients, but was improved in exploratory analysis designed to account for this bias [61].

Summary

The nature and scope of chemotherapy has changed dramatically in the past 70 years. Therapeutic strategies that were initially empirical, highly toxic and broadly based have given way to rationally predicated, specifically targeted approaches.

The more recent emphasis of drug design has been to apply our knowledge of the human genome and the regulators of the cell cycle to identify useful therapeutic targets, and also to create new compounds or analogues of old agents that have reduced toxicity profiles. The concepts of dose density and dose intensity have become less important with the advent of effective targeted treatments, but still may offer other potential options for increasing the cure rate of the remaining resistant cancers, perhaps in the context of adjuvant therapy. Further success in the domain of targeted therapeutics will depend upon the identification of specific biomarkers to help predict response and improved surrogate endpoints to facilitate selection among competing therapies. In addition, cancer genomics is rapidly evolving and will allow clinicians to develop more comprehensive and personalized strategies for these malignancies.

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Chapter 14
Principles of Radiotherapy in Urologic Tumors

Irwin H. Lee and Howard M. Sandler

Practical Considerations

Attempts at using radiation for treating human malignancies began soon after the discovery of x-rays by Wilhelm Roentgen in 1895. Radiotherapy is a local treatment-modality in which ionizing radiation is delivered to areas either with gross tumor or with a high-risk of harboring microscopic disease. It is essentially noninvasive when delivered from an external source **(teletherapy)** or minimally invasive when using implanted radioactive sources (**brachytherapy**). Over the past century, advances in the understanding of the physics and biology of radiotherapy, as well as developments in imaging and radiation sources, have led to improved efficacy of radiation in controlling cancers while decreasing toxicity. Currently, radiotherapy plays a central role in the management of many genitourinary malignancies, for both definitive management of localized disease and palliation of metastatic disease.

Radiotherapy uses ***ionizing*** **radiation**, which refers to any radiation with sufficient energy to generate ionized species by freeing electrons from their orbits. Ionizing radiation may consist of either electromagnetic waves (e.g., x-rays) or small particles (e.g., electrons, protons, or neutrons). In the case of x-rays, the energy is carried in the form of photons, which are small packets of energy. As the radiation passes through matter, energy is deposited along its path; the amount of energy absorbed is the ***dose*** **of radiation** and is measured in gray (Gy), with

I.H. Lee, MD, PhD
Kaiser Permanente,
Rohnert Park, CA, USA
e-mail: ihlee@post.harvard.edu

H.M. Sandler, MD, MS, FASTRO (✉)
Department of Radiation Oncology, Cedars Sinai Cancer Center,
8700 Beverly Blvd, Los Angeles, CA 90048, USA
e-mail: Howard.Sandler@cshs.org

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1 Gy = 1 J/kg. The total amount of energy deposited during therapeutic radiation is low, so that there is essentially no increase in temperature, however, the deposition of energy is very discrete and locally is intense enough to cause ionization and breakage of molecular bonds. The dose of radiation within a radiation field can vary widely from one point to another, depending on (among other things) the type of radiation, the energy of the beam, the distance from the radiation source, and the depth of the point in question. In general, the goal of radiotherapy is to maximize dose to the target while minimizing dose to normal tissues.

Megavoltage Radiation and Skin-Sparing

Modern radiotherapy became possible only with the development of relatively high-energy radiation sources, which permit safe delivery of a high-dose radiation to deep tissues. With early radiation sources, which consisted of relatively low-energy x-rays, dose was highest at the surface and decreased as the radiation moved deeper into tissue. As a result, in order to treat a deep target to a given dose, more superficial structures would necessarily be treated to a much higher dose than the target itself. Skin toxicity thus represented a major limiting factor when attempting to treat deeper structures, such as the prostate or bladder. In the 1950s, however, higher-energy megavoltage radiation sources became available using cobalt-60. Radiation with energy in excess of 1 MV has the important property of *skin-sparing*, meaning that the depth of maximal energy (Dmax) deposition is not right at the surface. In the case of cobalt-60, which emits two photons of similar energy that average of 1.25 MeV, Dmax is ~0.5 cm. More recently, linear accelerators capable of delivering even higher energy photons (in the range of 10–20 MV) have become available. At these energies, Dmax increases to ~2.5 cm, making it feasible to treat deep targets, often with minimal skin reaction.

Logistics and Simulation

In order to minimize toxicity, it is important not only to use appropriate beam energy but also to exclude normal structures as much as possible from the radiation field. *Simulation* and subsequent planning are the essential steps in accomplishing this goal. In the simulation process, the patient is marked either with temporary skin indices or small, ~1 mm permanent tattoos to facilitate accurate repositioning of the patient at the time of treatment, any needed immobilization devices are customized to the patient, and imaging is obtained – usually with high resolution axial CT – in order to delineate treatment targets and normal structures to be avoided when delivering the radiation. With more reliable patient setup, toxicity is reduced because during the treatment planning process, one must always create a margin for

uncertainty in target location. As this uncertainty is decreased, the field may be more tightly focused on the target, reducing the exposure of normal tissues to radiation.

Mechanism of Action

DNA Damage and Repair

Although many of the details on how radiation leads to cell death are unknown, it is clear that radiation-induced damage of DNA plays a central role. DNA damage may result from a *direct* interaction between the ionizing radiation and DNA molecules, or it may occur through *indirect* action as free radicals are generated when radiation interacts with other molecules, particularly water, in the neighborhood of the DNA. The result, in either case, may be single- or double-stranded DNA breaks. Although there exists mechanisms for DNA repair, the latter type of damage is particularly challenging to reverse and is thought to be the type of damage most important in radiation-induced killing. The two main mechanisms of repairing double-stranded breaks are homologous recombination, which depends on the presence of an undamaged template which is copied to damaged DNA, and non-homologous end-joining, which simply reconnects two broken DNA fragments in a somewhat haphazard fashion. The latter mechanism is clearly error-/mutation-prone. Cells that inadequately repair radiation-induced DNA damage will most often die or at least become unable to divide further. In general, normal tissues are more likely to be successful in repairing radiation damage than rapidly dividing cancer cells, and this difference in the capacity for repair is an essential component of the therapeutic index of radiotherapy.

Cell-Cycle Regulation

It is important to recognize that at a minimum, successful DNA repair requires adequate time for these mechanisms to occur. Normally dividing cells progress through the "cell cycle" which consists of four phases (M-mitosis, G1, S-synthesis of DNA, G2), with molecular checkpoints at each transition. These checkpoints ensure that the cell has enough time to complete any repairs that may be necessary before proceeding to the next phase of the cell cycle. One of the best characterized molecules involved in cell-cycle regulation is the P53, which causes delays in G1 and G2 when activated [1]. P53 is regulated by phosphorylation by many different

kinases, among them ATM, a DNA damage 'sensor' which is activated specifically after radiation-induced DNA damage.

Following exposure to radiation, it is likely that multiple cell cycle "brakes" are activated in order to allow for attempts at repairing radiation-induced damage. Of course, most malignant cells have defects in their cell-cycle regulation, including mutations in p53, and might therefore be more prone to advancing to the next phase of the cell cycle despite DNA damage from radiation.

Cell Death

If repair fails, either because of excessive DNA damage or because of a failure in cell-cycle regulation, cell death may occur through two fundamentally different mechanisms: (1) apoptosis or (2) necrosis. Apoptosis ('programmed cell death') occurs through activation of pathways that are a normal part of tissue development and homeostasis. In cells with intact apoptotic pathways, radiation-induced DNA damage may provide a trigger for them to undergo apoptosis either immediately or after a failed attempt at repair. For example, P53 is known to be important in promoting apoptosis in addition to regulating the cell-cycle following exposure to radiation. Unlike apoptosis, necrosis is a pathological process that does not require the presence of any specific pathways. It may occur after vascular damage or in damaged cells that are unable to undergo apoptosis. Cells dying by necrosis are more likely to generate an inflammatory response as cellular contents are spilled in an uncontrolled fashion.

Radiation-induced cell death may also be classified based on its timing. While the majority of radiation-induced cell-death occurs as cells are dividing ('mitotic death'), some cells may die a rapid 'interphase death'. The latter phenomenon occurs on the time scale of hours, requires relatively low doses of radiation, and is dependent on apoptosis. It is therefore found mainly in cell populations that are more prone to undergo apoptosis and that are clinically observed to be 'radiosensitive'. In contrast, mitotic death may occur in any cell that attempts to divide following radiation exposure. Death may be apoptotic or necrotic, and it may result from problems with spindle formation, improper chromosome segregation, or from a 'mitotic catastrophe' after failure of cell cycle arrest.

Radiation Response and Sensitivity

Different tumors exhibit a wide range of sensitivities and responsiveness to radiotherapy. The cells which are most sensitive to radiation are likely those that undergo an interphase death, with lymphocytes being the prime example. Seminomas are also extremely radiosensitive, presumably because germs cells are also more prone to apoptosis, which perhaps makes sense on a genome-protection, teleological level. Except for cases in which interphase death is a major contributor to the overall rate of radiation-induced killing, the clinical responsiveness of a tumor depends largely on the underlying rate of turnover since radiation-induced death does not occur until

cells try to divide. As a result, cancers that grow more slowly, such as prostate cancer, are likely to take longer to respond to radiation and may also be less sensitive, i.e., require higher doses to be eradicated.

The radiosensitivity of cells is also modulated by oxygenation and cell-cycle phase. It has been shown that hypoxic cells are relatively resistant to radiation [2]. Specifically, two to three times more radiation may be required to produce the same effect for cells in a hypoxic environment compared to those in an aerobic environment. The relevant range of oxygen tensions in these experiments was between 0 and 10 mmHg. It is believed that oxygen is important in *fixing* or making permanent the chemical changes induced by free-radical generation during radiation exposure. Similarly, the effectiveness of radiation can vary dramatically depending on the cell-cycle phase during which radiation occurs. Exposure during G2/M phase produces much greater cell-kill than does exposure during late S phase, which is the phase most resistant to radiation-induced cell death. The relative sensitivity is also roughly two to threefold.

Dose and Fractionation

The 4 R's of Radiotherapy

Radiotherapy is most often delivered in multiple *fractions*, or treatments, over the course of several weeks. A typical regimen for prostate cancer is to give a total of 70 Gy in daily 2 Gy fractions, 5 days per week, so that treatment takes 7 weeks.

The advantage of fractionating radiotherapy over delivering a single high-dose treatment is that the therapeutic index (i.e., the effect of radiation on tumor relative to normal tissue) is generally increased with fractionation for several reasons. First, tumors that have hypoxic cores may shrink over the course of therapy, so *reoxygenation* of hypoxic areas may occur, enhancing the effect of later fractions. Second, with each fraction, cells in the most sensitive portion of the cell cycle will be selectively killed by the radiation, and between fractions, cells in less sensitive phases may move into a more sensitive phase for the next fraction. This process, commonly referred to as *reassortment*, may occur in both tumor and normal tissue but is likely to play a greater role in rapidly cycling cell populations. Finally, by giving multiple small fractions, some degree of *repair* is permitted between treatments. This opportunity for repair generally favors normal tissue over cancer cells, whose repair mechanisms are more likely to be defective. These "3 R's" reoxygenation, reassortment, and repair generally increase the effectiveness of radiation with fractionation. In considering the impact of fractionation schedule on outcome, however, there is generally a fourth "R" – *repopulation* – that must be included since repopulation of tumor cells over time precludes the use of an excessively protracted course of radiotherapy.

Linear-Quadratic Model

A simple mathematical model, known as the linear-quadratic model, has been developed to predict the effects of different fractionation schedules [3]. This model is based on experimental measurements of cell-killing as a function of radiation dose. These measurements show that the relationship between the surviving fraction of cells and dose delivered is not linear. For example, if a treatment of 2 Gy resulted in a 50 % reduction in cell survival, a simple linear model would predict that treating with 4 Gy would result in a surviving fraction of 25 % (the result of giving 2 Gy twice). In fact, however, the surviving fraction after a single dose of 4 Gy is observed to be substantially smaller than that. The difference between the observed effect and the effect that would be predicted based on a linear model alone can be estimated by a quadratic function, i.e., it varies as the square of dose. Thus, the linear-quadratic model includes two parameters, α and β, which quantify the linear and quadratic contributions to cell-killing.

Note that the quadratic component is the one which yields different effects depending on fractionation. Therefore, the ratio of α to β, which may be different from one tissue (or effect) to another, provides a measure of sensitivity to fractionation, with smaller α/β ratios reflecting relatively greater sensitivity.

Early and Late Effects

Clinically, the effects of radiation are generally divided into early and late effects. Early effects occur during the course of treatment or within the weeks immediately following radiotherapy while late effects tend to occur 6 months or even years after radiotherapy has been completed. In prostate cancer treatment, early effects include skin reaction, cystitis, and diarrhea; late effects include fibrosis, erectile dysfunction, and rectal bleeding. Estimates of the α/β ratio for early effects are relatively high (~10) and for late effects are generally lower (~3). Furthermore, most tumors are thought to have α/β similar to that of early responding tissues (~10). These estimates corroborate the empirical observation that schedules employing larger fraction sizes tend to increase late effects, assuming a fixed rate of tumor control. Early effects, on the other hand, are unlikely to be substantially affected by changes in fractionation.

Altered Fractionation

Experience has shown that 1.8–2 Gy fractions seem to provide a good therapeutic ratio in most cases being treated with definitive radiotherapy. However, there are situations in which it may be beneficial to use different fraction sizes, and the linear-quadratic formula is helpful for determining the appropriate total dose when using either smaller or larger fractions. Given the fraction size (d), total dose (D), and α/β,

one can compute the *biologically equivalent dose* (BED), which is given by the linear quadratic formula as:

$$\mathrm{BED} = \mathrm{D}\left(1 + \mathrm{d}/\left(\alpha/\beta\right)\right).$$

The BED normally carries a subscript corresponding to the assumed α/β since it is clearly different for large and small α/β. Thus, for any given fractionation schedule, one must determine BED for both early (including tumor) and late effects.

Two alternatives to a standard (1.8–2 Gy) fractionation schedule are known as *hyperfractionation* and *hypofractionation*. In a hyperfractionated schedule, smaller than standard fraction sizes are used, usually to a higher total dose, so that a higher rate of tumor control might be achieved for a fixed rate of late complications. In contrast, with hypofractionation, relatively large fractions are used to a lower total dose. The main benefit of such a schedule is a shorter overall course of treatment, but the risk of long-term complications may be relatively higher. In palliative cases, it often makes sense to expedite treatment and late effects may be less important in patients with a limited prognosis.

Interestingly, there is also some evidence that a hypofractionated schedule may also be beneficial in the definitive treatment of prostate cancer. This speculation arises from studies of dose and tumor control following treatment of prostate cancer with either external radiation or brachytherapy. Because different brachytherapy sources emit radiation at different rates, it is possible to get rough estimates of the α/β for prostate cancer; and some studies suggest that prostate cancer may have, among common human neoplasms, a uniquely low α/β of ~1.5. If these estimates are accurate, then the therapeutic ratio for prostate cancer relative to late effects may, in fact, be optimized by using larger than standard fractions. Trials of hypofractionation are in progress, but until they are complete, the standard of care is still to use the standard fractions (1.8–2 Gy) [4].

New Technologies and Equipment

Three Dimensional Conformal Radiotherapy and Intensity Modulated Radiotherapy (3DCRT and IMRT)

Along with innovations in computing and imaging, radiotherapy techniques have improved. Powerful workstations facilitate the examination of multiple treatment strategies and allow radiation oncologists to optimize the ratio of dose delivered to the tumor target and minimize the dose absorbed by uninvolved normal structures [5].

3DCRT is defined as treatment using a volumetric imaging dataset, such as CT or MRI, and segmentation of that dataset into relevant structures, usually tumor targets (i.e. prostate and seminal vesicles) and normal structures (i.e. rectum and bladder). Multiple beams are selected by the oncologist based upon separation of tumor from normal and the beams are each sharply collimated with movable lead leaves (multileaf collimation). The multiple beams (commonly 4–6 for prostate can-

cer) intersect at the target resulting in a high dose and uniform dose delivery. For 3DCRT, each beam is relatively "flat", that is the dose is uniform as one traverses the beam aperture. The dose received by normal tissues is also calculated and can be displayed volumetrically using a dose-volume histogram, which shows the percent of the structure that receives above a certain dose. The dose-volume histogram can be analyzed to predict the risk of toxicity, since toxicity is related the dose received by a certain volume of an organ. For example, many prostate cancer treatments are designed to treat the prostate fully to up to 78 Gy, but to limit the rectum such that no more than 25 % of the rectum receives more than 70 Gy.

IMRT is a more recent extension of the 3DCRT principles. However, as implied by the name, the intensity of each beam is non-uniform across the aperture. This allows even more conformal dose distributions and greatly increases the therapeutic ratio of external beam radiotherapy. Figure 14.1 illustrates schematically the variation in intensity across an IMRT aperture and illustrates the improvement in conformality that can be achieved with IMRT versus 3DCRT for prostate cancer.

As mentioned above, ionizing radiotherapy can be delivered with particles as well as with photons or x-rays. Electrons are commonly employed to treat superficial targets as these light particles have little ability to penetrate deeply into tissue. High energy protons, which weigh 2,000 times more than an electron, are capable of penetrating deeply into tissue. Because protons are charged particles, they deposit their energy via electromagnetic interaction with the charged particles in tissue (electrons and nuclei). Interestingly, as the proton begins to give up its energy and slow down, this increases its energy deposition, which makes it slow down even more quickly, increasing further the energy deposition, and so it stops quite abruptly.

This leads to a relatively large about of ionization and subsequent DNA strand breaks near the end of the protons range and this is called the Bragg peak. This peak in ionization is favorable for radiation planning and dose delivery and has led to the proliferation of somewhat expensive proton treatment facilities at selected locations world-wide. Clinical trials will be required to determine whether proton beam treatment is more favorable than the widely available IMRT techniques.

Daily Localization

As radiotherapy techniques (IMRT in particular) result in more focused radiation doses, there is more concern about accuracy in targeting. After all, the careful planning that goes into and IMRT treatment plan is only put to good use if the patient is treated in the same position as they were in during the imaging dataset used in the planning process. Traditionally this was done by obtaining bone images during treatment. However, if the target is moveable with respect to the skeleton (as the prostate can be, depending upon bladder and rectal filling), bone imaging may be inadequate. One strategy for daily location verification is to implant fiducial markers into the target organ, imaging these radio-opaque markers prior to therapy, and then correcting the patient's position, if necessary [6]. (Fig. 14.2) Other strategies use daily pretreatment ultrasound [7] or, for pelvic tumors, inflated rectal balloons [8].

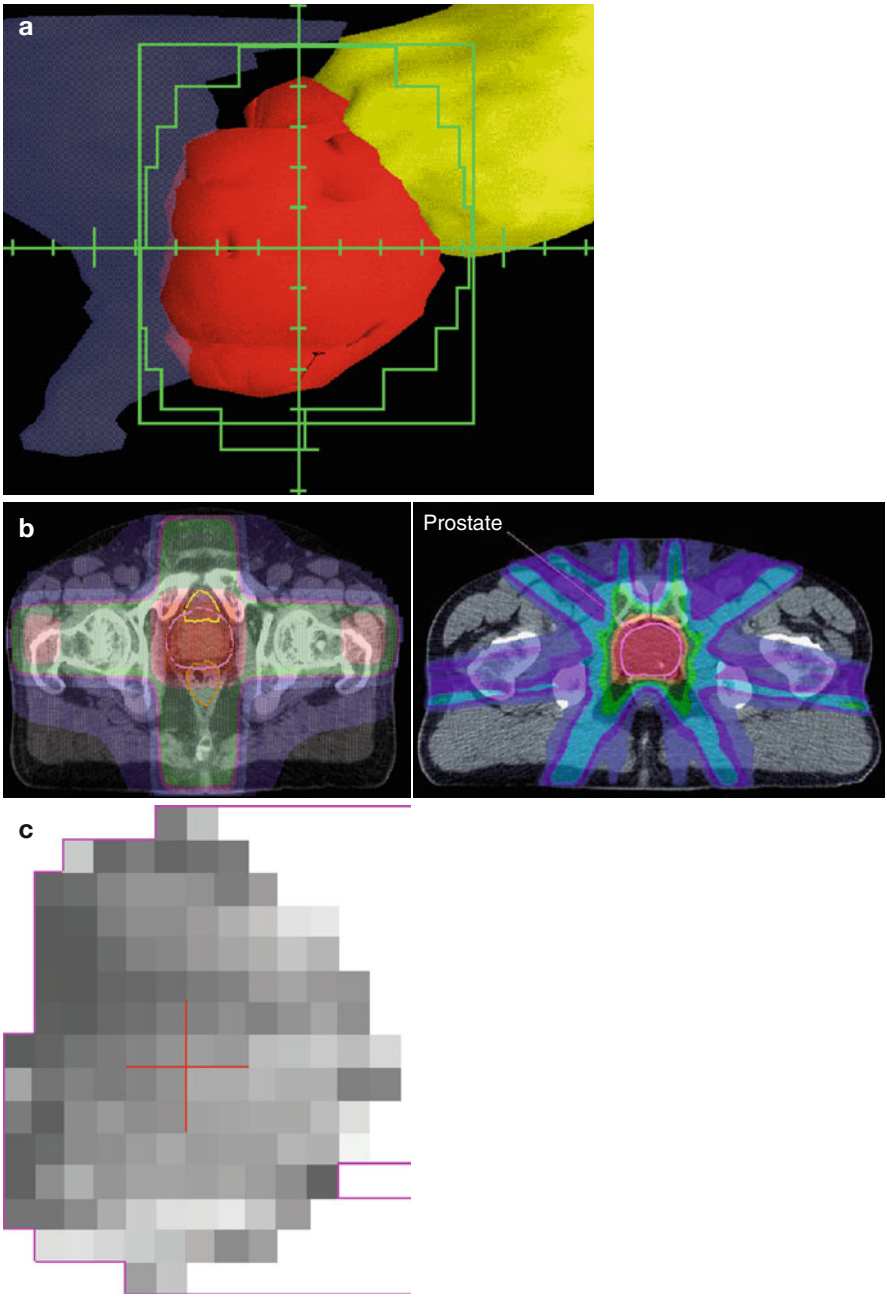

Fig. 14.1 (**a**) Beam's-eye-view display showing prostate (*red*) surrounded by custom aperture (*green*) which avoids rectum (*blue*) and bladder (*yellow*). (**b**) 3DCRT dose distribution (*left*) and IMRT dose distribution (*right*). The prostate target is outlined in *pink* and the high dose region is in *red*. Note the uniform intensity across the beam in the 3DCRT plan versus the modulated intensity across the beams in the IMRT plan. (**c**) *Gray* scale view if the intensity map of a single prostate IMRT beam showing the variation in intensity that, when combined with multiple similarly modulated beams, results in the highly conformal treatment seen in **b**

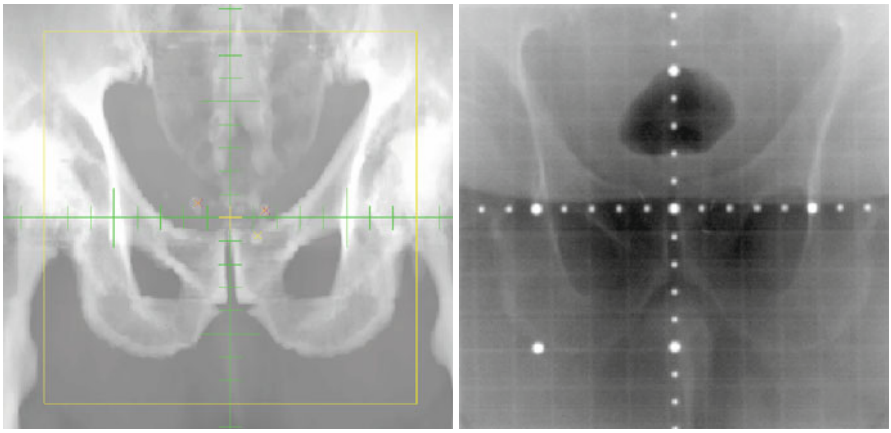

Fig. 14.2 *Left panel* shows digitally reconstructed radiograph (DRR, obtained from treatment planning CT with gold fiducial markers noted in the prostate by *colored x's*). The *right panel* shows an anterior image taken of the patient before treatment. Note that the gold markers are about 1 cm inferior compared with the DRR but that the center of the beam has been adjusted to account for the shift in prostate position

Brachytherapy

Prostate tumors are often treated by implanting the prostate with radioactivity. There are two main approaches: low dose rate radiotherapy that commonly uses permanently implanted 125-iodine seeds that have a half-life of approximately 60 days and thus deliver a continuous and ultimately high cumulative dose of radiation over several months and high dose rate radiotherapy that employs a highly radioactive wire that moves quickly – total treatment length is typically less than an hour – under computer guidance through temporarily placed catheters inserted through the perineum. These two approaches are widely used and because the sources are inserted directly into the prostate gland allow for a relatively conformal dose distribution by taking advantage of rapid dose absorption and the effect of the inverse square law.

For prostate cancer, compared to external beam IMRT, however, they may be accompanied by more acute and chronic urinary toxicity [9]. Both of the brachytherapy techniques – because of the nature of the rapid dose fall off – are often combined with 5 weeks of external beam radiotherapy that is used to broaden the treatment area to encompass microscopic extension that may be outside of the high dose brachytherapy volume and to homogenize the overall dose distribution by addition additional dosage to the prostate gland itself to fill in any inadvertent low dose regions. Generally the lowest risk prostate cancer patients are treated with monotherapy techniques and intermediate and high risk patients undergo the combined approach, which may add toxicity and decreases the convenience associated with the brachytherapy monotherapy strategy.

Systemic Radiotherapy

For prostate cancer, bone seeking radioactively labeled molecules have been used for diagnostic purposes extensively, i.e. bone scans. More recently, therapeutic amounts of radiation have been delivered to take advantage of the propensity that metastatic prostate cancer has for the skeleton. 89- strontium is a beta-emitting isotope with a physical half life of approximately 50 days and a shorter biological half life secondary to excretion, although it may be retained in metastatic bone longer than in normal bone, providing a therapeutic advantage [10]. This agent has a role in the palliation of metastatic skeletal disease, especially when there is widespread involvement not easily encompassed by a focal external beam field, which can conveniently deliver adequate palliation using a single 8 Gy fraction [11]. Interestingly, this agent is being tested along with chemotherapy as a possible life prolonging strategy. Another agent used in this situation is 159-samarium Samarium was superior to placebo in providing pain relief in randomized studies [12]. While systemic therapy is generally well tolerated there can be hematologic toxicity, especially thrombocytopenia, because of radiation effects on bone marrow. Although not formally tested, toxicity may be less for samarium than for strontium, and multiple courses of samarium have been safely given. Because these agents can lead to prolonged bone marrow depression, and especially thrombocytopenia, these agents are sometimes withheld when active chemotherapy is still under consideration. Given the hematologic toxicity that occurs with the beta-emitting radioisotopes mentioned above, there has been interest in using short range alpha emitting radioisotopes. Radium-223 is an alpha emitter with a half-life of 11 days and a range of less than 100 μm. Since radium is chemically similar to calcium, Ra-223 is taken up in areas of skeletal metastatic disease and the short range, high energy alpha particles deliver highly localized radiotherapy to regions of bone metastasis while potentially sparing radiosensitive normal marrow progenitors. Recently, a randomized, placebo-controlled study of Radium-223 among symptomatic, metastatic castration-resistant, prostate cancer patients who progressed after docetaxel, who could not receive docetaxel or refused docetaxel was reported and showed a meaningful survival extension from 11.3 to 14.9 months. This finding led to US Food and Drug Administration approval for Ra-223 [13].

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Chapter 15
Palliative Care in Urological Cancer

Jana Jeyakumar and David J. Feuer

Patients are living comparatively longer with incurable cancer than ever before. In fact, care may be needed for a considerable period of time after diagnosis and not just near the end of life. Patients need their medical, emotional and spiritual needs addressed, as well as the needs of their families.

Research indicates that high-quality end-of-life care in these patients results when health care professionals (1) ensure desired physical comfort and emotional support, (2) promote shared decision making, (3) treat the dying person with respect, (4) provide information and emotional support to family members, and (5) coordinate care across settings [1].

Modern Palliative Care was founded in the United Kingdom (UK) by Dame Cicely Saunders in 1967 [2]. It is important to note, however, that the UK operates a healthcare system that is free at the point of delivery, which differs from many other healthcare systems. The modern hospice movement was founded from Dame Cicely Saunders' observations of the need to care for people in whom aggressive medical treatment had failed to provide a cure. Dame Cicely Saunders' aim was to improve the lives of people with terminal cancer; however, the scope of palliative care now involves all life limiting illness, regardless of the cause. Publications around the time focussed on clinical experience on caring for dying patients rather than 'the degree of success or failure of treatment' [3]. Later in the 1960s there was a shift in focus from clinical, anecdotal experience to more evidence based practice.

J. Jeyakumar, MRCP, MBBS
Department of Medicine, Barts and The London NHS Trust, London, UK

D.J. Feuer, FRCP (✉)
Department of Palliative Medicine, Barts Health NHS Trust and Homerton Hospital NHS Foundation Trust, West Smithfield, London EC1A 7BE, UK
e-mail: david.feuer@bartsandthelondon.nhs.uk

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Concept of Palliative Care

The World Health Organisation (WHO) definition of Palliative Care is 'an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual' [4]. It encompasses multi-disciplinary, holistic care of patients with advanced, incurable disease, as well as the support of people close to the patient. The aim is to help patients achieve and maintain their maximum potential, improving the quality of life of the patient and their family [5].

Traditionally Palliative Care has become involved in the care of patients with life limiting disease in the last weeks or months of their lives, taking over care when active treatment has stopped. However, this practice is changing with palliative care involvement much earlier in a disease trajectory (Fig. 15.1). In the UK, the Policy Framework for Commissioning Cancer Services [6] states that 'the palliative care team should integrate in a seamless way with all cancer treatment services to provide the best quality of life for the patients and their family.' In the UK palliative care is included in many national service frameworks (including neurological disease and heat failure) as well as other Improving Outcomes Guidelines.

Recently published research in patients with metastatic non-small cell lung cancer has shown a clear benefit to the early involvement of palliative care (soon after diagnosis) in terms of quality of life and mood. There was also a survival benefit of about 2 months compared to a group who had standard care [7], which further supports an integrated approach.

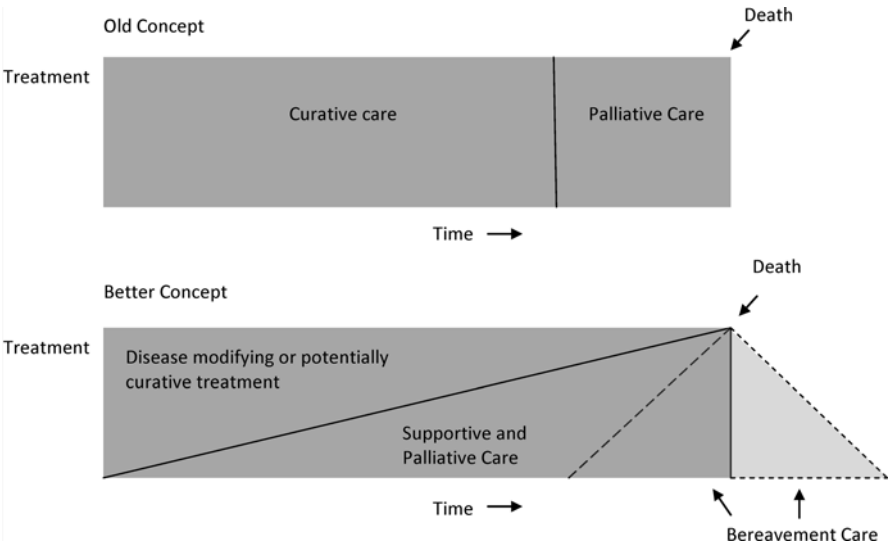

Fig. 15.1 Appropriate care near the end of life (Adapted from Lynn and Adamson [34]. With permission from RAND Corporation)

Role of Palliative Care in Urological Cancer

Palliative care has an important role in urological cancer care. This involves providing supportive care focusing on symptom control, psychological support and end of life care. A key recommendation from the National Institute for Clinical Excellence in the UK (NICE) document 'Improving Supportive and Palliative Care for Adults with Cancer [8] is that 'the assessment and discussion of patients' needs for physical, psychological, social, spiritual and financial support should be undertaken at key points (such as at diagnosis; at commencement, during, and at the end of treatment; at relapse; and when death is approaching).'

UK nationally published guidance focuses on the importance of Palliative Care in urological cancer care. The 2002 NICE guidelines 'Improving Outcomes in Urological Cancer' state that 'Palliative Care should be an integral part of patient management' [9]. Furthermore, the NICE 2008 Prostate Cancer Guidelines [10] state that palliative care should not be limited to hospice care but should be integrated into coordinated care and to ensure that it is available when needed.

Another role for Palliative Care practitioners is to provide education and teaching to other professionals who may encounter patients with incurable disease in their practice. This can take to form for formal education or 'on the job' teaching.

Clinical Aspects

Advanced cancer of any cause is debilitating. There are numerous symptoms that patients may get and each person is affected differently. Careful assessment of the patient and their symptoms are needed in order to manage their care effectively. Some of the most common symptoms are discussed below.

Pain

Pain is a very common symptom and can affect 70–90 % of patients with advanced prostate cancer [11]. It has a profound effect on a patient's quality of life and treatment of pain can be difficult to achieve.

Dame Cicely Saunders introduced the concept of 'total pain' which encompasses the physical, psychological, spiritual and social pain a patient may be experiencing (see Fig. 15.2). Not all patients will experience all of these facets of pain, however to treat one without addressing the other issues will not result in adequate control of symptoms. For example, if a patient is psychologically distressed it may be very difficult to control their physical pain until the psychological distress is established and efforts made to address it. This requires a multidisciplinary approach to care to ensure there is simultaneous focus on all the facets of pain. The multidisciplinary team may include doctors, specialist nurses, physiotherapists, occupational thera-

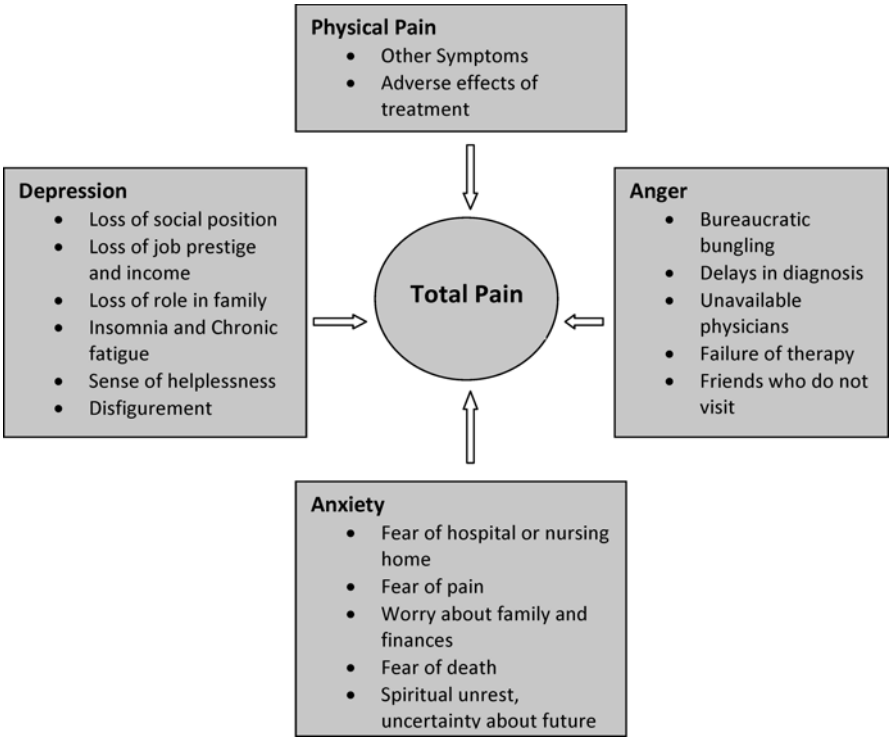

Fig. 15.2 Factors affecting patients' perception of pain (Reprinted from O'Neill and Fallon [2]. With permission from BMJ Publishing Group Ltd)

pists, counsellors, social workers, psychiatrists and dieticians, as well as other allied healthcare professionals. It is also important to remember that the pain a patient has may not be related to their cancer and may be of another cause for example long-standing osteo-arthritis.

The Pharmacological Treatment of Pain

The key to the effective pharmacological treatment is to establish the cause of the pain. This will guide the type of analgesia that will be most effective. We focus on some of the causes of pain below.

Once the cause has been established, the medication used can be tailored to the patient. Wherever possible oral analgesics should be used as first line. There will be occasions where this is not possible for example the patient is nil by mouth or too frail to manage oral medication.

Oral analgesics should be instituted using the World Health Organisation (WHO) analgesic ladder (See Fig. 15.3).

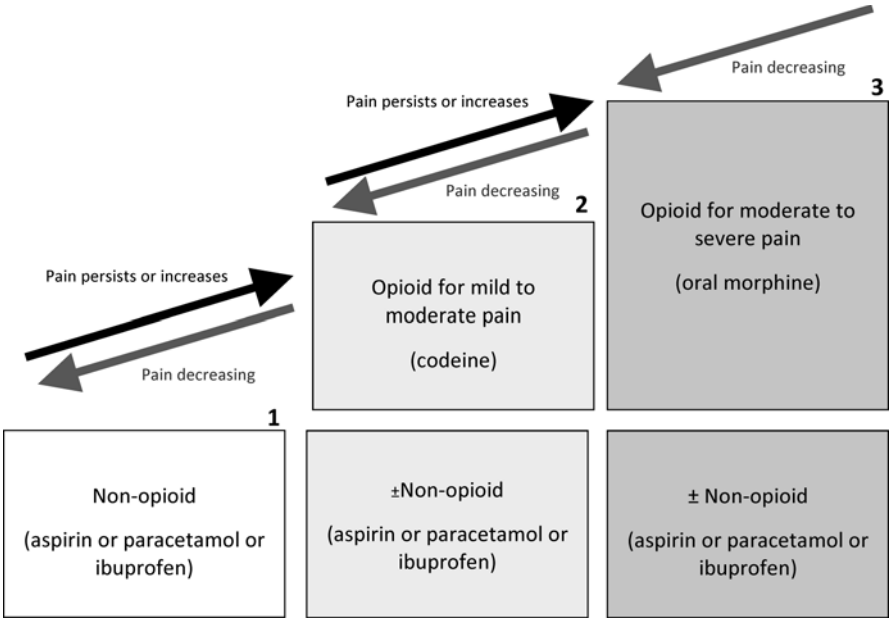

Fig. 15.3 World Health Organisation Analgesic Ladder (Adapted from World Health Organization (WHO) [35]. With permission from WHO)

The aim is to establish pain control using the simplest regime possible. Pain is a subjective experience and patients can start at any point on the ladder in accordance to the level of pain they are experiencing. Analgesia should then be titrated up or down in accordance with response to treatment and side effects. For example, if a patient is at step 2 of the ladder and their pain is not controlled they should be moved to step 3. If a patient is as step 2 and they undergo a treatment that may reduce their pain (e.g. radiotherapy to a bone metastases) it may be possible to reduce their analgesia with careful observation.

It is important to note that many patients will develop side effects from mild and strong opioids. Often these side effects can be managed effectively allowing a patient to continue taking the analgesia they need. There may be incomplete cross tolerance when starting opioids, which means that a patient may become tolerant to the side effects associated with the opioid but the analgesic effects persist, this is particularly true of opioid associated nausea. It is therefore important to warn patients of the side effects they may experience in order to increase compliance with a new medication. For example, when starting a strong opioid it is important to start a laxative at the same time as constipation occurs in almost all patients. The patient can be warned of this common side effect and advised to inform their doctor or nurse if it is becoming an issue so the laxatives may be increased. If a patient has uncontrollable or intolerable side effects with a medication it should be changed to another medication from the same class, for example opioid switching from morphine sulphate to oxycodone. However, there is little evidence that oxycodone

has fewer side effects than morphine sulphate, though individual patients may tolerate one better than the other [12].

The use of adjuvants with opioid-based analgesia is an effective way of managing pain and minimising the dose of opioids needed, thereby reducing side effects. Adjuvants that may be considered include non-steroidal anti-inflammatory drugs (NSAID), corticosteroids, neuropathic pain medication and bisphosphonates, all of which have their own side effects and contraindications.

Non-pharmacological techniques may also be useful in some patients. For example, use of transcutaneous electrical nerve stimulations (TENS) or cognitive behavioural therapy (CBT). Disease modifying therapies such as chemotherapy and radiotherapy also have a role in the management of pain.

Types of Pain

Tumour Pain

The tumours themselves, primary or secondary, may be painful. They can cause pain by compressing or invading local structures including nerves. Tumour pain can be effectively managed using the WHO analgesic ladder with adjuvants such as steroids which may be useful in reducing swelling around the tumour

Bone Pain

Bone metastases are common in urological cancer. Ninety percent of patients with metastatic prostate cancer have bone metastases. This pain can be managed using the WHO analgesic ladder and adjuvants including steroids. Radiotherapy is beneficial in the majority of cases. The 2008 NICE guidelines for the treatment of prostate cancer indicate that bisphosphonates should be used treat bone pain in hormone refractory prostate cancer where analgesics and radiotherapy have failed [10]. They also advocate the use of strontium-89 [10]. If a patient develops worsening pain in a long bone related to a bone metastasis, there is a risk of an impending fracture. If the patient has an appropriate functional level they should have an x-ray and an orthopaedic review to consider prophylactic surgery. An impending fracture is more likely if the metastasis is large or peri-tronchanteric. Newer drugs e.g. Denosumab a monoclonal antibody against RANKL (the main driver of osteoclast formation) have been licenced which may have a role in prevention of skeletal events in bone metastases [13].

Neuropathic Pain

This is pain caused by compression of a nerve either by the original tumour or a metastasis, or may be due to chemotherapy induced neurotoxicity. The patient may describe shooting, burning or stinging pain. In 2010 NICE produced guidelines for

the treatment of neuropathic pain. These guidelines advocate the use of amitriptyline or pregabalin as first line treatment [14].

Incident Pain

This is pain that occurs as a result of a particular event, for example mobilising or wound dressing changes. This pain is best managed using short acting analgesia. This can include the newer short acting nasal or buccal fentanyl preparations which have a quicker onset of action and a shorter duration of action [15, 16] than the older short acting opioids (e.g. oramorph and oxynorm) [17].

Metastatic Spinal Cord Compression (MSCC)

Within the UK, NICE defines MSCC as 'spinal cord or cauda equina compression by direct pressure and/or induction of vertebral collapse or instability by metastatic spread or direct extension of malignancy that threatens or causes neurological disability' [18]. In 2008 [18], NICE produced guidelines on the 'diagnosis and management of adults at risk of and with MSCC'. MSCC is common and is an oncological emergency. Delay in diagnosis and treatment can cause huge morbidity and distress. It affects 1–12 % of patients with metastatic prostate cancer, though can occur in any patient with boney metastatic disease affecting the spine [19] which would include many of the urological cancers.

MSCC can present in a number of ways. The earliest symptoms are pain in the back and spinal tenderness. It can cause a number of other neurological signs and symptoms, however once these are evident the MSCC may already have been present for a period of time, which can make functional recovery less likely. Early detection and diagnosis are vital to retaining function.

In the UK, if a patient has a suspected MSCC they must be discussed with the local MSCC co-ordinater within 24 h of presentation. This is to ensure prompt assessment and treatment, which takes into account the patient's functional level and preferences. The imaging of choice is magnetic resonance imaging, unless contraindicated, of the whole spine as there are often multiple levels of compression [18].

If a patient has suspected MSCC they should be nursed flat if there are any signs of spinal instability. High dose steroids should be initiated as soon as possible and will often precede imaging [18]. Once MSCC has been demonstrated on imaging, choice of treatment will be determined by patient preference and performance status. The options include radiotherapy or spinal surgery to decompress the spinal cord. There is strong evidence that surgery followed by radiotherapy provides a better functional outcome than radiotherapy alone. In a study of 101 patients with MSCC who were randomly assigned to radiotherapy alone or decompressive surgery followed by radiotherapy, significantly more patients were able to walk after the combined therapy (84 %) than after radiotherapy alone (54 %) [20].

Table 15.1 Common causes and suggested treatment of nausea and vomiting

Cause of nausea and vomiting	Suggested treatment
Impaired gastric emptying	Metoclopramide or domperidone
Chemical induced e.g. opioids, antibiotics	Haloperidol or levomepromazine
Chemotherapy	Granisetron or metoclopramide
Metabolic e.g. renal failure	Haloperidol or levomepromazine
Intracranial disease e.g. brain metastases	Cyclizine and consider dexamethasone if there is possible raised intracranial pressure
Vestibular i.e. movement related	Cyclizine or levomepromazine
Cause unclear	Haloperidol or cyclizine or levomepromazine.

Nausea & Vomiting

This is a common symptom in advanced cancer. There are a number of causes and appropriate treatment is dependent on the cause. The aim is to remove or treat the cause as appropriate (Table 15.1). It is important to remember that bowel obstruction is also a cause of vomiting in advanced pelvic or abdominal disease. Therefore careful assessment and examination of the patient is vital and any sign of bowel obstruction treated appropriately [21, 22].

Anorexia and Weight Loss

Patients with advanced cancer often report weight loss and anorexia. This can contribute to fatigue and lethargy and is often very distressing for family members. Often reassurance and techniques such as eating small amounts often are all that is needed. Involvement of a dietician may be beneficial as well as the use of nutritional supplements.

The most commonly used medications to treat these symptoms are corticosteroids and megesterol acetate [11]. Corticosteroids may also help treat associated nausea and pain. However, the appetite stimulation is only short lived [23]. Megesterol acetate begins to have an effect 2 weeks after initiating treatment and can stimulate increased food intake [11]. However, though there may be resultant weight gain, there is often no increase in skeletal muscle bulk [24].

Constipation

Constipation is very common in patients with advanced disease. It may be related to the disease itself, medications being taken or the overall effect of the cancer e.g. decreased mobility. Treatment involves changes in diet and fluid intake if possible,

as well as laxative medication. Often a combination of a softener and a pro-motility drug are needed. The aim of treatment is to allow comfortable defaecation rather than a particular frequency of defaecation [25]. In some cases it may be necessary to use suppositories or enemas.

Opioids are often a cause of constipation. This can usually be managed with adequate laxatives. However, if needed, it may be useful to switch to a less constipating laxative such as fentanyl [26]. There are also newer medications available, which are aimed at reducing the effect of constipation of opioids. For example, targinact is a combination preparation of oxycodone and naloxone [27].

Methylnaltrexone is a peripherally acting μ (mu) opioid receptor antagonist that has been shown to be useful in rapidly inducing defaecation (often within 4 h of administration) in patients with opioid induced constipation. As it has a restricted ability to cross the blood brain barrier, it does not appear to affect pain control or cause opioid withdrawal [28].

Lymphoedema

This is common in patients with advanced cancer of any cause. It is very distressing and can affect relationships with family and friends. It can cause difficulty with mobilisation and may lead to feelings of isolation [11]. It has a profound influence on a patient's quality of life.

It can occur as a result of changes in lymphatic flow, immobility, a large tumour mass in the pelvis and low oncotic pressures. In most cases lymphoedema is as a result of a combination of factors. Treatment should be aimed at comfort, maintaining skin integrity and treating infection if present.

Simple measures such as elevating the affected limbs may help. Manual lymphatic drainage and multilayer lymphoedema banding are also beneficial [29]. Any sign of infection should be treated promptly with antibiotics. Stenting of the inferior vena cava may be useful in some cases [30]. Scrotal supports promote comfort. Diuretics are often not helpful in reducing lymphoedema [31]. It is important to consider deep vein thrombosis (DVT) as a possible co-existant cause of leg swelling, especially if one side is more swollen than the other or it is painful. If a DVT is suspected a doppler ultrasound should be used for confirmation [11].

Haematuria

Haematuria is common in patients with renal, bladder or prostate carcinoma. It can be very distressing to patients and their families. It is important to monitor a patient's haemoglobin level if haematuria is present and transfuse as necessary. Management of intractable haematuria is described in the chapter on Urological emergencies.

Psychological

The exact prevalence of psychological or psychiatric problems is not known. In a meta-analysis of studies on the subject after 1980, Spijker et al. [32] showed that with the exception of depression there was not much difference between cancer patients and normal population. More studies are needed in this direction.

How to Manage End of Life Care

A holistic approach to end of life care is vital to ensure the best possible care for the patient and their family. Care of the dying patient includes appropriate physical, social, cultural and spiritual care [2, 33].

A vital step to managing end of life care is diagnosing dying. It is important to diagnose death promptly to allow appropriate care to begin and to allow the patient's family to prepare. Diagnosing death can be difficult. Some common signs that a patient is approaching death are that they are increasingly weak and perhaps bedbound, semi-comatose, not able to manage oral medication and are only managing sips of water. A useful skill is to determine how the patient has been over the preceding few days and establish whether there has been a change in condition and a progression toward becoming bedbound and less rousable.

The aim of care at the end of life should be to provide complete, holistic care to the patient and their family. The focus should be on comfort measures and symptom control, using a multidisciplinary approach. If the multi-professional team looking after the patient feel that the patient is dying, there should be an initial assessment involving reviewing medication and discontinuing unnecessary medication. There should also be a focus on converting medications that need to be continued to the subcutaneous route, if possible.

There are four common symptoms at the end of life

- Pain
- Nausea and vomiting
- Agitation
- Respiratory secretions

Each of these can be managed using subcutaneous medications. These medications should be prophylactically prescribed on an as required basis, even if the symptom is not present at the time of the initial assessment. If a symptom is present, it should be treated using a subcutaneous infusion if appropriate.

There should be regular assessment of the patient to ensure they are comfortable. If a patient is not comfortable action should be taken to improve comfort. This requires a multi-professional approach. Examples of actions that can ensure comfort are alterations to medication or insertion of a catheter if a patient is in urinary retention.

There should also be a focus on bereavement care after a patient has died. This is vital to ensure a family can access the support they need.

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Chapter 16
Life After Urological Cancer – Psychological Issues

Paul Symonds, Karen W.E. Lord, and Alex J. Mitchell

Introduction

The treatment of urological cancer may have a profound psychosocial impact upon the patient's life. This chapter will deal with factors not often considered when the results of treatment of urological cancer are assessed. They include anxiety, depression and distress amongst urological cancer patients, the effect of treatment including body image problems and reduced quality of life after radical treatment. Hormone treatment is often viewed as a 'soft option' in the treatment of prostate cancer. The side effects of such treatment are often underestimated. One under-recognised phenomenon is impairment in cognitive function following androgen deprivation. Fatigue may be a direct consequence of treatment, the cancer itself or emotional distress. Fatigue is a poorly recognised symptom that may, in fact, be the most important symptom affecting an individual patient. The recognition of these sequelae of cancer and appropriate treatment to treat these under-recognised effects may markedly improve a patient's quality of life.

Prevalence of Psychological Complications in Cancer Patients

Distress has been defined by the National Cancer Comprehensive Network (NCCN) [1] as 'a multifactorial unpleasant emotional experience of a psychological (cognitive, behavioural, emotional), social and/or spiritual nature that may interfere with

P. Symonds, MD, FRCP (✉) • A.J. Mitchell, MBBS, BMedSci, MSc
Department of Cancer Studies and Molecular Medicine, University of Leicester, Level 2, Osborne Building, Leicester Royal Infirmary, Leicester LEI 5WW, UK
e-mail: rps8@le.ac.uk

K.W.E. Lord, PhD
Department of Palliative Care, University Hospital of Leicester NHS Trust, Leicester, UK

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the ability to cope effectively with cancer its physical symptoms and its treatment'. Distress should be considered a treatable complication of cancer that can present at any stage in the cancer pathway [2]. As distress is a broader and more patient friendly concept than depression, many propose that the focus in clinical practice should not be psychiatric disorder but rather the attempt to identify people suffering broadly defined distress who require professional help [3, 4]. A recent meta-analysis found that the prevalence of distress was 47.8 % in ten studies using a robust gold standard [5]. The presence of distress is associated with a reduced health related quality of life [6] and possibly reduced survival [7]. Depression may well be the most important component of distress and has certainly been the most commonly studied mood complication associated with cancer. Indeed depression is one of the most common mental health problems worldwide with a 30 day prevalence in the community of about 5 % increasing to 9 % over 12 months [8]. The incidence of depression is higher among cancer patients early after diagnosis, although the prevalence diminishes somewhat in long-term cancer survivors. The incidence also varies depending on the patient's age, sex, ethnic background and the type of tumour from which they suffer. Mitchell and colleagues [9] studied the prevalence of depression and anxiety and adjustment disorder in oncological, haematological and palliative care settings in a meta-analysis of 94 interview-based studies. The authors found that some combination of interview defined mood disorder occurred in 30–40 % of patients in hospital settings without a significant difference in incidence between palliative care and non-palliative settings. As a rule of thumb the authors found that about a quarter had some type of depression often in combination with another mental health issue. Although these rates seem relatively modest, these are cross-sectional estimates and it remains extremely important that these patients are recognised. In clinical practice is easy to overlook the signs and symptoms of depression in a busy clinic.

Recognition of Psychological Complications

A useful study involving 1,439 patients seen between January 1999 and October 2009 was carried out in the Rapid Response Radiotherapy clinic, Sunnybrook Health Sciences Centre in Toronto [10]. 17 % had prostate cancer. The authors showed that symptomatic patients on the Edmonton Symptom and Assessment System (ESAS) were more likely to have anxiety and depression and psychological symptoms but these could be 'drowned out' by the physical symptoms. This diagnostic over-shadowing is likely when clinicians focus only on the main presenting symptom. fifty-five percent of patients reported at least mild symptoms of depression and 65 % reported at least mild anxiety. In the univariate analysis, patients who were female, who had a low performance status, or primary lung cancer were more likely to report depressed and anxious feelings. Interestingly primary prostate cancer patients were significantly less likely to report depression and anxiety. Paradoxically patients referred for treatment of spinal cord compression were

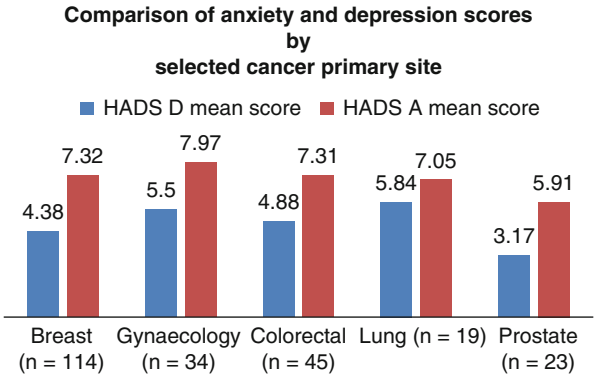

Fig. 16.1 Comparison of emotional distress by cancer site

significantly less depressed. The univariate model showed that younger patients were significantly more anxious than older patients and females reported more anxiety than males. Patients who reported increased feelings of nausea, tiredness, drowsiness, dyspnoea and worse appetite and overall wellbeing on the ESAS were more likely to feel feelings of depression. Patients who reported higher levels of drowsiness, dyspnoea and overall wellbeing were more likely to have higher feelings of anxiety.

Prostate cancer patients seem to have a lower incidence of anxiety and depression. We investigated the incidence of anxiety and depression in 279 ethnically diverse cancer patients. Anxiety and depression scores as assessed by the Hospital Anxiety and Depression Scale (HADS) are shown in Fig. 16.1. The incidence of anxiety and depression was significantly less in prostate cancer patients.

Hinz and colleagues [11] looked at the degree of psychological distress (anxiety and depression) in urological cancer patients over a period of 1 year using the HAD scale. Eighty-seven patients had prostate cancer and 196 patients had other urogenital cancers (bladder, kidney, testis, penis and ureter). Anxiety and depression was highest at the time of admission into hospital but had fallen by the time of discharge. The same questionnaire was administered 6 months and 1 year later. The incidence of anxiety and depression was similar to scores recorded at the time of discharge from hospital and over the following year. Anxiety scores were similar to the general population and lower than cardiac patients. Depression mean scores were lower than the general population. The incidence of anxiety and depression tended to be lower in prostate cancer patients than other urological cancer sites. It is noteworthy in this series (in common with others) that younger age was predictive of higher psychological distress scores.

There may be several reasons for the lower levels of anxiety in prostate cancer patients even in those seen in palliative care settings (as shown in Toronto by Salvo and colleagues). Prostate cancer patients generally have a good prognosis, good quality of life and mild physical symptoms. They may well be more philosophical and accepting. This attitude was summed up by a retired local General Practitioner who was treated by radical radiotherapy aged 72 for a T3 carcinoma of prostate. He said to one of the authors (RPS) at the time of his initial treatment “you have got to

die of something haven't you". RPS was pleased to receive a bottle of champagne when the patient was discharged back to the care of his General Practitioner aged 77 for continued PSA follow-up. This retired doctor remains well aged 80. However he said to RPS that he did not expect to live to that age and he quite accepted that his prostate cancer was likely to be lethal. The primary method of recognition of anxiety and depression is clinical. It is worth remembering that it is General Practitioners (family physicians) rather than hospital specialists who are most likely to recognise depression within the community [12]. Non-specialists tend to recognize about 50 % of true cases and 80–90 % of non-cases with an appreciable risk of false positive and false negative errors. It is particularly difficult to identify depression in busy settings with short consultations, when a symptom of depression is not the presenting complaint, and when expectation of depression is low. According to the Diagnostic Statistical Manual of Mental Disorders (DSM-IV) diagnosis of a major depressive disorder (MDD) requires five out of nine key symptoms together with one core symptom for a minimum period of 2 weeks together with either distress or impaired function [13] (see Table 16.1).

Table 16.1 Diagnostic criteria for the diagnosis of depression, adjustment disorder or dysthymic disorder

Diagnosis	Symptom requirement	Clinical significance	Minimum duration
ICD-10 depressive episode	Requires two of the first three symptoms (depressed mood, loss of interest in everyday activities, reduction in energy) plus at least two of the remaining seven symptoms (minimum of four symptoms)	At least some difficulty in continuing with ordinary work and social activities	2 weeks unless symptoms are unusually severe or of rapid onset.
DSM-IV major depressive disorder	Requires five or more out of nine symptoms with at least at least one from the first two (depressed mood and loss of interest).	These symptoms cause clinically important distress OR impair work, social or personal functioning.	2 weeks
DSM-IV minor depressive disorder	Requires two to four out of nine symptoms with at least at least one from the first two (depressed mood and loss of interest).	These symptoms cause clinically important distress OR impair work, social or personal functioning.	2 weeks
DSM-IV adjustment disorder	Requires the development of emotional or behavioral symptoms in response to an identifiable stressor(s) occurring within 3 months of the onset of the stressor(s). Once the stressor has terminated, the symptoms do not persist for more than an additional 6 months.	These symptoms cause marked distress that is in excess of what would be expected from exposure to the stressor OR significant impairment in social or occupational (academic) functioning	Acute: if the disturbance lasts less than 6 months. Chronic: if the disturbance lasts for 6 months

Table 16.1 (continued)

Diagnosis	Symptom requirement	Clinical significance	Minimum duration
DSM-IV dysthymic disorder	Three symptoms – persistently low mood + two (or more) of the following six symptoms:	The symptoms cause clinically significant distress OR impairment in social, occupational, or other important areas of functioning.	Requires depressed mood for most of the day, for most days (by subjective account or observation) for at least 2 years
	(1) poor appetite or overeating		
	(2) Insomnia or hypersomnia		
	(3) low energy or fatigue		
	(4) low self-esteem		
	(5) poor concentration or difficulty making decisions		
	(6) feelings of hopelessness		

Depression Following Cancer

The point prevalence of major depression following a cancer diagnosis is approximately 15 % but major depression is only one of several important mood complications. Minor depression is also common and comprises two to four key symptoms along with the same criterion as MDD. Those with minor and sub-syndromal depressions are at risk of major depression but also suffer high co-morbidity and distress in their own right. We recently carried out a study to try and tease out which somatic symptoms (if any) are indicative of depression in the cancer setting [14]. We approached 279 patients up to three times within 9 months of the first presentation of the diagnosis of cancer. In total there were 559 contacts of which 176 (31 %) were treated with palliative intent. Patients completed PHQ-9 and the HADS-D scales and these scales were analysed to assess the diagnostic value of individuals' somatic and non-somatic symptoms in attempting to diagnosis depression in these cancer patients. Using DSM-IV criteria the prevalence of major depression was 12.7 and 29.6 % had major or minor depression. A single question 'are you feeling down, depressed or hopeless?' had a positive predictive value of 61.9 % but did have excellent screening utility and could be used as a first step screening question with follow-up questions addressed to those who answered positively. The least discriminatory question was the complaint of fatigue or low energy (see next section) as 27.9 % of non-depressed cancer patients complained of this symptom. The answers to three questions "trouble concentrating on such things as reading" combined with either feeling "down, depressed or hopeless" or feeling "bad about yourself or that you are a failure" give very good accuracy. We found that the most useful symptom in terms of clinical utility was sleep disturbance (or falling or staying asleep or sleeping too much). Sleep disturbance should alert the busy urological oncologist to the possibility of depression and further questions should be asked. Identification of psychiatric complications of

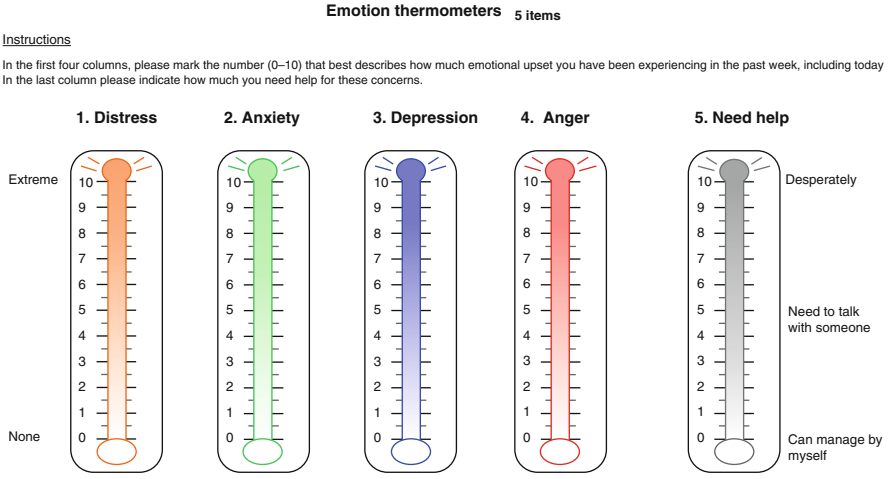

Fig. 16.2 Emotion thermometers tool (Courtesy of Alex J. Mitchell ©2012: Inspired by NCCN's standalone Distress Thermometer)

cancer can often be improved by the use of a suitable diagnostic scale provided the scale is acceptable to both staff and patients. The Hospital Anxiety and Depression Scale (HADS) developed by Zigmund and Snaith in 1982 [15] is the most widely used scale in clinical practice. This has anxiety (HADS-A) and depression (HADS-D) subscales. In a meta-analysis of 50 studies using the depression subscale (HADS-D) the anxiety subscale (HADS-A) or combined scales (HADS-T) and a semi-structured psychiatric interview showed that the scale was a good initial screening instrument [16]. In the identification of depression the HADS-T, HADS-D and HADS-A had a pooled sensitivity of specificity of 82 %, 77 %; 71.6 %, 82.6 % and 85 %, 77.8 % respectively. When assessing anxiety the HADS-T and HADS-A had a pooled sensitivity of specificity of 83.9 %, 69.9 % and 48.7 %, 78.7 %. Many consider the HADS to be a rather cumbersome tool for routine use. We developed a simple visual-analogue scale consisting of a total of five domains (the emotion thermometers) which is much less laborious to use. The patient just marks a point on each of the visual analogue scales for distress, anxiety, depression, anger and the need for help (see Fig. 16.2). Studies in our Department have shown that this gives comparable results to the HADS-D scale but in a simpler to understand format [17, 18].

Cancer and Treatment Related Fatigue

Fatigue is increasingly recognised as the most common symptom associated with cancer and its treatment [19]. It has also been reported to be strongly associated with emotional distress [20]. Cancer related fatigue has been described by Hickok et al. [21] as pervasive, unusual or excessive tiredness that involves the whole body, is disproportionate to or unrelated to activity or exertion and is usually not relieved by rest or sleep. Excessive fatigue may be present prior to treatment, be worsened by treatment and persist well after successful treatment when patients are tumour free.

Moderate fatigue was reported in over 66 % of a group of 1,397 patients with advanced cancer prior to radiotherapy. Fatigue was assessed using the ESAS [22]. A larger study of cancer fatigue was carried out in Edinburgh on a group of 3,424 consecutive patients attending for follow-up visits between June 2003 and December 2004 in outpatient clinics specialising in the following cancer types: colorectal, breast, gynaecological, genitourinary, sarcoma, melanoma and miscellaneous cancers (including Phase I trials). Fatigue was measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-30) fatigue sub-scale. Emotional distress was measured using the Hospital Anxiety and Depression Scale. Clinically relevant fatigue (CRF) was found in 32 % of patients. Variables independently associated with clinically relevant fatigue were primary cancer site, having disease present, type of cancer, treatment and emotional distress [19]. Emotional distress (total HADS score ≥ (greater than or equal to) 15) had a strong association with fatigue but half of the patients with clinically relevant fatigue were not distressed. Radiotherapy treatment can worsen levels of fatigue in patients especially those with pre-existing fatigue prior to treatment. Hickok from the University of Rochester in the USA [21] assessed fatigue in a group of 372 patients undergoing radical radiotherapy (5 weeks' treatment) using an adaptation of a scale developed at the MD Anderson Hospital. The most common diagnosis was breast cancer (42 % of patients) followed by prostate cancer (22 %) of patients. Prostate cancer patients were the least likely to report fatigue at the beginning of treatment with only 42 % having some degree of fatigue at baseline measurements. The highest degree of fatigue (76 %) was in patients with brain tumours and this is certainly consistent with the author's experience. Fatigue worsened during radiotherapy with the frequency and severity of fatigue being increased by approximately 30 % by the end of treatment.

Fatigue can certainly persist well after the end of treatment. Storey and colleagues in Edinburgh [23] recently assessed prostate cancer patients on follow-up greater than a year after treatment using the Brief Fatigue Inventory. These patients also filled in the Hospital Anxiety and Depression scale, the International Prostate Symptom Score, the EORTC QLQ-30 Quality of Life Questionnaire and the HADS score. Data was available for a total of 377 patients, 240 had been treated by radical radiotherapy and 133 by radical prostatectomy. The results in this group of patients were compared to a group of non-cancer controls. Interestingly the frequency of urinary symptoms was greater in the non-cancer controls than in the patients treated for prostate cancer. However, the prevalence of Clinically Relevant Fatigue (CRF) was 29 % in the prostate cancer patients versus 16 % of controls ($p = 0.31$). CRF was more common post-radiotherapy than post-prostatectomy (33 % versus 22 % $p = 0.024$). However, when other factors (current depression, anxiety, urinary symptoms, medical co-morbidities, pain and insomnia) were controlled for previous treatment did not predict CRF. Depression (HADS scale ≥ (greater than or equal to) 8) was by far the strongest association (OR 9.9 95 % CL 4.2–23.5).

There is some evidence that our advice to patients suffering from cancer fatigue in the past was detrimental. Typical advice given to such patients has been that they should rest and avoid physical effort. A study from Windsor and colleagues from Dundee [24] suggests this advice is wrong. Sixty six men receiving radical radiotherapy for prostate cancer were randomised to either an exercise group or another

group who were not discouraged from performing normal activities but were advised to rest and take things easy if they became fatigued. Patients were assessed using the Brief Fatigue Inventory and walking distance was measured in a modified shuttle test before and after radiotherapy. The control group had a significant increase in fatigue scores from baseline at the end of radiotherapy ($p=0.013$) with no significant increase observed in the exercise group ($p=0.203$). A non-significant reduction (2.4 %) in shuttle test distance at the end of radiotherapy was observed in the control group, however in the exercise group there was a significant increase (13.2 %) in distance walked ($p=0.0003$). Patients suffering from cancer fatigue should be screened for depression which is likely to be present in about half of these patients. A graded aerobic exercise programme should be considered for these patients rather than the classical advice of rest which could be detrimental.

Psychological Problems Associated with Androgen Deprivation Therapy

Androgen deprivation therapy is used frequently along with radiation treatment. Both a short course of neo-adjuvant treatment (3 months) in low to intermediate risk cases or 2–3 years adjuvant treatment in high risk cases has been shown to improve survival. Androgen deprivation is widely used to treat patients with metastatic disease and alleviates tumour-induced symptomatology.

Androgen deprivation therapy (ADT) is not without side effects. All urological oncologists are familiar with the common side effects including hot flushes (flashes), sexual dysfunction and metabolic side effects. These include osteoporosis, loss of muscle bulk and accumulation of fat. There is some evidence of increased cardiovascular disease and an increased incidence of diabetes.

Relatively little attention has been paid to the psychological side effects of these drugs. Reduced testosterone levels may modulate neurotransmitters particularly serotonin. This has been shown in both man and animals. Testosterone deficiency may also lead to decreased cognitive function and have an overall effect upon emotion.

A recent study carried out in Italy [25] listed the incidence of depression, anxiety, self-body image perception, sleep disturbance and quality of life in two groups of prostate cancer patients. 49 were receiving adjuvant ADT and 54 were not. The two groups were not particularly well matched. Patients receiving ADT were slightly older, they were more likely to have had more advanced stage and grade tumours and more received radiotherapy rather than treatment by radical prostatectomy.

However, the prostate cancer patients receiving ADT had higher levels of depression ($p=002$), worse self-body image perception ($p=0.01$), worse quality of life ($p=0.001$) and worse sleep quality ($p=0.04$). ADT was significantly associated with depression at multivariate analysis after adjustment for age, stage, Gleason score as well as demographic and social variables ($p=0.001$). As one would expect the diagnosis of depression was inversely correlated with quality of life.

Interestingly patients receiving ADT were less anxious than those not receiving this medication. Saini and colleagues hypothesised that men receiving ADT may be

reassured as they were receiving anti-neoplastic treatment while those on follow-up only were more afraid of a tumour recurrence and more anxious.

Neuro-anatomical studies have demonstrated both testosterone and oestrogen receptors in varying densities in various parts of the brain [26]. The Hippocampus appears to be an important target for testosterone in both man and animals [27, 28]. Testosterone and its metabolite dihydrotestosterone (DHT) and oestrogen all appear to affect cognition in men including visuospatial abilities, verbal fluency and memory, particularly working memory in a task-specific manner. A review by Nelson and colleagues [29] showed that between 47 and 69 % of men on ADT declined in at least one cognitive area most commonly visuospatial abilities and executive functioning. They found that ADT was linked to subtle but significant cognitive declines in men with prostate cancer. A recent study from Toronto compared neurocognitive function in men over 50 with either prostate cancer not receiving ADT, prostate cancer with continuous ADT or healthy controls. The investigators found that in one test there was a reduction of immediate memory ($p = 0.029$), working memory ($p = 0.031$) and visuospatial ability ($p = 0.034$) in men receiving ADT compared to controls after 12 months' treatment. The patients were subjected to a battery of neuropsychological tests and not all tests showed adverse effect of cognitive function amongst prostate cancer patients receiving ADT.

Clinical experience is that the effects of ADT on neurocognitive function vary markedly between patient and patient. A small minority of patients can be virtually incapacitated by changes in neurocognitive function. We particularly remember one man who was a high-powered personnel director who received ADT as part of his radical treatment for T3 prostate cancer. He found that he could not make decisions whilst he was receiving ADT. After this treatment was discontinued and his serum testosterone returned to near normal he was able to function effectively and his decision taking ability improved. The capacity for ADT to induce or worsen depression and reduce neurocognitive ability, particularly memory function, spatial abilities and decision taking skills should be borne in mind amongst patients treated with anti-androgens.

Unmet Psychosocial Needs

Given the broad range of psychological complications that may follow Urological Cancer screening for depression alone, or even depression and anxiety is likely to be insufficient. An alternative is to look for broadly defined emotional distress allied with assessment for unmet needs. Unmet needs may be physical, social, psychological or spiritual. A large number of tools have been developed to assess the unmet needs of cancer patients [30]. Several such as the Supportive Care Needs Survey Short Form (SCNS-SF34) have been evaluated in patients with prostate cancer [31]. However only two tools were developed specifically with prostate cancer in mind. Further work needs to take place to validate these tools and to test them in routine clinical care. See Table 16.2

Table 16.2 Instruments to identify unmet needs in prostate cancer patients

Instrument	Tool purpose and population	Question format and administration	Content validity	Construct validity	Internal consistency	Test-retest reliability
PCNA	Measures the importance and unmet needs of men with prostate cancer	Self completed	Literature review Interviews	Education correlated with care delivery r = −22 and support r = −.20	Not reported	Not reported
Prostate Cancer Needs Assessment	204 prostate patients	135 item in 3 domains:	Expert review	Age correlated with unmet need information r.16		
Boberg et al. [32]		Information		Overall health correlated with importance support		
		Support		r = −.16 and r = −.19		
		Care delivery		Health care satisfaction correlated with unmet need r = −.37 to -.51		
		10 point scale Importance : 1 ‘not all important’ to 10 ‘extremely important’				
		10 point scale met: 1 ‘not all met’ to 10 ‘totally met’				
PCNQ	To assess the needs and desire for help of men diagnosed with prostate carcinoma	Self-completed	Qualitative –interviews/ focus groups	Principal component factor analysis:	Study 1:	Study 1:

Instrument	Tool purpose and population	Question format and administration	Content validity	Construct validity	Internal consistency	Test-retest reliability
Prostate Cancer Needs Questionnaire	Study 1:	Study 1:	Expert opinion	*Study 1:*	All α >0.70	100/150 completed 2nd PCNQ (2 weeks): Part 1 ICC = 0.61 to 0.78; Part 2 ICC = 0.60 to 0.82.
Study 1:	Version 1 385 prostate	64 items:	Pilot testing	Part 1–7 factors (61.7 % variance); Part 2–6 factors (63.5 % variance)	Part 1 α = 070 to 0.88	
Duke et al. [33]	Study 2:	Part 1 (past issues)		*Study 2:*	Part 2 α = 0.71 to 0.87	
Study 2	Version 2 300 prostate	Part 2 (current issues)		Part 1–8 factors (68 % variance); Part 2–6 factors (68 % variance)	Study 2:	
Duke et al. [34]		Study 2:		Convergent validity:	All α >0.70	
		Part 1 39 items		*Study 1:*	Part 1 α = 0.71 to 0.90	
		Part 2 30 items		EORTC QLQ-C30 Spearman r = .30 to .63.	Part 2 α = 0.80 to 0.92	
		(Four items modified from PCNQ v1; 5 new items added).		*Study 2:*		
		Level of need:		EORTC QLQ-C30 Spearman r = .30 to .63.		
		'Strongly Disagree' to 'Strongly Agree'				
		Desire for help: 'not at all' to 'a lot'				

Conclusion

The quality of life of patients treated for urological cancer will be improved if distress, anxiety and depression are promptly recognised and treated. Emotional complications are often linked with unmet needs. Fatigue is an important symptom induced by the cancer and may be exacerbated by treatment. About half of patients with significant fatigue have symptoms of psychological distress, particularly depression. The neurocognitive effects of androgen deprivation vary markedly between different individuals but can cause deterioration in memory and executive function. It should be borne in mind that lack of testosterone can worsen depression.

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Chapter 17
Renal Cell Carcinoma: Overview

Christopher J. Ricketts and Eamonn R. Maher

Renal cell carcinoma (RCC) is not a single uniform disease entity but comprises a number of different types of cancer and can be subdivided according to the histological presentation. Interestingly, different histopathological subtypes of RCC display different genetic, biological and clinical characteristics. By far the most common histological type is clear cell renal cell carcinoma (CCRCC) (also known as conventional RCC), which represents 75–80 % of all RCC. Papillary (PRCC) (10–15 %), chromophobe (5 %) and other more rare forms including collecting duct carcinoma (<1 %) comprise the remainder. Oncocytomas represent 3–7 % of renal masses but are invariably benign and thus their exclusion from classification as true RCCs has been recommended [1]. Distinct tumours of different cell types can occasionally be seen in the same kidney and an individual may present with a tumour of mixed histology. Additionally, 3–5 % of RCCs cannot be classified into any existing type and are simply referred to as unclassified RCC. In cases of uncertain histopathology, immunohistochemical, cytogenetic and molecular genetic studies may be informative. Historically, sarcomatoid RCC was considered a separate subtype of RCC, but now sarcomatoid change is thought to represent undifferentiated cells associated with progression of disease and may be seen in all RCC cell types [1].

Currently, pathologic stage, based on the size of the tumour and the extent of invasion, is the most important prognostic indicator. The stage of RCC is classified using the TNM staging system, which defines the local extension of the primary tumour (T), the involvement of regional lymph nodes (N) and the presence of

C.J. Ricketts, PhD
Department of Medical and Molecular Genetics, IBR,
University of Birmingham, Birmingham, UK

E.R. Maher, BSc, MD, FRCP, FMedSci (✉)
Department of Medical Genetics, University of Cambridge,
Box 238, Cambridge CB2 0QQ, UK
e-mail: e.r.maher@bham.ac.uk; erm1000@medschl.cam.ac.uk

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Table 17.1 TNM classification

A. Primary tumour (T)	
Tx	Primary tumour cannot be assessed
T0	No evidence of tumour
T1a	Tumour ≤4 cm in maximal dimension, limited to the kidney
T1b	Tumour ≥4 cm but ≤7 cm
T1b	Tumour ≥7 cm and ≤10 cm in maximal dimension, limited to the kidney
T2a	Tumour more than 10 cm in maximal dimension limited to the kidney
T2b	Tumour more than 10 cm in maximal dimension, limited to the kidney
T3a	Tumour directly invades adrenal gland or perirenal and/or renal sinus fat but not beyond Gerota's fascia
T3b	Tumour grossly extends into the renal vein or its segmental (muscle-containing) branches or invades the vena cava below the diaphragm
T3c	Tumour grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumour invades beyond Gerota's fascia (including continuous extension into ipsilateral adrenal gland)
B. Regional lymph nodes (N)	
Nx	Lymph nodes cannot assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single regional lymph node
N2	Metastasis in more than 1 regional lymph node
C. Distant metastasis	
Mx	Distant metastasis not assessed
M0	No distant metastasis
M1	Distant metastasis

distant metastases (M) (Table 17.1). In the 2002 AJCC Staging guidelines, T1 and T2 were subdivided into T1a/T1b; T1a RCCs are ≤4 cm, T1b are 4–7 cm. In 2010 AJCC staging guidelines T2 tumours were subdivided into T2a and T2b: T2a tumours being 7–10 cm and T2b >10 cm in size, but all of which confined within the kidney [2]. T3 and T4 RCCs involve invasion outside the kidney and are defined as, T3a with direct invasion of the adrenal gland or perirenal and/or renal sinus fat, T3b with gross extension into the renal vein or its segmental (muscle-containing) branches or the vena cava below the diaphragm, T3c with gross extension into the vena cava above the diaphragm or invasion of the wall of the vena cava and T4 with invasion beyond Gerota's fascia. T3 is the equivalent of stage III and T4 being the equivalent of stage IV, but with the involvement of any lymph nodes, near or distant to the kidney, or any metastases automatically upgrading the RCC to stage IV.

Additionally for clear cell RCC, the Fuhrman grading scheme for grading alterations to the nuclei can be used to give grades of I-IV (Table 17.2) that have been reported to correlate with prognosis, but the utility of the grading is less agreed on

Table 17.2 Fuhrman grading

F1	Nuclei are small (<10 μm) and round, with dense chromatin and inconspicuous nucleoli
F2	Nuclei are slightly larger (15 μm), with finely granular chromatin and small nucleoli
F3	Nuclei are 20 μm in size and may be oval in shape, with coarsely granular chromatin and prominent nucleoli
F4	Nuclei are pleomorphic, with open chromatin and single or multiple macronucleoli

Table 17.3 Anatomic stage/Prognostic groups

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T1 or T2	N1	M0
	T3	N0 or N1	M0
IV	T4	Any N	M0
	Any T	Any N	M1

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for other histological subtypes, though low grade and high grade can be used as one of the criteria to separate papillary RCC into types I and II. The vast majority of chromophobe RCC are low grade while oncocytomas are not graded. Within an individual stage, grade has prognostic value for clear cell RCC [3].

An analysis of the incidence of RCC in the US from 1986 to 1998 based on SEER data reported stage at presentation to be 54 % localized (stage I or II), 21 % regional (stage III), 25 % advanced (stage IV) [4] (Table 17.3).

Individuals with chromophobe RCC appear to have better survival rates than those with clear cell RCC. While individuals with a localized papillary RCC demonstrate a more favourable outcome than those localized clear cell RCC, this difference in tumour type has no apparent effect on the 5-year survival rates for extrarenal papillary RCC compared to extrarenal clear cell RCC [5].

Clear cell RCCs (CCRCC) have a higher propensity for vascular invasion than for lymphatic invasion, with malignant cells found within small intrarenal veins even in 18–29 % of organ-confined tumors [6–8]. Thus, for CCRCC, invasion into the renal sinus usually involves extension within the renal vein, leading to a higher propensity for distant metastasis than for loco-regional spread and involvement of the regional lymph nodes, which are more common pathways of spread in chromophobe and papillary RCC, respectively [7, 9–11].

The 5-year survival rate is high for patients with tumours limited to the kidney, 95 % in patients with T1 RCC and 88 % in patients with T2 RCC. However survival declines rapidly with the tumour invasion outside the kidney: patients with T3 RCC have a 5-year survival rate of 59 %, and those with T4 disease had a 5-year survival rate of 20 %.

The 5-year survival rates after radical nephrectomy for stage I and stage II RCC are approximately 94 and 79 % respectively, essentially the same as T1 and T2 RCC. Although renal vein involvement does not have a markedly negative effect on

prognosis, the 5-year survival rate for patients with stage IIIB (T3b) renal cell carcinoma is 18 %. In patients with effective surgical removal of the renal vein or inferior vena caval thrombus, the 5-year survival rate is 25–50 %. Patients with regional lymph node involvement or extracapsular extension have a survival rate of 12–25 %. Unfortunately, 5-year survival rates for patients with stage IV disease are low (0–20 %).

Five survival prognostic factors for metastatic RCC patients have been used to categorize such patients into three tiered risk groups [12]. The prognostic factors were (1) low Karnofsky performance status (<80 %), (2) high serum lactate dehydrogenase (LDH) level (>1.5 times upper limit of normal), (3) low haemoglobin (below lower limit of normal), (4) high "corrected" serum calcium (>10 mg/dL) and (5) previous history of nephrectomy. Patients in the lowest risk group (zero risk factors) had a median survival of 20 months, while patients with intermediate risk (1 or 2 risk factors) had a median survival of 10 months and patients in the highest risk group (3 or more risk factors) had a median survival of only 4 months. Other factors reported to be associated with increased survival in patients with metastatic disease include the presence of only pulmonary metastases, the removal of the primary tumour and a good general performance status. Notably, a long disease-free interval between the initial nephrectomy and the first appearance of metastases is important, with progression-free survival at 3 and 6 months predicting better overall survival among patients with metastatic renal cell carcinoma [13].

Molecular Basis and Genetics of Renal Cell Carcinoma

Both inherited and acquired (somatic) genetic changes are implicated in the pathogenesis of familial RCC whereas somatic changes cause sporadic RCC. The best recognised inherited disorder predisposing to development RCC is von Hippel-Lindau (VHL) disease (see Chap. 3), resulting from the germline mutation or deletion of the VHL gene at chromosome 3p25 [14]. Affected individuals are at increased risk to tumours within multiple organ systems, including cysts and tumours of the kidney (lifetime risk of RCC >70 %), with a mean age at onset of 40 years. The patients frequently present with multifocal and/or bilateral RCC tumours and they are always of the CCRCC histologic type.

Inherited constitutional chromosome 3 translocations can predispose to RCC (most commonly CCRCC). However, individuals who have an incidentally detected chromosome 3 translocation with no personal or family history of RCC are unlikely to be at high risk of RCC.

Further major inherited disorders associated with RCC include: hereditary papillary renal carcinoma (HPRC), Birt-Hogg-Dubé (BHD) syndrome, hereditary leiomyomatosis renal cell carcinoma (HLRCC) and succinate dehydrogenase mutation associated renal cell carcinoma (SDH-RCC) [14, 15]. Also RCC may rarely complicate Tuberous Sclerosis (TS), and Cowden syndrome (Multiple hamartoma syndrome).

Hereditary papillary renal carcinoma and hereditary leiomyomatosis renal cell carcinoma are both associated with the development of papillary renal cell carcinoma

(CCRCC) histologic types: type I with HPRC and type II with HLRCC. Birt-Hogg-Dubé syndrome predisposes to the development of a variety of histopathological subtypes including chromophobe, hybrid oncocytic, and CCRCC [16]. Succinate dehydrogenase mutation associated renal cell carcinoma also is not confined to a specific histologic type of RCC [17].

In addition there are patients with features of inherited non-syndromic RCC (e.g. family history of RCC, multifocality, bilaterality, and early age of onset) in whom no known genetic cause can be detected. Further investigation of these individuals should lead to the identification of novel hereditary RCC genes.

Clear Cell RCC

Clear cell RCC can be sporadic (>95 %) or familial (<5 %). Most sporadic RCC have somatic inactivation of the von Hippel Lindau (*VHL*) tumor suppressor gene located at chromosome 3p25 [18, 19] but *VHL* functions as a classical tumour suppressor gene in that inactivation of both alleles of the gene are required to initiate tumorigenesis. In sporadic RCC somatic mutation, loss or (less commonly) promoter methylation produce the two "hits" required for tumourigenesis whereas in patients with VHL disease the first "hit" is the germline VHL gene mutation and only one somatic hit is required for tumourigenesis.

The protein encoded by the *VHL* gene (pVHL) is a component of the elongin complex and is involved in targeting the hypoxia inducible factor alpha (HIFα) proteins for ubiquitination and subsequent degradation. Thus pVHL plays a critical role in the regulation of gene expression in response to oxygen levels. Inactivation of the *VHL* gene stabilises the levels of hypoxia-inducible factor-1α (HIF1α) and hypoxia-inducible factor-2α (HIF2α), which in turn activates expression of hypoxia response genes involved in the angiogenesis (e.g. vascular endothelial growth factor (VEGF)), cell proliferation (e.g. transforming growth factor alpha (TGFα)), apoptosis and other signalling pathways [20, 21]. Many recently introduced therapies for metastatic RCC target the tyrosine kinase receptors for HIF-regulated growth factors (e.g. VEGF). Though both HIF1 and HIF2 may be upregulated in pVHL-deficient clear cell RCC it appears that HIF2 is most responsible for promoting oncogenesis [21]. Amplification of, or activating mutations within, known proto-oncogenes is relatively infrequent in clear cell RCC though amplification of the *MYC* proto-oncogene on chromosome 8q can be detected in ~12 % of clear cell RCC [22]. Deletions of chromosome 3p occur in the majority of clear cell RCC and copy number loss on chromosomes 14, 8, 9, and 6 may be detected in 0–20 % [22]. Large scale candidate gene and exome sequencing studies of clear cell RCC have demonstrated that, after *VHL* inactivation, the most commonly mutated genes are those implicated in chromatin modelling/histone modification. Thus Varela et al. [23] undertook exome sequencing and found that the SWI/SNF chromatin remodelling complex gene *PBRM1* demonstrated truncating mutations in 41 % of clear cell RCC. In addition *SETD2*, *JARID1C*, *UTX* and *MLL2* have each been reported to be mutated in up to 5 % of clear cell RCC [24]. Interestingly,

PBRM1 and *SETD2* map to chromosome 3p21 an area of frequent allele loss in clear cell RCC that also contains the *RASSF1A* tumour suppressor gene that is frequently inactivated in sporadic clear cell and non-clear cell RCC.

Papillary RCC

Papillary RCC has been divided into two subtypes though familial cases are rare. Inherited Type I papillary RCC is associated with germline *MET* point mutations [25]. The *MET* proto-oncogene is a cell surface receptor tyrosine kinase for the ligand hepatocyte growth factor, both of which are located on human chromosome 7. The identification of germline activating missense point mutations in the tyrosine kinase domain of *MET* as a predisposition gene for hereditary type I papillary renal cancer (HPRC) highlighted the importance of the gene. In sporadic type I papillary RCC *MET* is somatically mutated in between 5 and 13 % of cases, far less commonly that *VHL* in sporadic clear cell RCC, but in many cases there is trisomy of chromosome 7 without mutation of *MET* [25, 26]. Type II papillary RCC is more frequent than Type 1, is usually of higher nuclear grade and does not harbour *MET* mutations. Type II papillary RCC may occur as component of the rare inherited cancer syndrome caused by germline mutations in the fumarate hydratase (*FH*) gene [27]. Individuals with germline *FH* mutations are predisposed to develop cutaneous leiomyomas, RCC (lifetime risk ~15 %) and, in women, multiple uterine fibroids at a young age. The *FH* gene appears to be rarely mutated in sporadic papillary RCC.

The most common cytogenetic events associated with papillary RCC are trisomy of chromosomes 7 and 17 and loss of the Y chromosome [28]. Comparison of gene expression profiles in clear cell RCC and papillary RCC has been reported to demonstrate prominent deregulation of hypoxia response pathways secondary to VHL inactivation in the former group, AKT pathway activation in both RCC subtypes and prominent MYC pathway activation in high grade papillary RCC [29].

A specific somatic cytogenetic abnormality occurs in a rare subset of papillary RCC. The Xp11.2 translocation typically occurs in children or young adults. The translocation breakpoint involves the *TFE3* gene at Xp11.2 and the translocation is associated with the formation of a fusion gene between *TFE3* and a variety of partner genes. The translocation results in overexpression of the fusion protein and although Xp11.2 translocations are rare, expression of TFE3 is a more common finding and can result from TFE3 amplification [30].

Chromophobe RCC

Chromophobe carcinomas have been found to be characterized by frequent (75–100 %) monosomy of multiple chromosomes, particularly 1, 2, 6, 10, 13, 17, and 21, and thus a lower than diploid cell copy number [31]. Mutation of *VHL* has not been found in chromophobe RCC [32].

Birt-Hogg-Dube (BHD) syndrome, caused by germline mutations in the folliculin (*FLCN)* tumour suppressor gene (located on chromosome 17p12q11.2) predisposes to facial fibrofolliculomas, lung cysts and pneumothorax and RCC (lifetime risk ~25 %) [33, 34]. The most characteristic form of RCC in BHD syndrome is a hybrid RCC, with microscopic features of both chromophobe RCC and oncocytoma but other types including pure chromophobe or clear cell RCC also occur.

Collecting Duct RCC and Other Rare Forms of RCC

Collecting duct RCC represents a rare but highly aggressive tumour of the distal nephron (renal medulla) that shows loss of heterozygosity (LOH) for chromosomes 1q, 6p, 8p, 13q and 21q [35]. Addition types of RCC include renal medullary carcinoma, which is associated with African-Americans and with the sickle cell "trait", and mucinous tubulocystic RCC.

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Chapter 18
Renal Cancer – Epidemiology and Aetiology

Adam Alleemudder, Amlesh Seth, and Vinod H. Nargund

Renal cell carcinoma (RCC) accounts for an estimated 90 % of all renal tumours. It is the 13th most common malignancy worldwide with an incidence of 271,000 cases per year in 2008, of which 88,400 were in Europe [1]. For unknown reasons, incidence rates are highest in North America, Australia and Europe, particularly in the Czech Republic, Lithuania and Estonia, but lowest in India, China and Africa [1]. The mortality rates worldwide and in Europe are 116,000 and 39,300, respectively [1, 2]. Whilst there has been a steady increase in incidence during recent years, estimated at 2 % per year and in part accounted for by the availability of better imaging techniques, there is now a downward trend particularly in the Scandinavian countries [1, 3].

Men are more at risk than females with incidence increasing with age and peaking at 70–75 [1, 4]. The highest incidence rates are seen in African Americans, possibly as a result of low socioeconomic status, limited access to health care, and genetics [4]. Caucasians are at a higher risk than Asians [1]. RCC is uncommon in childhood and accounts for only 2.3–6.6 % of all renal tumours [5].

Aetiology

The exact cause for RCC is unknown but several risk factors have important significance.

A. Alleemudder, MBChB, BSc, MRCS (Ed) (✉)
Department of Urology, Barts and The Royal London Hospital, London, UK
e-mail: adamalleemudder@doctors.org.uk

A. Seth, MBBS, MS, DNB, MCh(Urol)
Department of Urology, All India Institute of Medical Sciences, New Delhi, India

V.H. Nargund, PhD, FRCSEd, FRCSUrol, FEBU
Department of Urology, Homerton University Hospital, London, UK
e-mail: vinodnargund@gmail.com

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Tobacco Smoking

There is an established but weak association between smoking and developing RCC. The risk increases with cumulative or pack-years whilst smoking cessation is not thought to reduce the risk [6]. The risk however is modest and the effect is not as strong as for bladder or lung cancers. A history of smoking could be associated with worse pathologic features and survival outcomes and mutation of p53 [7].

Obesity

In keeping with the trend seen in other cancers, there is an association between obesity and RCC possibly resulting from an increased exposure to oestrogen or androgens, lipid peroxidation causing DNA adducts or increased expression of insulin-like growth factor-1 [8]. An increased hip to waist ratio is also a risk factor [9].

Hypertension

There is a known risk between hypertension and the development of RCC in both blacks and whites and in particular in black women [10]. The pathogenesis is unclear but may involve lipid peroxidation, oxygen radicals (reactive oxygen species-ROS) and upregulation of hypoxia inducible factors [11]. The duration of hypertension required for increased risk is unknown but subsequent blood pressure control is thought to reduce the risk [12]. It is now accepted that antihypertensive medications do not contribute to the increased risk that was previously thought. In a cohort of Swedish men, a reduction in blood pressure over a period of time was associated with a decrease in renal cancer risk, suggesting that effective hypertension control may lower risk [13].

Nutrition and Diet

Diet is implicated as a risk factor because of the varied geographical incidence of RCC but intakes of fat and protein or their subtypes, red and processed meat, poultry and seafood are no longer thought to increase the risk of RCC [14]. On the contrary, intakes of fruit and vegetables may provide a protective role [15]. Interestingly, moderate alcohol consumption greater than 15 g per day appears to have an inverse association with the development of RCC [16]. The association with coffee intake and RCC remains unclear.

Physical Activity

Most of the studies so far have shown an inverse relationship between risk of developing RCC and physical activity. Physical activity may decrease the risk by controlling the body weight, blood pressure, improving insulin sensitivity and by reducing oxidative stress and chronic inflammation [4].

Occupation

A definite occupational carcinogen associated with RCC has not yet been found due to the difficulty in retrospectively assessing exposure. One industrial agent that is under intense investigation is trichloroethylene (TCE), a solvent used in metal degreasers, which is thought to increase the risk by two to six fold [17]. Other agents implicated include exposure to lead, polycyclic aromatic hydrocarbons and plastics [18].

Miscellaneous

There appears to be a dose-response association between the use of non-steroidal anti-inflammatory drugs (NSAID) and RCC, but not with Aspirin or Paracetamol [19]. Diabetes Mellitus and a history of urinary tract infections remain controversial risk factors.

Chronic Renal Failure, Dialysis and Renal Transplantation

Acquired cystic kidney disease (ACKD) is characterized by epithelial proliferation and occurs in the setting of prolonged azotemia and is therefore common in dialysis patients. Its major complication is the development of renal cancer. The incidence of renal cancer is significantly increased in ACKD patients and is probably increased overall in the end-stage renal disease (ESRD) population also [20].

Origin, Cell Type and Natural History

RCC is believed to arise from the cells of nephron, which is the structural and functional unit of the kidney. It therefore comprises of many histological varieties. Both papillary and clear cell RCC arise from the lining of the proximal convoluted tubule

(PCT) while chromophobe RCC, oncocytoma and collecting duct RCC are thought to originate from the distal parts of the nephron probably from cells of the collecting duct [21]. It is important to note that each histological type has its own morphological features, biological behaviour and genetics. The most common histological type is clear cell carcinoma accounting for 70–80 % of RCC. The remainder comprise of papillary (10–15 %, chromophobe (5 %) and other rare types (<1 %) [21].

The natural history of small renal lesions is not properly understood as the majority are either removed at diagnosis or after a short period of observation. Any solid lesion of the kidney on either ultrasound or other cross-sectioning imaging modality should be considered as a malignant tumour until proven otherwise. There are no specific tumour-related or molecular markers to assess the progress of malignant renal lesions. The majority of the small, incidentally discovered, enhancing renal masses are malignant. High-grade tumours grow at a faster rate (0.93 cm/year) compared with intermediate and low-grade tumors (0.28 and 0.37 cm/year) [22]. As expected these lesions will have metastatic potential particularly if they have significant interval growth. In a single institution study of 2,935 renal tumors, Frank et al. [23] demonstrated that for each 1-cm increase in diameter, there was a 17 % increase in the likelihood of the lesion being malignant.

Another area of interest is the progression of untreated renal lesions particularly in relation to metastasis. Lamb et al [24] studied the natural history, complications and outcome in a group of 36 patients who were medically unfit and whose tumour had not been removed. In a median follow up of 24 months, 13 had died due to unrelated causes and one patient developed metastasis at 132 months and on follow up he was still alive at 136 months. There was no change in the tumour size during the follow up period.

Genetics of RCC and Its Clinical Implications

The genetic basis of RCC has already been described earlier in this Chap. 17, and also in Chap. 3, which deals with the genetics of genito-urinary cancers. Kidney cancer is now known to be a genetic disease made up of a number of different cancers each with their own histology, genetic alteration, clinical course and response to therapy [25]. Over the past two decades, advances in molecular genetics has identified several familial syndromes which in turn has helped to characterise the "culprit" genes responsible for both familial and sporadic forms of RCC. Subsequently, this has enabled the development of novel therapies to improve the survival of patients with advanced disease.

Several case-controlled studies have found that a family history of RCC is, in fact, a risk factor even in sporadic cases [26]. In the nationwide Swedish Family Cancer Database, including 23,137 kidney cancer cases, the standardized incidence ratio was 1.6 for family history of the same cancer in offspring and 4.7 in siblings [27].

It is crucial to know the role of von Hippel-Lindau (VHL) gene in order to understand the biology of clear cell RCC (ccRCC). According to Knudsons 2-hit theory, both alleles of the VHL gene must be mutated or inactivated for development of the disease [28]. Nearly all patients with VHL have germline mutation of one allele

whilst the other allele is commonly lost by gene or chromosomal deletion. Similarly, in two-thirds of sporadic ccRCC, there is evidence of biallelic inactivation of the VHL gene with loss of heterozygosity seen in 87 % [21]. One allele is germline mutated or inactivated whilst the second allele is inactivated by somatic mutation, hypermethylation of promoter regions causing transcriptional silencing or more commonly (45–90 %) by chromosome 3p deletion. Homozygous deletion and rearrangement may account for further cases of biallelic inactivation [29]. The initiating event in ccRCC seems to be due to allelic inactivation whilst little is known of the secondary and later genetic alterations that drive progression of the disease. In sporadic ccRCC, both mutations are acquired after birth, which causes the later onset of the disease and its unifocal nature.

The VHL tumor suppressor gene that encodes 30 kDa protein (pVHL) has several putative cellular functions, but it is well known for its role in the oxygen sensing pathway by regulating cellular response to oxygen availability in the local microenvironment. This protein exists in the cytoplasm bound to Elongin B, Elongin C, Cullin-2 and ring box protein 1 (RBX1) to form an E3 ubiquitin ligase complex. Under normal conditions, this protein complex targets hypoxia-inducible factors (HIF1-α and HIF2-α) 1 and 2 for ubiquitin-mediated proteosomal degradation to keep their levels low. Under normal conditions, HIF-α is hydroxylated and binds to pVHL leading to HIF degradation. Hypoxia inducible factor- 1(HIF-1) controls oxygen delivery (via angiogenesis) and metabolic adaptation to hypoxia (via glycolysis). HIF-1 consists of a constitutively expressed HIF-1 beta subunit and an oxygen and growth factor regulated HIF-1 alpha subunit [30] (Fig. 18.1).

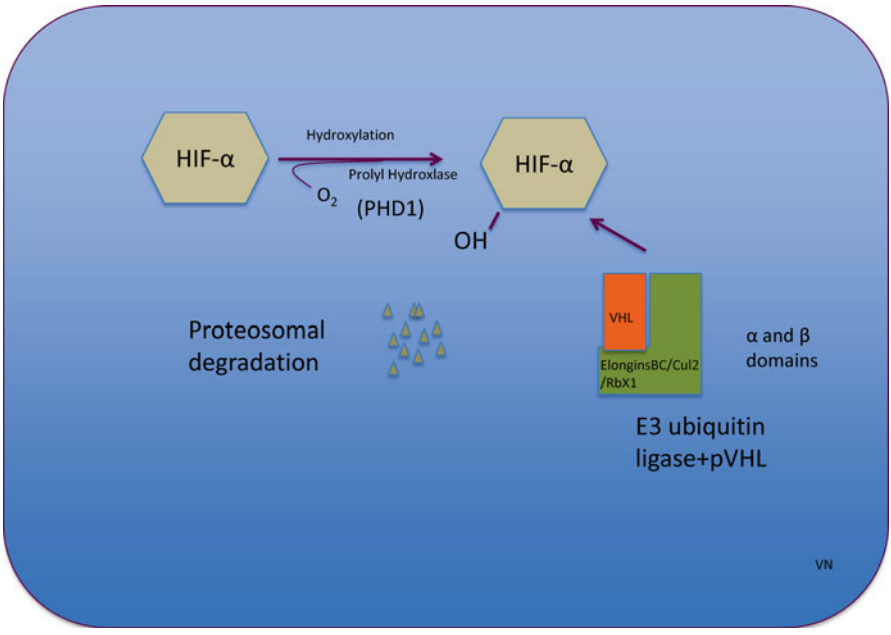

Fig. 18.1 Cellular function with normal O_2 levels and normal VHL System

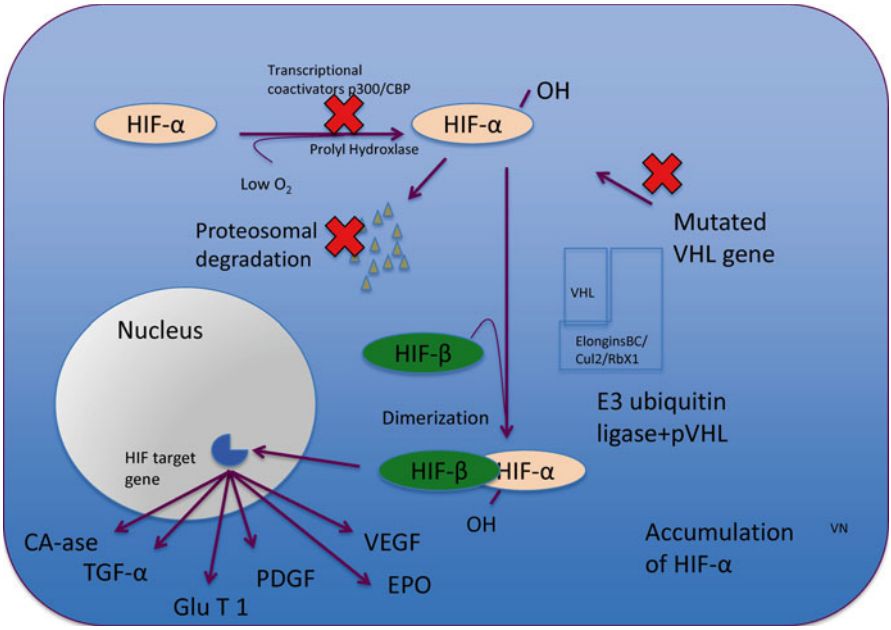

Fig. 18.2 Target gene activation in VHL loss

When there is hypoxia or mutation of pVHL, binding of pVHL to HIF-α cannot occur and the pVHL-HIF complex is not formed leading to accumulation of HIF-α. After escaping the proteolytic pathway HIF-α gains access to the cellular nucleus to bind with HIF-β and induce gene activation to restore normoxic conditions. There is upregulation of a variety of proangiogenic and growth factors, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) involved in angiogenesis, transforming growth factor-α (TGF-α) involved in autocrine and paracrine growth stimulation, on glucose transport (Glut-1), and erythropoietin (EPO), which are all believed to play critical roles in the development and progression of ccRCC (Fig. 18.2).

While most contain mutation of the VHL gene, it seems likely every tumor has its own unique genetic signature. Molecular analysis continues to search for these other genetic alterations. To date, more than 1,500 germline and somatic mutations have been sequenced from the three exons of the VHL gene [31]. Excluding 3p deletions, loss of genetic material and heterozygosity affecting chromosomes 14, 8, 9, and 6 has been is found in 20–40 % of RCC [21]. Other tumor suppressor genes implicated in RCC include p53 on 17p, Rb(Retinoblastoma) on 13q, p16*INK*4*a*/p14*ARF* on 9p and PTEN on 10q [21]. The latter is of significance for targeted therapy as the PTEN protein inhibits phosphatidylinositol-3-kinase dependent activation of protein kinase B. Loss of this protein leads to consecutive activation of the mTOR-pathway which promotes tumorigenesis [32].

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Chapter 19
Pathology of Renal Cancer

Abigail Lee and Sohail Ibrahim Baithun

Renal cell carcinoma (RCC), which arises from the renal tubular epithelial cells, accounts for more than 90 % of primary renal tumors in adults [1]. RCC consists of a heterogeneous group of tumors with distinct genetic and metabolic defects, as well as histopathological and clinical features [2]. Renal cell carcinoma (RCC) has variable clinical outcomes that range from indolent to overtly malignant. The application of molecular genetic techniques to the study of renal neoplasms has resulted in an improved classification of these entities and a better understanding of the biologic mechanisms responsible for tumour development and progression. Nearly each RCC type occurs in a sporadic and in a hereditary form [3]. The hereditary renal tumours have already been described in Chaps. 3 and 17.

The classification of adult malignant renal tumours was updated in 2004 by the World Health Organisation and is shown in Table 19.1 [4]. The 3 most common major histological subtypes are described first (Clear cell, Papillary and Chromophobe).

The pathology of familial renal cancers is summarised in Table 19.2.

Table 19.3 outlines rare tumours in the kidney in WHO classification [5].

Table 19.4 summarizes the grouping of the tumours according to the prognosis: good prognosis, intermediate and poor prognosis.

A. Lee
Department of Morbid Anatomy, The Royal London Hospital,
Barts Health NHS Trust, London, UK

S.I. Baithun, MB, FRCP (✉)
Department of Histopathology, King Howard University, Busaiteen, Bahrain
e-mail: siabaithun@yahoo.co.uk

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Table 19.1 WHO (2004) classification of renal tumours

Malignant renal cell tumours
Clear cell renal cell carcinoma
Multilocular clear cell renal cell carcinoma
Papillary renal cell carcinoma
Chromophobe renal cell carcinoma
Carcinoma of the collecting ducts of Bellini
Renal medullary carcinoma
Xp11 translocation carcinomas
Carcinoma associated with neuroblastoma
Mucinous tubular and spindle cell carcinoma
Renal cell carcinoma unclassified

Adapted from Algabaa et al. [4]. With permission from Elsevier

Clear Cell RCC (ccRCC)

The cells of ccRCC have a clear cytoplasm due to the high content of glycogen and lipid but may have an eosinophilic or granular appearance when the mitochondrial content is high (Fig. 19.1). The ccRCC accounts for more than 60 % of all malignant renal tumours with 4 % being multifocal and 3 % bilateral [4]. Compared to other RCCs, they tend to be more aggressive in men, progress to metastatic disease twice as frequently after nephrectomy and have lower overall survival [6].

Macroscopically, the cut surface has yellowish appearance often with areas of haemorrhage, scarring and calcification, ossification and extension to renal vein. They maybe solid, tubular or cystic, the latter of which has given rise to a subtype known as multilocular cystic RCC when the there is a complete cystic appearance. Sarcomatoid changes are seen in 5 % of tumours, which represents high-grade transformation and carries a poor prognosis.

Papillary RCC (PRCC)

These are the second most common type, with a male predominance and accounting for up to 15 % of all RCCs [7] (Fig. 19.2).

Tumours less than 5 ml are considered to be adenomas and those greater than 5 ml to be carcinomas [7]. The underlying genetic abnormalities are trisomy of chromosomes 3q, 7, 8, 12, 16, 17 and 20 with loss of the Y chromosome [8]. Macroscopically, they are round and white or beige in colour and may contain central necrosis or haemorrhagic areas. The cells are usually small containing scanty cytoplasm and foamy macrophages. The growth pattern is predominantly papillary but may also be tubular or solid. Two morphological types are typically described, although recently a third group has emerged composed entirely of oncocytes and shows different clinic-pathological features [9].

Table 19.2 Pathology of hereditary RCC

Syndrome	Chromosomes involved	Gene	Protein	Histological type	Involvement of other organs
Von Hippel-Lindau	3p25	VHL	pVHL	Bilateral, cystic renal lesions and clear cell Carcinoma	Cysts in other organs, phaeochromocytoma neuroendocrine tumours
Hereditary papillary Ca	7p 31	c-MET	HGF-R	Bilateral & multiple Papillary RCC	None
HLRC (Hereditary leiomyomatosis RCC	1q 42	FH	FH	Papillary RCC (non type 1)	Uterine leiomomyoma/leiomyosarcoma
Familial papillary thyroid carcinoma	1q 21	Not known	Not known	Papillary RCC & oncocytoma	
Hyperparathyroidism jaw tumour (HP-JT)	1q 25	HRPT2	–	Epithelial stromal mixed tumours, papillary RCC	
Birt-Hogg-Dube	17p 11	BHD	Folliculin	Multiple chromophobe RCC, oncocytic adenoma, papillary RCC	Pulmonal cysts; spontaneous Pneumothorax, facial fibrofolliculoma
Constitutional translocation chromosome 3	3p13-14			Multiple, bilateral clear cell RCC	–

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Table 19.3 Benign and other rare malignant tumours

1. Benign: papillary adenoma, oncocytoma
2. Metanephric tumours (metanephric adenoma, metanephric adenofibroma, metanephric stromal tumours)
3. Nephroblastic tumours (cystic nephroma, mixed epithelial and stromal tumours, synovial sarcoma)
4. Nephroblastic tumours (nephrogenic rests, nephroblastoma, cystic partially differentiated nephroblastoma)
5. Neuroendocrine tumours (carcinoid, neuroendocrine carcinoma, primitive neuroectodermal tumour, Neuroblastoma, pheochromocytoma)
6. Miscellaneous (mesenchymaltumours, haemopoetic & lympoidtumours, germ cell tumours, metastatictumours)

Adapted from et al. [5]. With permission from Elsevier

Table 19.4 Clinical classification according to prognosis

Good prognosis	Papillary adenoma (benign); oncocytoma (benign)
	Metanephric adenoma; angiomyolipoma
	Multilocular clear cell renal cell carcinoma (malignant)
	Mucinous tubular and spindle cell carcinoma (malignant)
Intermediate prognosis	Papillary carcinoma (malignant), chromophobe renal cell carcinoma
Poor prognosis	Clear cell carcinoma, metastatic cancers, collecting duct carcinoma
	Renal medullary carcinoma, Xp11 translocation carcinomas
	Sarcomas

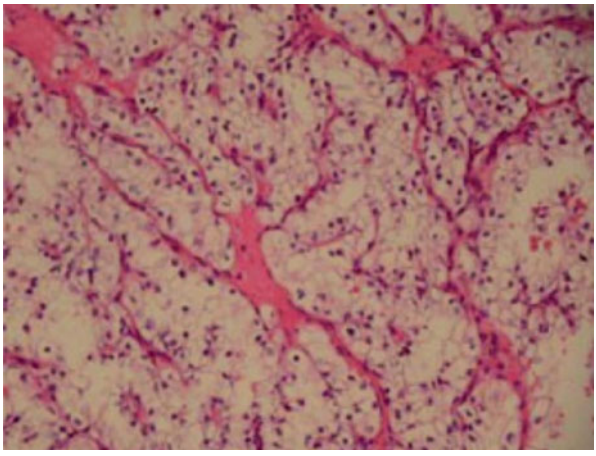

Fig. 19.1 Clear cell carcinoma (×100)

Type I

The papillae and tubular structures are lined by cuboidal cells with small oval nuclei, inconspicuous nucleoli and pale cytoplasm. The papillary cores often contain foamy macrophages and psammoma bodies are common. These patients have a longer survival.

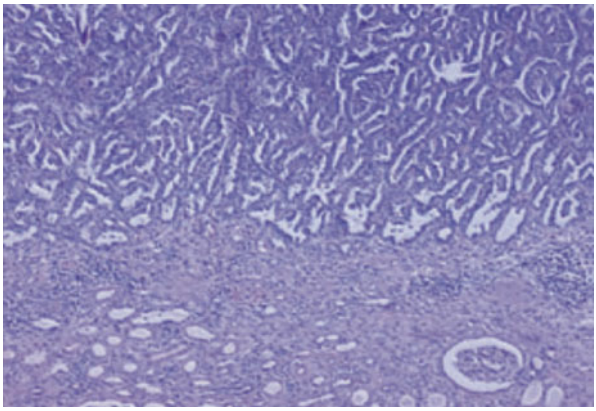

Fig. 19.2 Papillary RCC (×100)

Type II

The papillae contain large cells with higher nuclear grade, copious eosinophilic cytoplasm and large nuclei with prominent nucleoli. Foamy macrophages within the papillary cores and psammoma bodies are uncommon. In general, the type 2 tumours are larger and present in younger patients with advanced stage.

Type III

Oncocytic PRCC – Rarely, PRCC can display extensive areas of solid and non-papillary architecture and extensive areas with oncocytic cytoplasm. The oncocytic features in PRCC may pose a diagnostic problem in differentiating oncocytic PRCC from oncocytoma. Papillae and trabeculae are present with fibro-vascular cores covered with cells containing an eosinophilic cytoplasm packed with mitochondria and aggregates of foamy macrophages, round nuclei and a low nuclear-cytoplasmic ratio. There are no cytogenetic or molecular tests for this variant of PRCC [10].

Chromophobe RCC (CRCC)

They account for 5 % of RCC and are characterised by a combination loss of chromosomes 1, 2, 6, 10, 13, 17 and 21 [4]. Macroscopically, the tumour appears lobulated; the cut surface containing one or more solid tumour nodules but well circumscribed. The cells are large and pale and polygonal usually with a clear but sometimes eosinophilic cytoplasm containing condensed, hyperchromatic and sometimes bifid nuclei. The growth pattern is typically solid although rarely maybe cribiform (Fig. 19.3).

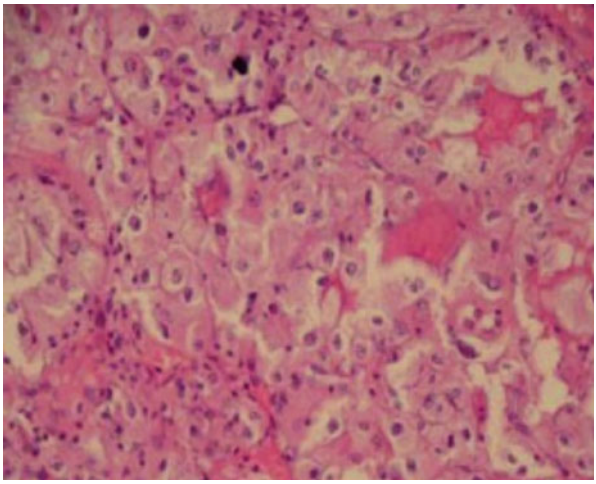

Fig. 19.3 Chromophobe RCC

Rare Types of Renal Cell Carcinomas

Multilocular Clear Cell RCC (MCRCC)

This accounts for an estimated 3.5 % of RCCs and whilst it may be considered as a separate entity it is essentially a well-differentiated ccRCC [7]. The cysts are lines by a single layer of clear cells with fibrous septations containing epithelial cells [7]. They present as a Bosniak type II or III cystic lesion although this type of Bosniak lesion can also be due to a benign cystic nephroma, multilocular cyst or mixed epithelial and stromal tumor of the kidney. Biopsy or frozen section of the lesion often cannot distinguish between these lesions and the usual management is surgical excision. The clinical outcome in these cases is excellent.

Collecting Duct (of Bellini) Carcinoma (CDC)

These rare tumours are derived from the cells of collecting ducts in the renal medulla and account for less than 1.8 % of RCCs [11]. There is a male predominance and poor prognosis with up to 40 % having metastatic disease on clinical presentation [12]. The most frequent genetic abnormality is deletion of chromosome 1q32 [13]. Macroscopically, they have a whitish grey appearance with a solid growth pattern. There is dilation of the tubules and papillae, which are lined by cuboidal cells, giving a cobblestone appearance under microscopy. At presentation they are usually advanced with metastasis with Fuhrman grade 3 or 4 nuclear features (Fig. 19.4 [14], Fig. 19.5).

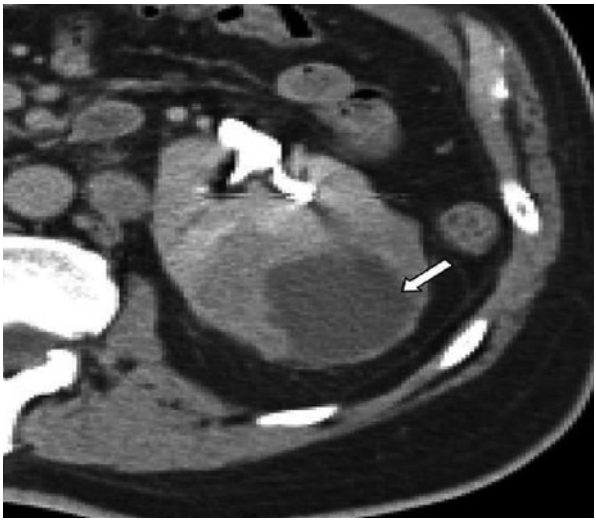

Fig. 19.4 Axial contrast-enhanced CT scan image demonstrates a heterogeneously hypodense mass in the left kidney; Histology revealed CDC (Reprinted from Shanbhogue et al. [14]. With permission from Springer Verlag)

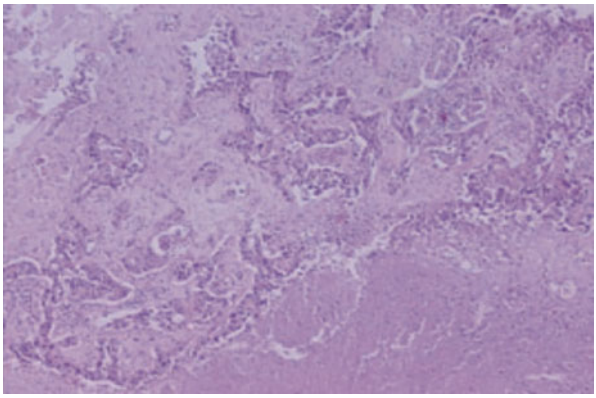

Fig. 19.5 Collecting duct RCC (×100)

Renal Medullary Carcinoma (RMC)

This is an extremely rare type of malignant tumour, which is poorly differentiated and carries a poor prognosis. RMC is found almost exclusively in young adults with sickle cell trait and sickle cell disease with a male predominance [12]. It occurs more commonly in the right kidney as a solitary, poorly circumscribed mass with a tan or grey-white colour. It shares many histological features with collecting duct carcinoma but additionally consists of cribiform glands surrounded by a desmoplastic reaction. Sickle-cell erythrocytes are a frequent finding within the tumor and adjacent renal tissue [12]. Cytogenetic anomalies seen in RMC include monosomy of chromosome 11, translocations involving chromosome 3 and 8 and tetraploidy with bcr/abl translocations involving chromosomes 9 and 22 [15] (Fig. 19.6).

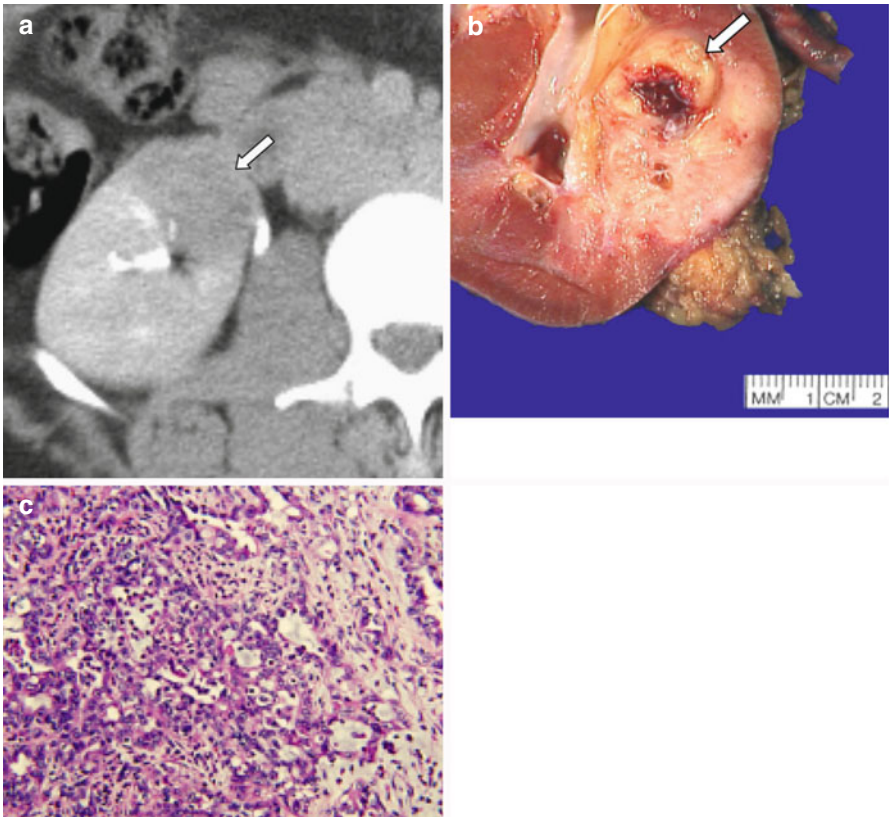

Fig. 19.6 RMC in a sickle cell trait patient. (**a**) Axial contrast enhanced CT shows a poorly defined hypodense lesion in the middle pole of the right kidney .(**b**) Heterogeneous mass with areas of necrosis and haemorrhage. (**c**) Histopathology showing sheets of poorly differentiated cells with inflammatory cell infiltrates (Reprinted from Shanbhogue et al. [14]. With permission from Springer Verlag)

Genetic locus in chromosome 11 encoding the beta-globin gene has been proposed to play a central role in the pathogenesis of RMC. Metastatic disease is found on presentation in 95 % of cases. The underlying genetic alteration is not yet known.

RCC Ass RCC Associated with Xp11.2 Translocation

These occur more commonly in children and adolescence with a female predominance where they account for a third of renal tumours in this age group [12]. They follow an indolent course despite often presenting at a late stage. In 90 %, the transcription factor *E3* (*TFE3*) located on Xp11.2 is involved with fusion commonly between *ASPL-TFE3* and *PRCC-TFE3* [16]. They tend to be large in size with a 6–7 cm mean diameter and resemble ccRCC with a yellow cut surface and containing necrosis or haemorrhage. The growth pattern may be papillary, nested or solid.

The histological characteristics vary with the type of translocation; in *ASPL-TFE3* RCC's the papillae are covered with cells containing clear to eosinophilic cytoplasm, have discrete cell borders, vesicular chromatin and prominent nucleoli. The histology consists of cells with granular eosinophilic cytoplasm with nuclear immunoreactivity to TFE3 protein [17].

Renal Cell Carcinoma Associated with Neuroblastoma

There is an increased risk, which may be as high as 329-fold, of developing RCC in those with a history of childhood neuroblastoma who received radiotherapy and/or chemotherapy [18]. The tumours are heterogeneous and vary in size. Allelic imbalances occur at 20q13 locus [5]. Histologically they have a solid or papillary growth pattern composed of oncocytoid cells with eosinophilic cytoplasm and irregular nuclei.

Mucinous Tubular and Spindle Cell Carcinoma (MTSCC)

These are typically low grade tumors that have previously been described under a variety of different terms and have a female preponderance. They have three salient histological components, namely tubules lined by cuboidal cells, spindle cell areas and mucinous extracellular stroma. Because of its rarity, the underlying genetic anomaly is yet to be determined but may be the result of trisomy of chromosomes 7 and 17 [19]. There seems to be a combination of losses of chromosomes 1, 4, 6, 8,13 and 14 and gains of chromosome 7, 11, 16 and 17 [7, 20]. On gross examination, they are well circumscribed with cut surface showing a tan, grey or pale yellow areas associated with necrosis. Microscopically, there are elongated tubules separated by pale mucinous stroma. Parallel and collapsed tubules give a spindle cell appearance [20, 21] (Fig. 19.7).

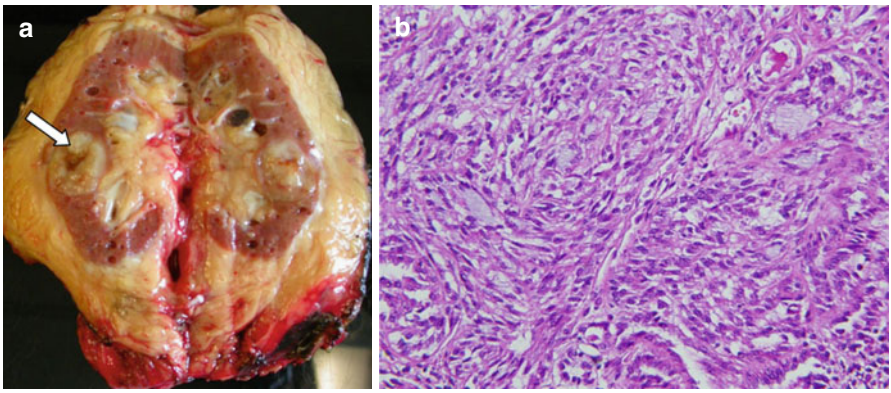

Fig. 19.7 Tumour (*arrow*) in the lower pole area showing heterogeneous *yellow* tan cut surface. Histology shows spindle cell pattern with stromal mucinous areas (Reprinted from Shanbhogue et al. [14]. With permission from Springer Verlag)

RCC Unclassified

There are a group of tumours with atypical histopathological characteristics that cannot be classified into any subtype and they account for up to 7 % of RCCs [7]. They are large and aggressive high-grade tumours with poor prognosis and early metastatic potential [22].

New Histological Entities (Subtypes) of RCC

Several histological subtypes of renal tumours have emerged since the WHO classification was introduced in 2004 [7], for which there is currently very little data available on these tumours, but at a later date may become included in the classification when it is updated.

Tubulocystic Carcinoma

This rare and incidentally found low potential tumour appears to have a male predominance (M: F = 7:1) and may be a variant of or associated with PRCC [23] (Fig. 19.8). They are typically small and solitary, and macroscopically appear grossly cystic with a spongy or bubble wrap cut surface. They are made up of tubules and cysts of varying size lined by a single layer of cuboidal cells separated by delicate or variable thickness fibrotic septa. The cells usually have an abundant eosinophilic cytoplasm and have large nuclei containing prominent nucleoli.

The cell of origin is presumed to be from the lining of collecting ducts. Immunohistochemical studies have failed to provide discriminating immunohistochemical markers or conclusive evidence supporting a specific lineage of histogenesis.

Leiomyomatous RCC

There are only a few documented cases of this rare tumour and the genetic alteration is unknown but may involve loss of chromosome 3 or 3p [12]. They appear as a brown, yellow, tan or white tumour and have a thick capsule. Microscopically the tumors are composed of nests, cords and sheets of epithelial cells frequently forming solid areas, tubules or papillary structures. There is minimal nuclear pleomorphism with abundant clear cytoplasm. The stroma has the appearance of mature smooth muscle sometimes with scattered and dilated vascular spaces, which is more pronounced at the periphery and may extend into adjacent renal tissue.

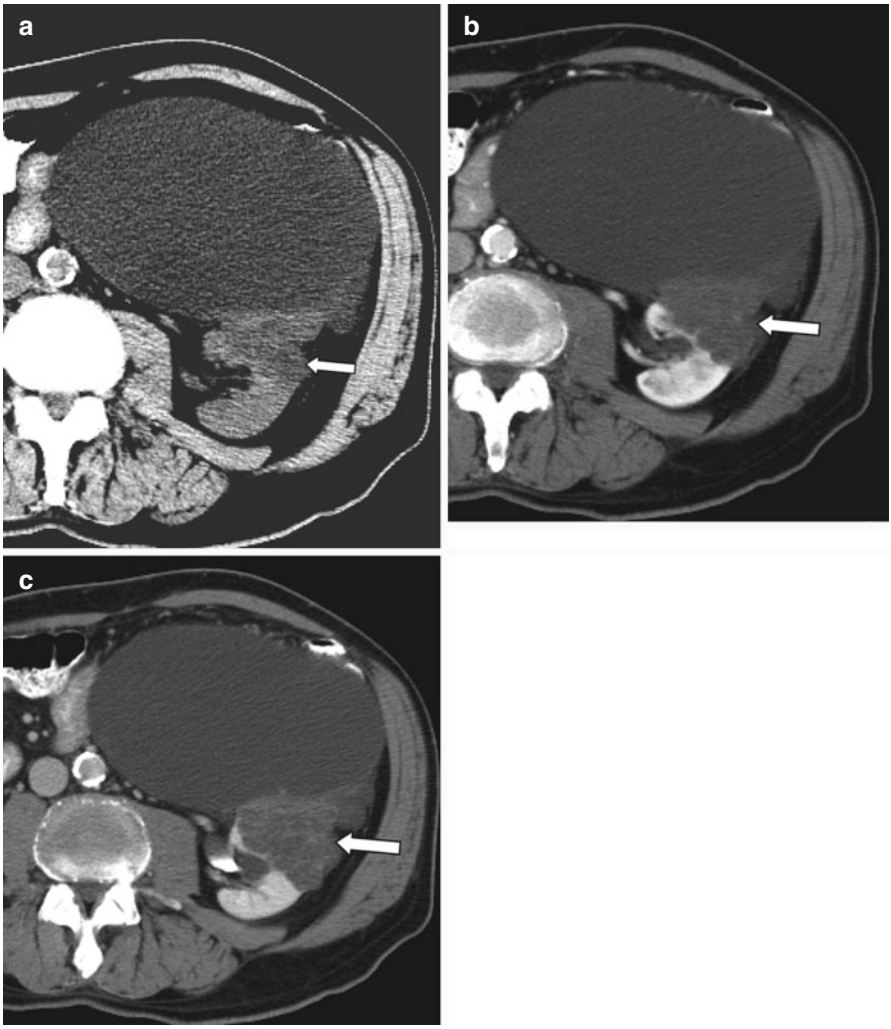

Fig. 19.8 Tubulocystic RCC: (**a**) Axial unenhanced; (**b**) Contrast enhanced; (**c**) Excretory phase-Multicystic lesion with enhancing septations (Reprinted from Shanbhogue et al. [14]. With permission from Springer Verlag)

Follicular RCC

Only a few cases of this rare tumour are described with resemblance to thyroid follicular carcinoma on histology [12]. Microscopically, there are tightly packed follicles containing colloid-like proteinaceous fluid and composed of pleomorphic cells with eosinophilic or amphophilic cytoplasm.

Carcinoma Associated with End-Stage Renal Disease (ESRD)

In those with end stage kidney disease, the incidence of acquired cystic kidney disease is 50 % and RCC 4 % in the native kidneys [12]. The most common histological subtype is papillary, followed by clear cell and chromophobe and the tumors tend to be bilateral and multicentric. There is predominance for younger male patients but the tumours tend to be less aggressive in comparison to transplant patients who are immunocompromised. The underlying genetic abnormality is unknown but VHL mutations have been found when the histology is of the clear cell type. Exact mechanism of pathogenesis is not well understood.

Adult Wilms' Tumour (Nephroblastoma) (WT)

Wilms' tumour during childhood is the most common primary malignant renal tumour but has a significantly high cure rate even in advanced stages [24]. The incidence of WT in adolescents and adults is extremely low with only 3 % being reported in adults [25]. WT is often indistinguishable from RCC. Prognosis in adults is worse than that in children. The histological diagnosis is made according to the criteria set out by Kilton et al [26]: a primary renal neoplasm in patient older than 15 years, showing primitive blastemic spindle, embryonal tubules or glomerular structures with no evidence of RCC.

Benign Renal Tumours

Papillary Adenoma

These are small (<5 mm) benign well circumscribed tumors often found incidentally in nephrectomy specimens that have a papillary or tubular or tubule-papillary architecture.

Oncocytoma

This is the most common benign renal tumor accounting for 3–7 % of all renal tumors. They have a male predominance and 5 % are bilateral and 13 % multifocal. Although typically small (<5 cm) larger lesions (>27 cm) have been described. They are associated with three characteristic genetic abnormalities, namely loss of chromosome Y or monosomy 1, translocations in the 11q13 area and genetic abnormalities such as trisomy, monosomy and/or a loss of heterozygosity [27].

Macroscopically, they are well circumscribed with a tan or light brown surface and an avascular central scar. They are composed entirely of oncocytes that are round or polygonal in shape that often have an abundance of granular cytoplasm. The cell of origin is the intercalary cell of the cortical portion of the collecting tubule. Although they are considered benign, atypical histological features may be present, including cellular atypia or pleomorphism, haemorrhage and extension into perinephric fat. Indeed, oncocytomas may coexist with RCC in upto 32 % of cases. Imaging characteristic cannot reliably distinguish between an oncocytoma and RCC whilst percutaneous biopsy has low specificity since oncocytes may be found in cRCC, granular variant of RCC and eosinophilic variant of pRCC.

Angiomyolipoma (AML)

It is a common benign tumour of the kidney; as its name suggests, it is composed of fat, smooth muscle, and abnormal blood vessels. AML can be accurately diagnosed by identifying the intratumoral fat component, which shows negative attenuation on unenhanced computed tomographic (CT) scans [28]. However in nearly 5 % of AML cases there is only a small amount of fat with prominent blood vessels and muscle tissue [29]. AML rarely cause symptoms but it may bleed or grow large enough to cause pain or even renal failure. The management therefore is expectant.

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Chapter 20
Renal Cancer: Clinical Features

Adam Alleemudder, Vinod H. Nargund, and Amlesh Seth

An estimated half of all RCCs are found incidentally on imaging used to investigate nonspecific abdominal symptoms. Many renal tumors are therefore asymptomatic until they become large enough to cause haematuria or systemic symptoms; or when the advanced stage of the disease is reached with symptoms of metastases or paraneoplastic syndromes occurring. The ability of RCC to produce paraneoplastic syndromes is a well-known entity. The classical descriptive triad of loin pain, haematuria and a palpable mass is a rare occurrence nowadays and seen in less than 10–15 % of cases [1].

In order to validate the response to various treatments for RCC, particularly in view of multiple symptoms RCC could produce, a symptom index has been described using RCC symptom burden with symptom questionnaires, literature review and caregiver observation [2]. The study reviewed 12 studies including 2 randomised comparative trials, 2 non-randomised comparative trials and 8 observational studies. Based on findings from these studies, the most frequently reported symptoms included fatigue, weakness, pain, lack of appetite, nausea, dyspnoea, flu-like symptoms, diarrhoea, constipation, headache and dry mouth. The results also showed impairment in patients health related quality of life (HRQL); in particular physical functioning, psychological impairment (depression, anxiety, irritability), sleep and social functioning [2].

A. Alleemudder, MBChB, BSc, MRCS (Ed) (✉)
Department of Urology, Barts and The Royal London Hospital, London, UK
e-mail: adamalleemudder@doctors.org.uk

V.H. Nargund, PhD, FRCSEd, FRCSUrol, FEBU
Department of Urology, Homerton University Hospital, London, UK
e-mail: vinodnargund@gmail.com

A. Seth, MBBS, MS, DNB, MCh(Urol)
Department of Urology, All India Institute of Medical Sciences, New Delhi, India

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The common sites for metastases from RCC are the lung (75 %), soft tissue (36 %), bone (20 %), liver (18 %), cutaneous sites (8 %) and central nervous system (8 %) [3]. One third of patients present with metastatic disease and may have bony pain or a persistent cough from phrenic nerve involvement. Clinical examination may reveal palpable cervical lymphadenopathy, a prominent varicocele or bilateral peripheral oedema suggesting venous involvement.

Incidental Diagnosis of RCC

Incidental diagnosis is usually made in a living patient with abdominal imaging such as ultrasound or a CT scan, which is done because of symptoms totally unrelated to the RCC. The trend of incidental detection has been increasing in the last two decades leading to a frequent diagnosis of RCC at a lower stage and even grade. The early diagnosis in an asymptomatic patient has a major implication on prognosis [4]. Firstly it reduces the risk of kidney loss (nephrectomy); secondly the earlier detection provides a better prognosis [4]. There is also evidence that prognosis in patients with systemic symptoms is far worse than in patients with localised or no [5].

Symptoms Directly Due to RCC

Haematuria

This is a relatively late sign and indicates that the tumour is extending into the pelvis and/or into the calyses. It is invariably painless but pain can occur due to clots obstructing the drainage of the system [6]. Pain can also be a feature due to sudden haemorrhage and distension of the kidney.

Loin Pain

The pain is likely to be a dull ache in nature and may radiate along the nerves when nerve involvement is present [6].

Palpable Mass

This is usually due to a large tumour as small tumours are not palpable.

Development of varicocele

This is due to obstruction of gonadal vein due to obstruction of left renal vein or due to involvement of the gonadal vein itself.

Cardiac Failure

High output cardiac failure is seen in some patients with RCC and is likely to be caused by massive arterial-venous fistulae within the tumor. There may also be a rise in blood pressure. Physical findings include a continuous bruit over the tumor. The issue may resolve with nephrectomy. Similarly, arteriovenous fistulae in a metastasis may also cause high output cardiac failure [7].

Weight Loss

As mentioned above weight loss may be as a result of loss of appetite or due to the direct effect of the growth itself.

Anaemia

Anaemia in RCC is frequently of the microcytic and hypochromic type and is seen in one third of patients [8].

Often patients with anaemia tend to show high levels of hemosiderin in the tumour cells indicating cancer cells remove iron from the circulation [8].

Paraneoplastic Syndromes of RCC

Paraneoplastic syndromes develop in 30 % of patients with RCC, which mostly result from the release of pathological amounts of substances usually produced by the kidney [1]. The common nonmetastatic manifestations are listed below in Table 20.1(A & B).

Nonmetstatic Manifestations

Hypercalcemia

This is the most common phenomenon affecting up to 20 % of patients with RCC [1]. Half of patients with hypercalcemia will have bony metastases [3]. Metastatic RCC related hypercalcemia is the result of activation of osteoclasts causing release of calcium from bone. In contrast, non-metastatic RCC related hypercalcemia is mediated by release of parathyroid hormone and parathyroid hormone-related peptides from tumour cells. These cytokines increases bone resorption, reduce renal excretion of calcium and increase phosphate wasting.

Table 20.1 Paraneoplastic syndromes in RCC and their pathogenesis

Clinical finding	Cause
A. Endocrine	
Hypercalcaemia	Tumor release of parathyroid hormone (PT) and parathyroid hormone related protein (PTHrP) causing increased bone reabsorption
Hypertension	Increased renin secretion activating the renin-angiotensin-aldosterone pathway
Polycythemia	Increased erythropoietin secretion stimulates colony forming unit-erythrocyte (CFU-E)
Nonmetastatic hepatic dysfunction	Release of hepatotoxins and lysosomal enzymes by the tumor
Galactorrhea	Caused by raised prolactin levels
Cushing's syndrome	Tumor conversion of pro-opiomelanocortin to ACTH which increases cortisol secretion
Alterations in glucose metabolism	Tumor secretion of insulin and/or (entero) glucagon
B. Non Endocrine	
Amyloidosis	Occurs in 3–8 % with RCC due to prolonged stimulation of immune system by tumor growth or necrosis
Anaemia	Poor nutritional status and chronic condition; also presence of lactoferrin, an iron-binding protein produced by RCC
Neuromyopathies	Rare effects ranging from nonspecific myalgia to bilateral phrenic nerve paralysis
Vasculopathy	Rare described effects. Pathogenesis not well understood
Nephropathy	
Coagulopathy	
Prostaglandin elevation	

Based on data from Ref. [1]

Hypertension

This occurs in up to 40 % of patients typically with low grade RCC [9].

There is an increase in renin secretion, which activates the renin-aldosterone-angiotensin system to cause a rise in blood pressure.

Polycythaemia

An elevated serum red blood cell concentration occurs in up to 8 % of patients with RCC as a result of increased erythropoietin production, which acts to induce differentiation of erythrocyte colony-forming units in the bone marrow [1].

Nonmetastatic Hepatic Dysfunction (Stauffer's Syndrome)

On occasion patients present with hepatic dysfunction without the presence of hepatic metastases. It is seen in up to 20 % of patients where there may also be hepatosplenomegaly, fever, and weight loss [1]. There are raised levels of liver

enzymes including aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and prothrombin time is increased. Bilirubin and **γ-**globulin may also be elevated. The cause is poorly understood but may be due to tumour secretion of inflammatory cytokines, hepatotoxins or lysosomal enzymes [10]. Resolution of the syndrome occurs in 66 % of patients undergoing nephrectomy, which suggests in the remainder that there may be residual metastatic disease [11].

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Chapter 21
Renal Cancer: Investigations and Staging

Adam Alleemudder and Amlesh Seth

There are a number of diagnostic and staging investigations available for the evaluation of renal tumours. The aim of the investigations is to determine whether the lesion is benign or malignant; radiological studies also characterise and help to stage the disease. The investigations for RCC also include assessment of pre-existing renal disease and likely future deterioration of renal function. Nearly 26 % of patients with a solitary, small, renal cortical tumour (<4 cm) and two normally functioning kidneys have pre-existing chronic kidney disease (GFR <60 mL/min/1.73 m^2) [1].

Laboratory Tests

Full blood count: This may show anaemia or polycythaemia. Whilst the serum creatinine is usually normal, a raised level indicates that the function of the contralateral kidney needs to be further assessed before nephrectomy. The eGFR should be assessed in all patients. Other recommended tests include the erythrocyte sedimentation rate, alkaline phosphatase, lactate dehydrogenase and serum corrected calcium. In addition, liver function tests, coagulation profile and serum calcium should be checked after diagnosis of the malignant lesion.

Urine: Analysis may show blood cells in the urine. When urothelial cancer is suspected, cytological evaluation is also required.

A. Alleemudder, MBChB, BSc, MRCS (Ed) (✉)
Department of Urology, Barts and The Royal London Hospital, London, UK
e-mail: adamalleemudder@doctors.org.uk

A. Seth, MBBS, MS, DNB, MCh(Urol)
Department of Urology, All India Institute of Medical Sciences, New Delhi, India

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Radiological Investigations

These are discussed in depth in Chap. 5 and will be mentioned briefly here.

Ultrasound

This is often used initially as a screening tool for suspected renal disease. It is also used for differentiating between a cystic and solid mass, for serial monitoring of renal lesions and for further assessing hyper-dense cysts found on CT scans. It is a readily available modality with no preparation required, has relatively low cost and avoids the need for intravenous contrast and exposure to ionizing radiation. The interpretation of US findings is operator-oriented and its sensitivity for detecting lesions less than 3 cm is only 67–79 %. Furthermore, lesions with similar echogenecity to normal parenchyma may be difficult to detect [2]. Additionally, any lesion detected other than a simple cyst will require further evaluation with CT or MRI. A novel technique being used is contrast-enhanced ultrasound to increase the detection of small renal masses where the use of contrast media is contraindicated [3]. Commercially available microbubbles are given intravenously which act as a highly echogenic medium to improve the visualization of a number of parameters which in some cases can result in upstaging of the lesion and affect treatment planning.

Computed Tomography (CT)

CT currently remains the preferred modality for characterizing and staging renal masses [4]. The sensitivity for detecting small renal masses is greater than 90 % and is better than MRI because of the higher spatial resolution. CT is also used to assess the function and morphology of the contralateral kidney, the extent of extra-renal spread, venous involvement, enlargement of lymph nodes and involvement of the adrenal glands and liver. The presence of enhancement of a renal mass is crucial for differentiating between malignant and benign lesions. Imaging must be performed before and after the administration of contrast to demonstrate enhancement and is confirmed by an attenuation increase of at least 15–20 Hounsfield units (HU) from the corresponding noncontrast image. An increase of 10–20 HU may be an enhancing hypovascular mass or renal cyst pseudoenhancement. Subsequently, a hypovascular papillary RCC may be mistaken for a benign cyst and additional MRI imaging is required. Additionally, images must be obtained from the nephrographic phase to identify certain masses that do not enhance to the same degree as renal parenchyma.

Multi-detector CT's are the latest generation of scanners that use multiple rows of detectors to provide nearly isotropic data sets [3]. They are able to reformat a large volume of data in various planes to near-equal resolution, albeit at a larger radiation dose. To overcome concerns with higher radiation dose, Dual Energy CT scanners

have been developed which can simultaneously acquire data at two different photon energies. Differences in material composition can be assessed by differences in photon absorption. Information such as that of iodine can be removed from post-contrast images to provide a "virtual noncontrast" image and avoid the need for additional imaging.

Magnetic Resonance Imaging (MRI)

MRI is useful in patients with an allergy to contrast and in pregnancy without renal failure where exposure to ionizing radiation is contraindicated. It is superior to CT in some aspects; the outstanding soft tissue contrast and multiplicity of sequences allows MRI to have a higher sensitivity for characterizing cystic lesions and demonstrating perirenal fat or venous involvement. Gadolinium is used to demonstrate enhancement and identify possible malignancy. Whilst CT is better at detecting enhancement than MRI, this can be improved by analysing subtraction images [5]. Furthermore, whilst not considered nephrotoxic at the doses used, caution is still advised when using gadolinium in patients with an eGFR less than 30 mL/min/1.73 m^2 due to the possibility of nephrogenic systemic fibrosis. An alternative to using gadolinium is the technique of diffusion-weighted imaging where the apparent diffusion coefficient seems to be lower for malignant than benign lesions and for higher grade tumors [3]. The standard sequences in MRI evaluation of a renal mass includes T1-weighted imaging, T2-weighted imaging in two planes, and fat-suppressed T1-weighted gradient echo acquisition before and after contrast administration at multiple time points, including arterial/corticomedullary, nephrographic, and urographic phases.

Renal Scintigraphy

This is an additional diagnostic option in patients who are prone to future renal impairment and those who have comorbid conditions such as diabetes, hypertension, urolithiasis and renal polycystic disease

Staging of RCC

The current recommended staging system for RCC is the Tumor Node Metastasis (TMN) classification which has been discussed earlier in Chap. 17 (Table 17.1). Although it has been revised several times to increase the accuracy of staging, the current system is not ideal as important prognostic information may be missed [6]. For example, the current classification does not discriminate between invasion of perirenal and renal sinus fat, as the latter is associated with a poorer prognosis.

An abdominal CT scan and chest x-ray is usually sufficient for radiographic staging once a renal mass with enhancement is identified. An MRI may also be used when there is contraindication to perform CT, whilst an ultrasound has a limited role in staging as overlying bowel gas and body habitus can hinder views of the retroperitoneal lymph nodes, renal vein or inferior vena cava. Abdominal lymph nodes greater than 2 cm indicate advanced disease and are equally detected with CT and most sequences on MRI [7]. An MRI however does have a greater accuracy in assessing tumor involvement of perirenal fat and Gerota's fascia and subsequently offers better delineation between stages T2 and T3a, as well as T3 and T4 [8]. It also has a sensitivity of almost 100 % for detecting thrombus in the renal vein or IVC compared with 79–85 % for CT [9]. A chest CT scan is required if the chest x-ray is abnormal or there are pulmonary symptoms. In the era of modern imaging techniques, renal arteriography and inferior venacavography are rarely used whilst the value of positron emission tomography remains undetermined due to poor sensitivity [6]. An isotope renogram is required to assess the function of the contralateral kidney when there are any signs of impaired renal function whilst an isotope bone scan is indicated when there are features suggesting bony metastases.

Renal Tumor Biopsy

The role of biopsy of a solid renal lesion is limited in the diagnosis of RCC and the biopsy rarely changes the clinical management [10]. It is also not widely used because of concerns regarding safety and sampling errors. However, biopsy may be helpful in patients who undergo minimally invasive tumour ablation treatments such as cryotherapy and radio-frequency ablation (RFA). Also, biopsy is necessary in patients with metastatic disease who are likely to receive targeted therapy. There has been a recent resurgence in the use of renal tumor biopsy to determine the need for surgical intervention as small renal masses are increasingly being detected and at least 20 % are found to be benign on final histopathology [11]. Furthermore, current imaging techniques are highly sensitive in detecting these masses but the specificity to distinguish between a benign and malignant lesion remains low [12]. Historical concerns of tumor seeding have been dismissed on account of its extreme rarity and should not be considered a deterrent to a tumour biopsy [11].

The biopsy is taken with a fine needle under imaging guidance, either as an aspiration for cytology (fine needle aspiration-FNA) or more commonly as a core biopsy specimen for histology. Whilst FNA is considered to be less invasive, it can be non-diagnostic in up to 19 % and requires an experienced operator and pathologist for accurate interpretation [13]. The preferred core biopsy is associated with a sensitivity and specificity of 92 and 100 %, respectively, and therefore has greater accuracy for determining the eventual malignancy, subtype and grade of the evaluated renal mass, although up to 15 % of biopsies do remain non-conclusive [14, 15]. The incidence of complications is extremely low but a pneumothorax, renal bleeding, subcapsular hematomas and pseudoaneurysm formation can occur.

Prognostic Factors

RCC is a heterogenous disease with widely varying prognosis [16]. In the past, TNM staging, Fuhrman grading (Chap. 17) and pathological subtyping have all been used as prognostic variables which are of limited value with regard to risk stratification. Several nomograms have been developed for localized and metastatic disease using factors such as histology, TNM staging, symptoms, performance status, and tumor size. With the advent of molecular markers, new biomarkers have been identified and are likely to be incorporated into standard nomograms for better predictive accuracy [17] (Table 21.1, see below). There is a need to predict prognosis in order

Table 21.1 Nomograms in patients with M0 and M1 disease

Nomogram	N	M status (n)	Clinical and pathological variables	Comments
Yacioglu et al. [24]	296	M0	Retrospective study, Tumour size and presentation	Biostatical prognostic model
Kattan et al. [23]	601	M0	Symptoms- incidental, local or systemic; histology (including chromophobe, papillary or conventional), tumor size, and pathological stage. Treatment failure recorded	A nomogram that can be used to predict the 5-year probability of treatment failure in patients with newly diagnosed RCC
Klatte et al. [25]	170	M0	Retrospective; demographic, clinical and pathological data; T stage; Performance status; Ki-67, p53, endothelial VEGFR-1, epithelial VEGFR-1, and epithelial VEGF-D (Only ccRCC studied)	Clinical and molecular indicators for ccRCC; Requires external validation
Frank et al. [26]	1801	M0 (1516) & M1 (285)	1997 TNM stage, tumor size, nuclear grade, histological tumor necrosis, sarcomatoid component, cystic architecture, multifocality and surgical margin status	Year specific survival rates (1,3,5,7 and 10 years)
Zisman et al. [27]	477	M0 (211) M1 (266)	Age, sex, Combinations of stage, grade, and Eastern Cooperative Oncology Group Performance status	Prospective external validation
Karakiewicz et al. [28]	2530	M0 (2203) M1 (327)	2002 TNM stages, tumor size, Fuhrman grade, histologic subtype, local symptoms, age, and sex	External validation of 1,2, 5 and 10 years done

(continued)

Table 21.1 (continued)

Nomogram	N	M status (n)	Clinical and pathological variables	Comments
Parker et al. [29]	634	M0 (564)	B7-H1, survivin, and Ki-67 for 634 consecutive ccRCC patients	Only ccRCC;
		M1 (70)		External validation required
Motzer et al. [30]	463	M1	Haemoglobin, LDH, Ca^{++}, Karnofsky performance status	Suitable for risk stratification of phase III trials
Motzer et al. [31]	375	M1	Corrected serum calcium levels, the number of metastatic sites, hemoglobin levels, prior nephrectomy, the presence of lung and liver metastases, thrombocytosis, Eastern Cooperative Oncology Group performance status, time from diagnosis to treatment, and serum levels of alkaline phosphatase and lactate dehydrogenase	Internal validation of the nomogram consisted of quantification of the discrimination with the concordance index and assessment of calibration
Kim et al. [32]	318	M0 (163) & M1 (155)	A custom tissue array constructed using clear cell RCC from 318 patients, representing all stages of localized and metastatic RCC, and immunohistochemically stained for molecular markers Ki67, p53, gelsolin, CA9, CA12, PTEN, EpCAM, and vimentin	ccRCC

to accurately counsel patients, plan surveillance protocols, to determine appropriate treatments and select patients for possible clinical trials. Anatomical, histological and clinical factors are used to determine prognosis and nomograms are useful particularly in validating drug trials. There is currently no biomarker available with proven prognostic significance and their use is currently not recommended [18].

Anatomical Factors

The anatomical factors incorporated into the TNM (2009) classification include tumor size, tumor growth beyond the renal capsule, invasion of the renal vein and/or inferior vena cava, lymph node invasion and distant metastases (Chap. 17). This staging

system is regarded as the most important prognostic factor for RCC and there is a clear distinction between the different stages and cancer specific survival as shown in the table below. In general, a poor prognosis and survival is associated with a higher T stage, lymph node involvement and distant metastasis [16]. Additionally, tumor size, pathological stage or lymph node status are regarded as an important independent prognostic factors.

Histological Factors

The Fuhrman nuclear grading (Chap. 17) is a widely used and accepted classification. In most survival studies undertaken over the past two to three decades, grading has been based on the criteria of the Fuhrman classification. This has gained widespread acceptance in clinical practice with Fuhrman's 1982 report being one of the most cited studies in the renal cancer literature [19]. It is defined by four nuclear grades 1–4 in order of increasing size, nuclear irregularity and nucleolar prominence. A poor prognosis and increasing metastatic rate is seen with increasing grade. The system is however subject to inter and intra observer error and its value in other histological subtypes apart from ccRCC remain questionable [20].

Of the three main histological subtypes, clear cell has the poorest prognosis, followed by papillary and then chromophobe [21]. Furthermore, type 2 papillary tumors tend to be of high grade with increased metastatic potential and have a poorer prognosis than type 1. The stage and grade of the tumor however have a greater impact on prognosis than subtype [21]. Tumors with sarcomatoid differentiation, tumor necrosis or that involve the collecting system have an extremely poor prognosis [16].

Clinical Factors

Performance status, weight loss greater than 10 % of body weight, anemia and local symptoms such as flank pain, palpable mass, haematuria, varicocele, constitutional and paraneoplastic symptoms, have all shown to have prognostic significance [16]. Additionally, presentation with symptoms rather than an incidental finding of a RCC carries a poorer prognosis [22].

Biomarkers

There are several biomarkers that have the potential to be used for screening, diagnosis or in follow-up of RCC which are currently under investigation and their value as prognostic markers is yet to be determined. A number of techniques including

microarray, RT-PCR and immunohistochemistry have been utilized to determine the behaviour of RCC. They include carbonic anhydrase IX, VEGF, HIF, Ki67, p53, PTEN, E-cadherin and CD44 [18].

Prognostic Systems and Nomograms

Whilst several prognostic factors have so far been described, with some having important independent prognostic value, there is no single feature which can yield sufficient predictive accuracy for a valid estimation of outcome. This has lead to the development of several prognostic models, or nomograms, which incorporate several established parameters in order to improve prognostic accuracy. Current European guidelines do not recommend using prognostic models for localized disease even though they can provide rationale for enrolling patients on to clinical trials [18]. The first nomogram that was used to predict the disease recurrence post-nephrectomy with a variable accuracy between 61 and 81 % was developed by Kattan [23]. The variables used included the presence of symptoms at diagnosis, histologic subtype, tumor size, and the 1997 TNM stage. Several nomograms have since been developed and there are currently three systems for localized and two for metastatic RCC.

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Chapter 22
Renal Cancer: Surgical Management

Adam Alleemudder and Vinod H. Nargund

Historically, the surgical resection by radical nephrectomy (RN) has been a gold standard treatment for malignant renal tumours. However, with a clear understanding of renal vascular anatomy and work done on cold and warm ischemia and cooling of the kidney, the concept of partial nephrectomy (Nephron-saving surgery) became popular in the 1980s. In last 10 years, surgical techniques such as laparoscopic and robot assisted procedures coupled with minimally invasive techniques such as cryotherapy, radiofrequency ablation (RFA) and high intensity focused ultrasound (HIFU) have put an extra impetus in considering nephron-saving procedures at the forefront of choices for small renal tumours. The treatment by RN also seems to be a significant risk factor for the development of chronic kidney disease [1].

Surgery remains the only curative option for the treatment of localized stage T1 and T2 RCC, (AJCC stage I and II), which can be either nephron sparing surgery (NSS) or standard radical nephrectomy. Nephrology input is required in patients with solitary kidney and patients should be warned about possible future dialysis. Knowledge of renal anatomy is imperative for nephron saving and radical surgeries particularly because of the limited view one gets with endoscopic (Laparoscopic) surgery. On the right side, the upper part of the kidney is related to the right lobe of the liver. Anterosuperiorly, the kidney is covered by the posterior layer of coronary ligament (hepatocolic ligament). This ligament has to be divided to expose the upper part of the kidney. The liver has to be mobilized superiorly and medially to expose the hilum on the right side. On the left side, the spleen and its ligaments are closely related to the left kidney. The spleen is mobilized carefully by dividing the spleno-phrenic ligament with care being taken with the greater curvature of the

A. Alleemudder, MBChB, BSc, MRCS (Ed) (✉)
Department of Urology, Barts and The Royal London Hospital, London, UK
e-mail: adamalleemudder@doctors.org.uk

V.H. Nargund, PhD, FRCSEd, FRCSUrol, FEBU
Department of Urology, Homerton University Hospital, London, UK
e-mail: vinodnargund@gmail.com

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Table 22.1 Indications for NSS

Absolute	Anatomical or functional solitary kidney, synchronous tumours; RCC in better functioning kidney with poorly or non-functioning opposite kidney
Relative	Contralateral kidney is at future risk of the condition and renal dysfunction; hereditary RCC, genetic diseases with risk of metachronous kidney cancer, diabetes, hypertension, stone disease, or renovascular disease
Elective	Localized unilateral RCC with normal contralateral kidney; indeterminate cysts with malignant potential in the presence of a normal contralateral kidney

Adapted from Aron et al. [6]. With permission from Elsevier

stomach. The ascending and descending colon are mobilized by dividing an avascular area laterally (line of Toldt) on the right and left sides respectively. The structures that are easily identified are the inferior vena cava (IVC) on the right side and the renal vein on the left. On the right side, the renal artery runs behind the IVC and posterior to the renal vein and on the left side posterior to the left renal vein. On each side, the renal artery branches into anterior and posterior segmental arteries, which are essentially end arteries.

Nephron Sparing Surgery (NSS)

NSS, or partial nephrectomy, has been the standard surgical approach in patients with bilateral or an RCC in a solitary kidney. It has increasingly gained acceptance and is currently the recommended option for stage T1a tumors when there is a normal contralateral kidney [2]. In experienced centres and carefully selected patients, NSS may also be feasible for larger stage T1b tumors [3]. Compared to radical nephrectomy, NSS has been shown to provide better long-term preservation of renal function with subsequent reduction in cardiovascular events and improved overall survival [4]. It is necessary to rule out multifocality before considering NSS. Overall, 7–25 % of RCC may be multifocal, and for tumours ≤4 cm the incidence of multifocality is between 0 and 5 % [5]. The main indications are summarised below (Table 22.1).

Surgical Principles

Open Approach

Access to the kidney is via either the transperitoneal or retroperitoneal approach (supra 12th, 12th or subcostal) depending on the surgeon's preference and tumor location. It is important that the side is marked when the patient is awake prior to the surgery. The surgical principles for an open procedure remain the same as for the minimally invasive techniques. The patient may be in the supine, lateral decubitus or full flank position, with a break in the table. The kidney is accessed by dividing along

the white line of Toldt and mobilization of the colon. After identifying the upper ureter and gonadal vein, the hilar vessels are carefully dissected in preparation for subsequent step of clamping. Intraoperative ultrasound may help to locate the deep-seated tumors. Gerota's fascia is then incised to expose the tumor and the surrounding renal capsule. Cooling the kidney down to 20–25 °C helps to prolong the ischemia time up to 3 h of arterial occlusion [7]. Laying ice slush around the kidney is the most common method. Other techniques include intra-arterial and intra-ureteric cooling which are not commonly used. The renal artery, which lies posterior to the vein, is clamped first before the vein using a bulldog or Satinsky clamp. After excising the tumour sharply with surrounding rim of normal renal tissue, the raw area is closed with interrupted absorbable sutures using surgicel rolls for a tamponade effect. Several clinical studies suggest that the maximum period of warm ischemia time (WIT) for preservation of renal function should not exceed 20 min [7].

Mechanism of Renal Failure Due to Ischemia

Ischemic insults such as clamping often results in cellular damage of the nephron and renal vasculature due to necrosis and apoptosis, inevitably leading to renal failure. Physiological changes include a fall in glomerular filtration rate, retention of nitrogenous waste products, increase in extra cellular fluid volume, and electrolyte and acid-base homeostasis. There are three mechanisms described in relation to ischemia/perfusion injury [8]: vascular, obstructive and reperfusion injury.

Vascular

There is an inflammatory response to ischemia which exacerbates impairment in blood flow caused by vasoconstriction and vascular congestion, leading to a vicious cycle [9]. This damage occurs in endothelial cells of the peritubular capillaries in the outer medulla, which are marginally oxygenated even without clamping. This is followed by congestion, decreased perfusion and appearance of adhesion molecules. Adhesion molecules and pro-inflammatory and chemotactic cytokines from ischemic cells initiate leukocyte infiltration [9]. Interaction between leukocytes and endothelial cells accentuates oedema of endothelial cells and subsequent injury. There is also possible mechanism involving the renin-angiotensin mechanism.

Obstructive

The ischemic insult causes cellular failure of oxidative phosphorylation and ATP depletion, leading to derangement of the sodium pump. This leads to passive diffusion of sodium and chloride resulting in cellular oedema. There is also impaired sodium

absorption by injured tubular cells leading to increased levels of tubular sodium concentrations. Cellular potassium and magnesium are lost, calcium is gained; anaerobic glycolysis and acidosis occur, and lysosomal enzymes are activated. These changes result in cellular death. During reperfusion, hypoxanthine, a product of ATP degradation, is oxidized to xanthine with the formation of free radicals that cause further cellular damage [10]. There is polymerization of Tamm-Horsfall (T-H) protein due to increased intratubular sodium. T-H is normally secreted by the loop of Henle, and polymerization leads to a gel and cast formation. As a result, brush-border membranes and cells slough to obstruct tubules downstream.

Once the debris starts forming the casts, the tubular obstruction gets aggravated leading to leakage of glomerular filtrate from the tubular lumen across denuded tubular walls into capillaries and into the circulation. This effectively reduces the glomerular filtration rate (GFR).

ATP depletion also activates harmful proteases and phospholipases, which, with reperfusion, cause oxidant injury to tubular cells, the so-called reperfusion injury [8].

Reperfusion Injury

The exact magnitude of reperfusion injury is not clear. The insult of warm ischaemia is aggravated further by restoration of blood flow because of the inflammatory response [11]. The reperfusion injury can be mediated by several mechanisms including the generation of reactive oxygen species (ROS), cellular derangement, microvascular congestion and compression, polymorphonuclear (PMN)-mediated damage, and hypercoagulation. Reperfusion with the resulting reintroduction of molecular oxygen of constricted capillaries leads to congestion and red cell trapping. This vascular effect can reduce renal blood flow by as much as 50 % [12].

NSS Without Hilar Clamping

Radiofrequency ablation (RFA) assisted laparoscopic partial nephrectomy (RFA-LPN) may be the way forward to remove the tumour without warm ischemia and renal hilar clamping. In a study of 78 patients undergoing NSS, 36 patients underwent laparoscopic partial nephrectomy and 42 patients RFA-assisted robotic clampless partial nephrectomy (RF-RCPN). In the latter group, a Habib 4X RFA device was used to coagulate a margin of normal parenchyma around the tumour. There was no difference in blood loss, complication rate, postoperative bleeding, renal function and recurrence rate [13]. However long term results need to be assessed. Other centres have reported similar results [14].

Laparoscopic (LPN)/robotic-assisted PN (RAPN) *vs*. open partial nephrectomy (OPN): Open partial nephrectomy remains the gold standard operation for NSS because it allows the operator to have adequate exposure, easy control of hilum, cold ischemia and tactile sensation during surgery. In addition other methods of

vascular control such as manual compression or renal clamping could be used during OPN. In summary, the technique of tumour excision, reconstruction of renal parenchyma and control of bleeding are standardized in OPN. As mentioned earlier, OPN is increasingly being challenged by the introduction of minimally invasive techniques but LPN is carried out only in specialized centers with laparoscopic experience. LPN offers the benefits of faster post-operative recovery and lower morbidity over the open approach with similar oncological outcomes [15]. The overall cancer specific survival rate after 7 years is estimated at 92.7 and 95.5 % for laparoscopic and open NSS, respectively [16]. The main drawback of LPN is the steep learning curve required to perform this demanding procedure with concerns of higher warm ischaemia times and blood loss [17].

Over recent years there has been growing interest in RPN to overcome the limitations of laparoscopy but yet offers all the benefits of minimally invasive surgery. The main advantages of the robotic approach lie in its ergonomics with a greater range of wristed-instrument motion and 3-D vision that enables a shorter learning curve to be established. This technique, however, is still in its infancy and whilst emerging data appears promising, the long term functional and oncological outcomes remain to be determined [18]. In a retrospective review of 164 consecutive RAPN cases White et al. identified and classified 67 that were highly complex renal masses according to R.E.N.A.L. (R-Radius; E: Location & Depth- exophytic or endophytic; N: Nearness to the renal sinus fat or collecting system; A: anterior or posterior position; L- polar or non polar location) nephrometry score (>7). They concluded that WIT, blood loss and the rate of complications increased in highly complex renal masses [19].

Complications of NSS

Increased tumour complexity is associated with the development of major complications after NSS [20]. The complications for NSS include vascular injuries, haemorrhage, retroperitoneal haematoma, urinary fistulas and injury to surrounding organs (Table 22.2).

Table 22.2 Kidney related complications of LPN from metanalysis of medline database between 1995 and 2004

Type of complication	Percentage
Arterial injury	1.7 %
Venous injury	0.8
Blood transfusion	4.4
Retroperitoneal haematoma	0.8
Deep vein thrombosis	0.5
Renal failure	1
Ureteral injury	0.5 %
Urinoma	3.9
Re-exploration	1.4

Modified from Pareek et al. [21]. With permission from Elsevier

In addition there might problems with devices used for clamping (failure) and systemic complications involving the cardiovascular system. Re-exploration for complications can have its own set of problems. The complication rate is slightly higher for absolute indications than elective indications, especially concerning haemorrhage [22]. Proteinuria and segmental glomerulosclerosis cause progressive renal impairment, which can be delayed by using ACE inhibitors and a low protein diet.

Radical Nephrectomy

Up to a point involving the hilar dissection, the steps of a radical nephrectomy are similar to partial nephrectomy. Briefly, surgical steps include early ligation of the renal artery and vein, removal of the affected kidney along with the surrounding fat, fascia, ipsilateral adrenal gland and associated lymph nodes. However there are exceptions. For example, ipsilateral adrenal gland removal may not be necessary for smaller tumours or lesions involving the lower part of the kidney. Removal of lymph nodes outside the kidney is not routinely practised during standard radical nephrectomy (see below). For localized tumors larger than 7 cm (T2) or any tumour that is not suitable for NSS, a radical nephrectomy remains the only potentially curative option. Despite there being no apparent advantage in survival gain with open nephrectomy, the laparoscopic approach has become the standard of care for moderate volume localized tumors with no local invasion and limited venous involvement [2]. It provides the benefits of the minimally invasive techniques with comparable long term functional and oncological results to open nephrectomy [23]. It may also be a suitable approach for elderly or morbidly obese patients, or those with previous abdominal surgery.

Active Surveillance

This has been partly discussed in the section of natural history of small renal masses (see above). Smaller lesions which are indeterminate could be put under surveillance for a period of time but some patients do ask for observation only for their RCCs and they need careful counseling. This may be justifiable in patients who have a limited life expectancy or who are medically unfit to undergo surgery. Tumors that are T1b (4–7 cm) are at a higher risk with active surveillance [24]. Most tumours that are less than 4 cm (small renal masses SRM) in maximal axial diameter are incidentally diagnosed and have low malignant potential [25]. Nearly 20 % of SRMs are likely to be benign on excision or biopsy and nearly 50 % of them are in their mid 60's [26]. It may be justifiable to manage patients with SRMs by active surveillance at least for the initial period until the tumour characteristics become clearer for management purposes [27].

Locally Advanced (LARCC) and Metastatic RCC

An estimated 2 % of patients with RCC will present with pathologic stage T4 disease where there is invasion of adjacent structures [28]. There is usually pain from invasion of the posterior abdominal wall, nerve root or paravertebral muscles. Other organs that may be involved include the liver, spleen, pancreas and bowel. The treatment options for LARCC could be surgical resection, targeted therapy or palliation. Surgical management is complex in such cases as it is associated with higher morbidity and mortality rates and it therefore needs a multi-disciplinary surgical team in a specialist centre. Despite extended operations with *en bloc* resections, the survival benefit is only marginal due to significant risk of recurrence and progression. Detailed management of metastatic RCC is discussed later in the chapter.

Role of Lymphadenectomy

Cadaveric studies have shown that renal lymphatics reach very distant nodes and the thoracic duct. Inferiorly, they reach iliac nodes and medially, the coeliac nodes [29]. There is also cri-crossing of lymphatics across the midline. Lymph node status in RCC is an independent prognostic factor and involvement implies a negative oncological outcome; there is a 7.8 greater risk of cancer related mortality in those with positive nodal disease with a 5-year cancer specific survival of only 21–38 % [30]. Lymph nodes that are identifiable on cross-sectional imaging, bulky lymph nodes on laparoscopy or palpable lymph nodes during open exploration could be taken as indications for lymph node dissection (LND). Only 32–42 % of lymph nodes that are >1 cm on cross-sectional imaging may harbor cancer [31, 32]. The EORTC 30881 trial showed that after appropriate clinical staging (in patients with clinical N_0M_0 disease), the incidence of unsuspected lymph-node metastases was only 4.0 % [33]. The results when compared with radical nephrectomy alone did not demonstrate advantage in terms of survival, local or distant disease progression. In summary, routine LND is not performed unless there is gross evidence of lymph node involvement.

Tumour Extension into Inferior Vena Cava

Up to 10 % of patients with RCC will present with extension of the tumor thrombus into the renal vein (RV) or inferior vena cava (IVC), which may in extreme cases reach the right atrium in 1 % of patients [34]. A third of these patients will also have one or more synchronous metastatic lesion [35]. Tumors with venous invasion have inherent aggressive behavior and poorer prognosis but there is a potential for a cure in 45–70 % with aggressive RN and IVC thrombectomy [36]. Whilst complete thrombus removal does not seem to affect prognosis, a poorer

Table 22.3 Levels of Tumour thrombus and principles of their management

Level	Description	Management
0	Thrombus limited to the RV, detected clinically or during pathological assessment	Radical nephrectomy – any approach
I	Thrombus extending to IVC, <2 cm above the renal vein	Reduce the thrombus into the RV if possible and apply Satinsky clamp so that IVC flow is not interrupted; otherwise control IVC below and above the thrombus
II	Thrombus extending >2 cm above the renal vein but below the HVs	Extensive mobilization of IVC + ligation of lumbar veins; proximal & distal control of IVC above and below the thrombus; accessory hepatic veins may need ligation
III	Thrombus at the level or above HVs but below the diaphragm	Challenging; In many cases it is possible to resect these transabdominally; Mobilization of right lobe of the liver exposing retrohepatic and suprahepatic IVC; Liver congestion could be avoided by milking the thrombus into IVC below the entry of hepatic veins and extracting it. Cardiac bypass may be required
IV	Supradiaphramatic extension of thrombus	CPB + HCA with cardiac surgeons

Modified from Refs. [39, 40]
IVC inferior vena cava, *RV* renal vein, *HV* hepatic vein, *CPB* cardiopulmonary bypass, *HCA* hypothermic circulatory arrest

outcome is associated with non-removal and complications such as severe bilateral lower extremity oedema, varicoceles, venous stasis ulcers and stasis dermatitis may *occur* [37]. An MRI is the imaging modality of choice to define the tumor and its level in the inferior vena cava. It is also a sensitive technique for detecting vessel wall invasion and provides important preoperative information for surgical planning [38].

Invasive techniques such as inferior venacavography or renal arteriography are not generally required in the era of modern cross imaging techniques. Based on imaging studies, different staging systems have been described. As the TNM classification (Chap. 17) describes all IVC tumour levels in T3 subcategories (Ta-c), a sub-categorization is required for treatment purposes; the system devised by Montie et al. (Table 22.3) is practical and more specific in description.

Veno-caval thrombectomy is done transabdominally by a midline (extending to thorax if required), thoraco-abdominal or roof top incision. The first step is to isolate and ligate the renal artery. If there is evidence of IVC involvement, it might be necessary to excise that part of the wall of the IVC or patch it with a tube graft. The perioperative mortality in these patients is 2–3 % with a complication rate of 15 % [41]. The surgery becomes more invasive with increasing levels of thrombus leading to more bleeding and increased transfusion rates. Early complications include myocardial infarction, haemorrhage, pulmonary embolism, wound infection, abscess formation, acute renal failure, ileus and pneumothorax. Late complications are chronic renal insufficiency, incisional hernia and proteinuria [40].

Post Nephrectomy Metastatic RCC

The management of post-nephrectomy metastatic RCC is multidisciplinary and is influenced by histology, tumour burden, prognostic factors, comorbidities, renal function and patient's ability to tolerate the treatment. The last decade has seen a huge advancement in targeted therapy and understanding of biomarkers. Although there is currently no cure for metastatic RCC, the introduction of systemic targeted therapy has improved the outlook for these patients. Metastatectomy is considered wherever it is anatomically feasible.

Cytoreductive Nephrectomy

Resection of the primary tumor in the face of unresectable metastatic disease prior to the initiation of systemic therapy may be done to reduce the tumour burden. The timing of systemic therapy has been a subject of debate; there is a rational for nephrectomy only in those patients who show an initial response to systemic therapy in order to avoid a futile operation and associated morbidity. Neoadjuvant therapy would allow prompt systemic treatment to be commenced and may reduce the tumor burden and potentially down stage the primary tumor to facilitate subsequent surgery. Furthermore, there may be a better tumor response to immunotherapy if the immunosuppressive effect of surgery is delayed. This will be discussed later in the chapter.

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Chapter 23
Nephron-Saving Procedures: Ablative Techniques (Non-surgical) Radiofrequency Ablation (RFA), High-Intensity Focused Ultrasound (HIFU), Cryotherapy

Nicos Fotiadis

Introduction

The incidence of renal cell carcinoma (RCC) is increasing steadily the last three decades [1]. This is largely the result of increased detection of localized small (<4 cm) renal masses (SRMs) in asymptomatic patients who undergo cross sectional imaging for unrelated causes. Approximately 20–25 % of these lesions are benign, and the majority of the remainder show a slow growth rate and variable malignant potential [2]. These facts have generated an enormous demand for nephron-sparing and minimally invasive treatments. Although partial nephrectomy remains the main choice and gold standard treatment for SRMs, ablative techniques performed percutaneously or laparoscopically have an expanding role in the management of SRM in patients who are poor candidates for surgical resection [3]. The fact that a significant proportion of SRMs are benign tumors or low-grade RCCs with relatively indolent clinical behavior has led to the development of less invasive treatment options [4]. Radiofrequency ablation (RFA) and cryotherapy are the two most commonly used modalities in clinical practice while High intensity focus ultrasound (HIFU), microwave ablation and irreversible electroporation are in an experimental stage.

Potential advantages of ablative procedures are the reduced morbidity, shorter or no hospitalization, faster convalescence, preservation of renal function, lower costs, and the ability to treat patients who are at high risk for surgery [4, 5]. The currently recommended indications are small, incidentally found renal cortical lesions in elderly patients, patients with a genetic predisposition for developing multiple tumors, those with bilateral tumors, and patients with a solitary kidney who are at

N. Fotiadis, MD, FRCR, EBIR
Department of Interventional Oncology, The Royal Marsden NHS Foundation Trust, Fulham Road, Chelsea, London SW3 6JJ, UK
e-mail: fotiadis.nicholas@gmail.com

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high risk of complete loss of renal function following nephron saving surgery [5]. Contraindications to ablative therapies are tumors with a low chance of successful treatment due to size >4 cm, central tumor location, healthy young patients, the presence of multiple metastases, and irreversible coagulopathy [5].

Of the available ablative techniques, RFA and cryoablation are the most investigated approaches. High intensity focus ultrasound (HIFU), microwave ablation and irreversible electroporation are in an experimental stage.

Radiofrequency Ablation

RFA causes tumor necrosis by converting the radiofrequency waves to heat, resulting in thermal tissue damage and coagulation necrosis [6]. The key aim for RFA is to achieve and maintain a 50–100 °C temperature range throughout the entire tumor volume. In fact, temperatures >100 °C result in tissue vaporization and carbonization that usually obscures optimal ablation because of the resulting decrease in energy transmission [7]. RFA is usually performed percutaneously by interventional radiologists under the CT guidance but it could be performed after surgical exposure of the tumor with a laparoscopic or open approach. Currently, 94 % of all the reported procedures have been performed through the percutaneous approach [8].

Zagoria et al. reported that percutaneous RFA achieved complete ablation after one session in all 95 RCCs <3.7 cm and in only 14 of 30 RCCs >3.7 cm A tumor size <3.7 cm was significantly associated with complete tumour eradication ($p<0.001$) [9]. A recent study including 41 patients reported that RFA can result in durable oncologic control for RCCs <4 cm. There were no recurrences when RCCs <4 cm were treated [10]. Tracy et al. recently published the largest series of RFA of renal tumours, treating 208 patients with 243 SRMs over 7.5 years. They indicated a minimal risk of disease recurrence beyond 3 years after RFA. The overall 5-years recurrence-free survival rate was 93 % [11].

The effect of RFA on renal function is minimal. In 2008, Lucas et al. [12], compared the effect on renal function of patients with small renal masses (<4 cm) who underwent RFA, partial nephrectomy, or radical nephrectomy. The mean pretreatment GFR was 73.4, 70.9, and 74.8 ml/min/1.73 m^2 in the RFA, partial nephrectomy, and radical nephrectomy groups ($p=0.59$). Following intervention, the 3-year freedom from stage 3 CKD was 95.2 % for RFA, 70.7 % for partial nephrectomy and 39.9 % for radical nephrectomy. Furthermore, patients undergoing radical and partial nephrectomy were 34.3 and 10.9 times more likely, respectively, to develop stage 3 CKD compared to RFA counterparts. Percutaneous ablation is increasingly used in patients with reduced renal function because it avoids the potential for renal ischemia that may be sustained during surgery, even in patients with a solitary kidney [13].

While complications attributable to RFA are generally self-limiting, there are rare instances of more significant sequelae. Specific major complications included

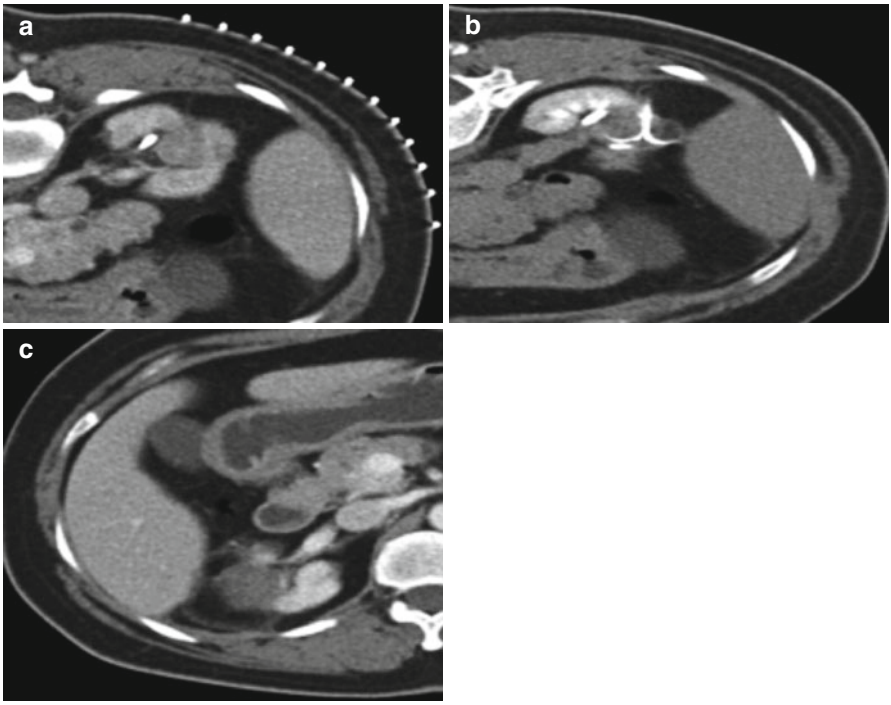

Fig. 23.1 (**a**) Central 2.2 cm tumour abutting the collecting system. 6 F ureteric catheter has been inserted and noted next to the lesion. (**b**) The RF probe is inserted and cool perfusion of the collecting system with Dextrose 5 % starts. (**c**) Follow up CT at 6 months showing complete ablation of the tumour

ureteral obstruction, pyelo-calyceal injury, bowel injury, and gross haematuria requiring exploration or embolization. The rate of these types of injuries ranges from 2.8 to 3.1 % [4, 8, 14]. The placement of a retrograde ureteric catheter before the ablation and the perfusion of the collecting system with cold dextrose during RFA, eliminates the risk of injury to the collecting system during treatment of tumours abutting the ureter or pelvicalyceal system (Fig. 23.1a, b).

Because the ablation treats the tumor *in situ* without surgical removal or assessment of surgical margins, imaging is vital to the assessment of the results of RF ablation. Areas of complete necrosis show no enhancement at CT or MR (Fig. 23.1c), whereas areas of viable tumor show persistent enhancement. In complete ablation is defined as any enhancement within the tumor ablation zone on CT or MRI on initial 6-week imaging after RFA. Recurrence is defined as any enhancement or increase in size of the tumor ablation zone, after an initial non-enhancing 6-weeks CT or MRI [15, 16]. These patients are given the option of a repeat ablation or extirpative surgery. However, post ablation surgery could be extremely difficult due to extensive fibrosis [17].

Cryotherapy

Cryoablation (CA) causes cell destruction by rapid cycles between freeze and thaw temperature. A temperature of −19.4 °C leads to complete cell death. If ice ball formation extends beyond the tumour by >3.1 mm, a temperature of −20 °C is reached in the tumour tissue [18]. Cryotherapy could be performed through a percutaneous, open or laparoscopic approach, with the majority of cases performed with the latter [8]. The percutaneous approach is associated with decreased postoperative pain, less hospital stay and shorter convalescence time but with a higher primary failure rate in comparison with the laparoscopic CA [19, 20].

In a meta-analysis, Kunkle and Uzzo [8] compared the outcome of cryoablation (n = 600; 65 % laparoscopic route) and RFA (n = 775; 94 % percutaneous route); cryoablation was associated with a lower re-ablation rate (1.3 % *vs.* 8.5 %), lower local tumor progression rate (5.2 % *vs.* 12.9 %), and fewer metastases (1.0 % *vs.* 2.5 %; $p = 0.06$) than RFA. The meta-analysis was flawed in that it was consisted of retrospective series each with their own selection biases [21]. Furthermore, RFA was primarily performed percutaneously (compared with laparoscopic cryoablation) where incomplete treatment and re-ablation is more commonly acceptable because retreatment is easier to perform [21]. In another meta analysis by Kunkle et al. [22] analyzed 99 studies with 6471 small renal tumours (<4 cm) managed with partial nephrectomy, cryoablation, RF ablation, and observation. The local recurrence was overall more frequent after RFA (11.7 %) than CA (4.6 %). Both techniques had significantly increased local progression rates compared with surgery (relative risk 7.45 for CA and 18.23 for RFA). Progression to metastatic disease though was described in 1.2 % of cases after CA and 2.3 % of cases after RFA, with no statistical difference compared with partial nephrectomy.

High Intensity Focus Ultrasound (HIFU)

HIFU uses high intensity ultrasound waves that focus on the tumor under imaging guidance and aiming to achieve a temperature sufficient for immediate thermal destruction of all tissues within the target zone. Current problems include the intervening tissues and the mobility of the kidney during breathing [23]. In a very recently published study, including 17 renal tumours HIFU achieved local tumor control in 2/3 of the lesions [24]. This technique is still considered experimental and further studies are required to define its role in the management of localized RCC [5, 24].

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Chapter 24
Medical Management of Metastatic Renal Cell Carcinoma

Brian I. Rini and Ronald M. Bukowski

The management of advanced renal cell carcinoma (RCC) has evolved greatly in recent years. Long-considered an immunoresponsive tumor, cytokines such as interferon alpha (IFNA) and interleukin-2 (IL-2) evolved into the standard initial treatment for advanced RCC through clinical trials in the 1980s and 1990s. More recently, the biology underlying clear cell RCC has been further defined as leading to the overproduction of an angiogenic factor, vascular endothelial growth factor (VEGF). Additionally, therapy targeted at mammalian target of rapamycin (mTOR) has shown clinical effect. Clinical trials have demonstrated results that have evolved the standard of care and introduced new treatment options in this historically treatment-refractory disease. This chapter will focus on standard cytokine therapy for advanced RCC as well as targeted approaches.

Cytokine Therapy in Advanced RCC

IL-2 is a cytokine which stimulates activated T cells and natural killer (NK) cells, for the purpose of inducing an anti-tumor immune response [1]. Interferon-alpha (IFNA) is a naturally occurring glycoprotein stimulated by viral infections and foreign antigens with multiple hypothesized mechanisms of action including immunomodulation [2, 3], antiproliferative activity [4] and inhibition of angiogenesis [5].

Two large randomized trials have examined high-dose (HD) interleukin-2 (IL-2) in comparison to low-dose cytokine regimens. The Cytokine Working Group randomized 193 cytokine-naive metastatic RCC patients to HD IL-2 or low-dose

B.I. Rini, MD (✉) • R.M. Bukowski, MD
Department of Solid Tumor Oncology, Cleveland Clinic Foundation Taussig Cancer Center, Cleveland, OH, USA
e-mail: rinib2@ccf.org

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subcutaneous (s.c.) IL-2 [6]. The second trial conducted by the National Cancer Institute randomized 283 mostly untreated metastatic RCC patients to one of three treatment regimens: HD IL-2, low-dose IV bolus IL-2 or low-dose s.c. IL-2 [7]. These trial each demonstrated objective response rate advantages for the high dose regimens, but without overall progression-free survival (PFS) benefits, and at a cost of greater toxicity. Importantly, the percentage of durable complete responders to HD IL-2 is roughly 5 % based on these trials and other series [8, 9]. Taken together, these data suggest that HD IL-2 has a higher overall and complete response rate compared with low-dose therapy, with the major benefit realized in patients who achieve a durable complete response. Intense patient selection efforts to identify this 5 % prior to therapy have been undertaken. In sum, no reliable predictive biomarker has been discovered, aside from restricting such therapy to patients with clear cell histology. The role of HD IL-2 in the current era of targeted therapy remains in evolution, but is selectively applied to young, healthy clear cell mRCC patients.

Overall response rates of approximately 15 % have been demonstrated in large series of IFNA in RCC [10]. Older randomized studies demonstrated a modest but clinically significant overall survival advantage of IFNA over inactive therapy such as medroxyprogesterone or vinblastine [11, 12]. The ease of administration (compared to HD IL-2) made IFNA a community standard of care in RCC prior to the advent of targeted therapy. Currently, aside from combination with bevacizumab (vide infra), IFNA monotherapy has little to no role in the management of RCC patients. All attempts to improve cytokine therapy with combination regimens using chemotherapy, hormone therapy or other immune therapy have not demonstrated benefit.

VEGF-Targeted Therapy in RCC

The von-Hippel Lindau (*VHL)* gene is a tumor suppressor gene which encodes a 213 amino acid protein (pVHL). pVHL is the substrate recognition component of an complex that targets the hypoxia-inducible protein transcription factors (HIF1 alpha and HIF2 alpha) for proteolysis [13–15]. In conditions of hypoxia, or with VHL inactivation as occurs in the majority of clear cell RCC patients [16–24], the pVHL-HIF interaction is disrupted and stabilization of the HIF transcription factors occurs (Fig. 24.1). Activated HIF leads to transcription of several hypoxia-inducible genes [25]. Most notable is VEGF, with potent pro-angiogenic and other effects which drives RCC tumor progression. RCC universally develops highly vascular features as a result [26].

VEGF-Targeted Therapy in Renal Cell Carcinoma

Several approaches to inhibit VEGF activity in renal cell carcinoma, including binding of the VEGF protein and blockade of the VEGF receptor, have undergone clinical testing in the setting of metastatic RCC (Fig. 24.1) [27, 28].

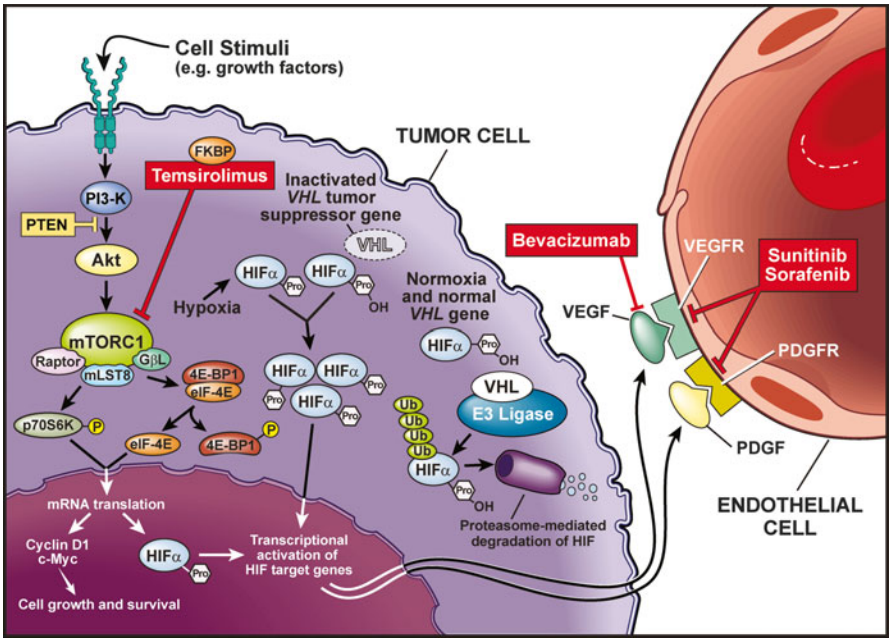

Fig. 24.1 Relevant biologic pathways in RCC. In hypoxia or with an inactivated VHL gene, there is stabilization of HIF transcription factors. mTOR phosphorylates and activates p70S6K leading to enhanced translation of certain proteins including HIF. Activated HIF translocates into the nucleus and leads to transcription of hypoxia-inducible genes including VEGF and PDGF. Temsirolimus binds to FK506-binding protein (*FKBP*), and the resultant protein–drug complex inhibits the kinase activity of the mTORC1 complex. Bevacizumab is a VEGF ligand-binding antibody. Sunitinib and sorafenib are small molecule inhibitors of the VEGFR and PDGFR tyrosine kinases. Abbreviations: *pVHL* von Hippel-Lindau protein gene product, *HIF* hypoxia-inducible factor, *VEGF* vascular endothelial growth factor, *PDGF* platelet-derived growth factor, *TGF* alpha, transforming growth factor alpha, *EGFR* epidermal growth factor receptor (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2014. All Rights Reserved)

Bevacizumab

One of the initial VEGF-inhibiting approaches was a recombinant human monoclonal antibody against VEGF (bevacizumab, Avastin®; Genentech, South San Francisco, CA) which binds and neutralizes all biologically active isoforms of VEGF [29]. An initial randomized study identified that high dose (10 mg/kg) bevacizumab given intravenously every 2 weeks significantly prolonged time to progression in refractory metastatic RCC patients compared to placebo [30, 31]. Subsequently, two phase III trials randomized clear cell RCC patients to either low-dose interferon alpha 2b (Intron A, Schering-Plough, Kenilworth, NJ), 9 MU subcutaneously three times weekly (plus placebo infusion in one trial) or the same dose and schedule of interferon-alpha 2b in combination with bevacizumab, 10 mg/kg IV every 2 weeks [32, 33]. These trials collectively demonstrated an objective response rate and PFS advantage to the bevacizumab-containing regimen (Table 24.1).

Table 24.1 Targeted therapy in metastatic RCC

	Response rate	Progression-free survival	Overall survival
VEGF receptor inhibition			
Sunitinib	30–45 %	11 months versus 5 months for IFN; ($p<0.000001$) in untreated patients [34]	26.4 months vs. 21.8 months for IFN-treated patients ($p=0.051$) [35]
		8.4 months in cytokine-refractory patients [16]	
Sorafenib	2–10 %	5.7 months (vs. 5.6 months in IFN arm; ($p=0.5$) in treatment-naïve patients [17]	17.8 months vs. 15.2 months ($p=0.146$) [18]
		5.5 months (vs. 2.8 months in placebo arm; ($p<0.000001$) in cytokine-refractory patients [36]	
Pazopanib	30 %	9.2 months vs. 4.2 months, ($p<0.0001$)	22.9 versus 20.5 months; ($p=0.224$)
Axitinib	19–44 %	13.3 months (cytokine-refractory RCC) [37]	20.1 months for axitinib vs. 19.2 months with sorafenib (one-sided ($p=0.3744$)
		7.4 months (sorafenib-refractory RCC) [38]	
		6.7 months (patients refractory to 1 prior sunitinib-, cytokine-, bevacizumab- or temsirolimus-based regimen) [39]	
VEGF ligand-binding			
Bevacizumab	10–13 % monotherapy [19, 30]	8.5 months in treatment-naïve patients as monotherapy [19]	23.3 months vs. 21.3 months; ($p=0.3360$) [20]
	26–31 % (+IFN)	8.5 months and 10.2 months in treatment-naïve patients in combination with IFN [32, 33]	18.3 months for bevacizumab plus IFN-alpha vs. 17.4 months for IFN-alpha monotherapy, ($p=.097$) [21]
		4.8 months in cytokine refractory patients [31]	
mTOR inhibitors			
Temsirolimus	8.6 %	3.1 months for IFN vs 5.5 months for temsirolimus, vs 4.7 months for the combination [40]	7.9 months for IFN vs 10.9 months for Temsirolimus ($p=0.008$) vs 8.4 months for the combination ($p=0.70$) [40]
Everolimus	1 %	4.9 months for everolimus vs 1.9 months for placebo ($p<0.001$) [41]	14.8 months for everolimus vs 14.4 months for placebo arm ($p=0.162$) [41]

Abbreviations: *RCC* renal cell carcinoma, *IFN* interferon alpha

The precise role of interferon in this regimen remains debated. Retrospective analyses suggest that dose-reduction of interferon improves tolerability without a compromise of efficacy [22]. Large-scale trials that would be needed to definitively answer this question are unlikely to be undertaken. Currently, the use and dose of interferon with bevacizumab is variable in clinical practice.

Small Molecule VEGF Receptor Inhibitors

An alternative approach to VEGF inhibition involves targeting the cell surface receptor for VEGF using small molecule tyrosine kinase inhibitors. These agents inhibit VEGFR2, the major pro-angiogenic receptor for VEGF, and other receptors including the platelet-derived growth factor receptor (PDGFR). The main therapeutic effect of these drugs is felt to be due to VEGFR inhibition, and other 'off-target' effects likely contribute to toxicity with unclear relevance to efficacy.

Sunitinib

Sunitinib (Sutent®, Pfizer Inc. La Jolla, CA) is an orally bioavailable small molecule tyrosine kinase inhibitor of VEGFR-2 and related receptors [23, 24]. The efficacy of this agent as first-line treatment for metastatic RCC was demonstrated through a phase III clinical trial in which 750 treatment-naïve patients with metastatic clear cell RCC (largely good or intermediate risk groups per MSKCC model [42]) were randomized to receive interferon alpha (at a dose of 9 MU given subcutaneously three times weekly) or sunitinib (50 mg given orally once daily for 4 weeks, followed by 2 weeks without treatment; called 'schedule 4/2'). Median PFS was 11 months for the sunitinib arm vs. 5 months for the interferon arm (Table 24.1) [34]. Sunitinib treatment was also associated with a higher objective response rate (31 % vs. 9 %). The overall survival was 26.4 months with sunitinib vs. 21.8 months with interferon ($p = 0.051$) [35]. Common adverse events related to sunitinib included fatigue, diarrhoea, hypertension, hand and foot syndrome and cytopenia. These data have established sunitinib as a standard of care front-line agent based on the highest response rate and longest PFS.

Attempts at combination therapy with sunitinib have largely not been tolerated, and none have proven more effective than monotherapy [43–45]. Further, attempts to deliver lower dose (37.5 mg), continuous sunitinib have resulted in reductions in clinical efficacy in a randomized comparison versus 50 mg 4/2. Retrospective data supports the importance of adequate daily drug levels of sunitinib, and thus 50 mg 4/2 remains the standard of care with dose reductions as needed for tolerability [46]. Alternative scheduling of sunitinib (e.g. 2 weeks on/1 week off) are also being explored.

Sorafenib

Sorafenib (Nexavar®; Bayer Pharmaceuticals, West Haven, CT and Onyx Pharmaceuticals, Richmond, CA) is an orally bioavailable VEGFR and Raf kinase inhibitor [47, 48]. A phase III study randomized 903 patients with advanced RCC progressive despite prior therapy (largely cytokines) to receive either sorafenib (400 mg twice daily) or placebo [36]. The median progression-free survival was 5.5 months in the sorafenib group and 2.8 months in the placebo group (hazard ratio 0.44; $p < 0.01$). The median overall survival was 19.3 months for the sorafenib group and 15.9 months for the placebo group ($p = $ n.s.). This trial resulted in regulatory approval for sorafenib in late 2005. A subsequent randomized phase II front-line trial versus interferon did not demonstrate any PFS advantage (Table 24.1), and thus sorafenib has over time become used more in the refractory setting based on other data supporting its activity [49].

Pazopanib

Pazopanib is another VEGF-R inhibitor to receive regulatory approval. A phase III randomized double-blind clinical trial including 435 patients with treatment-naïve or cytokine-refractory clear cell metastatic RCC was conducted based on activity observed in previous phase II trials. Median PFS was longer with pazopanib vs. placebo in the overall population (median PFS 9.2 *vs.* 4.2 months), the treatment-naive subpopulation (median PFS 11.1 *vs* 2.8 months) and the cytokine-pretreated subpopulation (median PFS, 7.4 *vs* 4.2 months) [50]. Cross-over was permitted after PFS results became available and was widely employed. As such, the final OS analysis showed no significant OS advantage of pazopanib vs. placebo (22.9 versus 20.5 months, respectively = 0.224). Pazopanib has typical class effect toxicity including hypertension, fatigue and diarrhea. It is notable for a very low incidence of hand foot syndrome (6 % overall). Notably, however, there is an increased incidence of liver function abnormalities (grade 3 or higher ALT elevation in 12 %, AST elevation in 7 %). Pazopanib has been used in a refractory setting with increasing use in the front-line setting. The COMPARZ trial, a randomized trial of pazopanib versus sunitinib in previously untreated metastatic RCC demonstrated non-inferiority of pazopanib with some tolerability advantages, and thus pazopanib has also become a front-line standard of care [51].

Axitinib

Axitinib is a selective potent oral inhibitor of VEGFR1, 2 and 3, with greater potency against VEGFR compared to the other VEGFR inhibitors. Phase II studies data in refractory patients showed a high objective response arte and PFS [37, 38].

The subsequent phase III AXIS trial randomized clear cell mRCC patients who had progressive disease despite prior therapy with VEGF, mTOR inhibitors or cytokine-based therapy. Axitinib demonstrated a significantly longer PFS compared to sorafenib (6.7 months vs. 4.7 months; HR = 0.665; P < 0.0001) and a higher objective response rate (19.4 % vs. 9.4 %) [39]. These data support that more potent biochemical inhibition of VEGFR leads to enhanced clinical outcome. Common AEs including hypertension (40 %), fatigue (39 %), dysphonia (31 %), hypothyroidism (19 %) and hand-foot syndrome (27 %), typical for this class were observed. These data lead to regulatory approval of axitinib in refractory RCC.

mTOR Inhibitors in Advanced RCC

The clinical activity of inhibitors of mammalian target of rapamycn (mTOR) in patients with a RCC demonstrates the relevance of this pathway. mTOR is an intracytoplasmic kinase regulated by a complex system of upstream and downstream elements including phosphoinositide 3-kinase (PI3K), Akt, and the tumor suppressor phosphatase and tensin homologue (PTEN). A serine/threonine kinase that regulates cell growth and metabolism in response to environmental factors, mTOR also regulates the angiogenic pathway through the HIF-1α and VEGF and is linked to endothelial proliferation [52, 53]. Thus, signal blockade of mTOR kinase will in interrupt stress response signals, prevent protein translation in cancer cells, and may also affect the VEGF-dependent angiogenic pathway. Aberrant activation of PI3K/Akt pathway has been observed in RCC and may correlate with a more aggressive tumor phenotype [54]. The therapeutic potential of inhibiting this pathway in RCC is now being explored. Although there are many mTOR inhibitors in development, temsirolimus and everolimus have advanced to phase 3 testing and are approved for advanced RCC.

Temsirolimus

Temsirolimus is an intravenous rapamycin derivative, and was approved by the FDA for treatment of patients with advanced RCC in May 2007. The pivotal phase III trial randomized 626 patients with poor-prognosis metastatic RCC (all histologic subsets) to receive temsirolimus (25 mg IV weekly), IFN-α (3–18 MU three times weekly) or a combination (temsirolimus 15 mg weekly + 6 MU IFN-α three times weekly) [40]. The primary study endpoint was overall survival. Patients receiving temsirolimus monotherapy demonstrated statistically longer survival than those treated with IFN-α (10.9 months for the temsirolimus group, 7.3 months in the IFN-α group; 0.73 hazard ratio; p = 0.0069) [40]. Comparison of the two groups receiving IFN-α ± temsirolimus did not demonstrated significant improvement in survival. The most common adverse effects reported were asthenia, rash, anemia,

nausea, peripheral edema, hyperlipidemia and hyperglycemia. Retrospective radiologic review demonstrated temsirolimus related pneumonitis in 52/178 (29 %) evaluable patients receiving temsirolimus, and represents an important class-effect toxicity which the practicing oncologist should be aware of [55]. This study enrolled patients with metastatic RCC and at least 3 of 6 poor prognostic features (Karnofsky PS <80 %, time from diagnosis to randomization <12 months, serum LDH >1.5 ULN, Hemoglobin <LLN, corrected serum calcium >10 mg/dl and >1 metastatic site). Selection of these criteria was based on several prognostic factor analyses previously published [42, 56]. The rationale for this study in patients with multiple poor prognostic features was based on a retrospective analysis of phase II data suggesting efficacy in such a population [57]. Based on these results, temsirolimus is considered a first-line therapeutic option for patients with metastatic RCC who have poor risk prognostic features. Additionally, a retrospective analysis of histologic patient subsets suggests potential efficacy in the non-clear cell patients, although prospective validation is required [58]. An ongoing trial is randomizing non-clear cell RCC patients to either sunitinib or everolimus in the front-line setting.

Everolimus

Everolimus is an orally administered rapalogue, which was approved by the FDA in March 2009 for the treatment of advanced RCC patients who had failed previous therapy with either sorafenib, sunitinib or both. This was based on the clinical results from the RECORD-1 (**RE**nal **C**ell cancer treatment with **O**ral **R**AD001 given **D**aily. A phase III, randomized, double-blind, placebo-controlled trial, accrued 416 advanced RCC patients with a component of clear cell histology, who had failed prior treatment with sorafenib, sunitinib, or both. Previous therapy with other agents such as cytokines or bevacizumab was also permitted. Patients were randomized in a 2:1 fashion to receive either everolimus 10 mg PO once daily (n = 277) or a placebo (n = 139). The primary endpoint was progression free survival, and the trial was stopped at the second interim analysis. By central review the median PFS for patients treated with everolimus was 4.9 months as compared with 1.9 months in the placebo group (HR 0.33, 95 % CI 0.25–0.43; p < 0.001) [41, 59]. In the 124 patients previously receiving only sorafenib, the median PFS was 5.9 months for the everolimus group versus 2.8 months for the placebo group (HR 0.25; 95 % CI 0.16–0.42). In the 184 sunitinib patients, the median PFS was 3.9 versus 1.8 respectively (HR 0.34; CI 0.23–0.51). Response rates were low, with five everolimus (1.8 %) and no placebo patients having partial responses. Median overall survival was similar between the two groups (14.8 for everolimus arm versus 14.4 months for the placebo arm; HR 0.87; 95 % CI 0.65–1.15; p = .162). This endpoint was likely confounded by the crossover of patients with disease progression on placebo to open label everolimus. The most common adverse events reported were stomatitis (40 %), rash (25 %), fatigue (20 %), hypercholesterolemia (76 %), hypertriglyceridemias (71 %) and hyperglycemia (50 %). Pneumonitis was reported

in 14 % compared with zero in the placebo group. Based on these data, everolimus is considered a therapeutic option for patients who have experienced disease progression on VEGF-targeted tyrosine kinase inhibitors. The precise timing of everolimus use (second-line versus later) is still under debate, as 79 % of patients in the phase III everolimus trial had received two or more prior systemic therapies. The role of these mTOR inhibitors in the treatment of renal cancer will continue to evolve. Both temsirolimus and everolimus are being studied or considered in multiple other clinical scenarios and therapeutic strategies including in combination regimens, sequential therapy with VEGF pathway inhibitors, the adjuvant setting, and in patients with non-clear cell histology.

Conclusions

Clear cell RCC is characterized by *VHL* gene inactivation and subsequent VEGF overexpression, leading to angiogenesis which drives RCC growth and progression. Several agents targeted at either VEGF or mTOR have demonstrated clinical activity in RCC, most notably in tumor shrinkage and disease control as reflected in progression-free survival. Overall survival has been prolonged in the modern era, although this has been difficult to demonstrate within any single trial. Lacking is comparative data for targeted therapies against each other to better define the relative risk and benefit of each approach in different settings. Further, exploration of potential predictive biomarkers is ongoing to further refine the use of these agents.

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Chapter 25
Tumours of the Adrenal Gland

Veronica Greener and Shern L. Chew

Each adrenal gland is related to the upper pole of corresponding kidney and therefore is also called a suprarenal gland. The adrenal gland consists of cortex and medulla, which embryologically, structurally and functionally are two separate entities [1]. The bulk of the gland is formed by the adrenal cortex, derived from mesoderm. There are three zones in the cortex: zona glomerulosa (the outermost layer producing mineralocorticoids – aldosterone), zona fasciculata (the middle layer – glucocorticoids) and zona reticularis (the innermost layer producing androgens mainly dihydroepiandrosterone and androstendione). The medulla on the other hand is derived from ectoderm (neural crest) and contains chromaffin cells, which store noradrenaline (20 %) and adrenaline (80 %) as secretory vesicles also known as chromaffin granules. Some of the precursor chromaffin cells migrate to the sides of the aorta mainly found at the origin of inferior mesenteric artery and bifurcation of aorta (organ of Zuckerkandl) [1].

Surgical Anatomy

Knowledge of adrenal anatomy is important, as adrenalectomy is one of most commonly used modalities of treatment for adrenal conditions. The venous drainage of adrenal gland does not correspond anatomically to the arterial supply. There are three sets of adrenal arteries: (a) superior- a group of 6–8 arteries from inferior phrenic arteries (b) middle adrenal from the aorta (c) inferior adrenal (1–2 arteries from the

V. Greener, BSc, MBBS, MRCP, MD
Department of Endocrinology, Chelsea and Westminster Hospital, London, UK

S.L. Chew, BSc, MB, BChir, MD, FRCP (✉)
Department of Endocrinology, The London Clinic, London, UK
e-mail: sl.chew@thelondonclinic.co.uk

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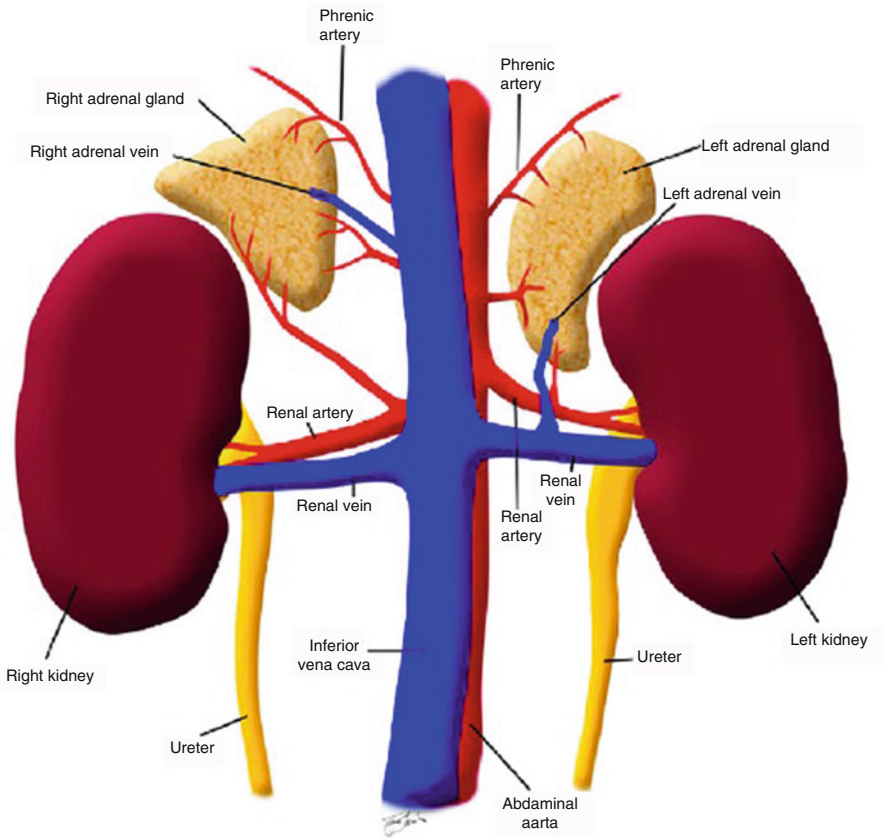

Fig. 25.1 Schematic representation of the blood supply of the adrenal glands

renal artery [2]. Venous drainage is comparatively simple with the left adrenal vein draining to the left renal vein, and the right adrenal vein draining to the inferior vena cava. The left vein is joined by inferior phrenic vein (Fig. 25.1). The right vein is quite short and needs caution during surgical dissection. The lymphatics go along the veins to renal hilar, para-aortic and nodes of posterior mediastinal nodes [2].

Radiology of Adrenal Gland

The major advantage of adrenal tumours is that it is often possible to reach the correct diagnosis pre-operatively, based on clinical assessment and non-invasive radiological and endocrinological investigations. This important feature allows safe and well-planned treatment strategies, with avoidance of unpleasant surprises. An expert radiologist is vital in sorting out renal from adrenal lesions and whether adrenal lesions are invading the adjacent kidney. The details of various radiological investigations are discussed in Chap. 4.

Computerised Tomography is the cornerstone of adrenal imaging and performed before and after intravenous injection of contrast medium [3]. On a normal CT, adrenals look homogeneous and symmetrical [3]. The combination of unenhanced CT and contrast washout values of adrenal masses can assist in characterisation and distinguishing adenomas from other adrenal tumours with 98 % sensitivity and 92 % specificity [3, 4].

Magnetic Resonance Imaging (MRI)

T1 and T2 weighted images with chemical shift imaging (CSI) is desirable with MRI of adrenals [3]. CSI relies on differentiating lesions by their lipid content, as malignant lesions do not have lipid in them. Multi-planar MRI helps in precise anatomical localisation and separation of adrenal masses from the surrounding structures, particularly the liver on the right side, spleen, stomach, pancreas and kidneys. Normal adrenal glands have T1 and T2 signal intensity equal or slightly lower than that of the normal liver [5].

Functional Imaging of Adrenal Cortical Masses

This involves imaging using isotopes based on physiological and pathological aspects of the adrenal gland. These investigations are particularly helpful when lesions are not adequately characterised by CT or MRI. At present ^{18}F FDG PET seems an ideal method for characterising these tumours as benign or malignant [6]. Of those tumours that are malignant secondary tumours from a lung or gastrointestinal primaries are more common than a primary adrenocortical tumour. Within the adrenal gland itself ^{18}F FDG PET can be positive in both primary and secondary malignancy within the adrenal gland with the probable diagnosis depending on the pattern of activity and clinical history.

The most common functional benign adrenocortical tumour is the aldosterone producing Conn's syndrome. This was traditionally imaged with ^{75}Se methionine but this has been withdrawn from use. An alternative is ^{131}I-iodocholesterol, but this is both very expensive and is associated with a very high radiation burden [7]. More recently a few centres have looked at ^{11}C-metomidate PET-CT this allows rapid high quality imaging of Conn's syndrome and can be used to find and characterise tumours as small as 4 mm [8].

Functional Imaging for Adrenal Medulla

Most pheochromocytomas express the noradrenaline transport system [9]. This transport system is responsible for the uptake of noradrenaline and adrenaline. The alkylguanidine meta-iodobenzylguanidine (MIBG), a noradrenaline analogue, is used in the diagnosis of pheochromocytoma as its cells take up MIBG. Imaging

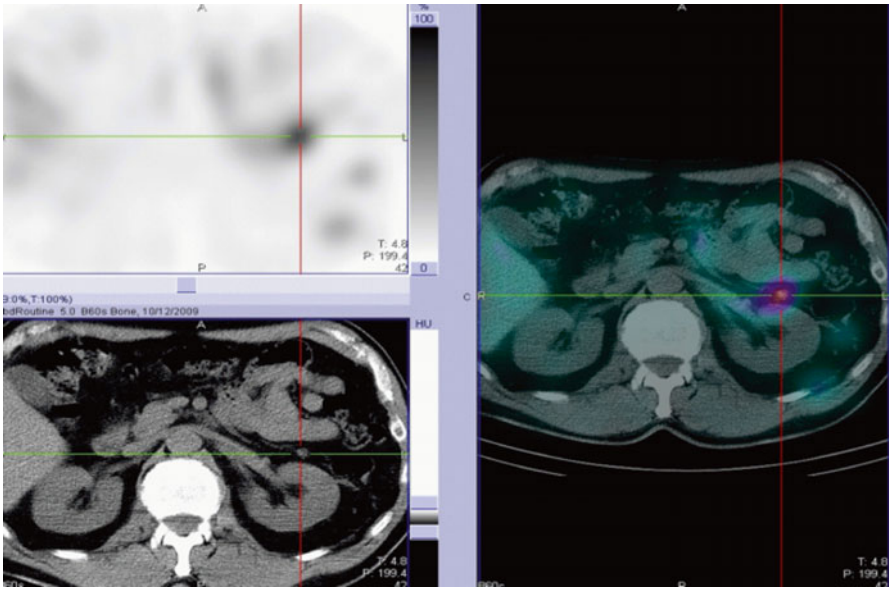

Fig. 25.2 A SPECT-CT ^{123}I-mIBG image of the upper abdomen. Both the CT images and the SPECT image shows a small lesion in the post left adrenalectomy bed. However, only the combined SPECT-CT image confirms small volume residual tumour (Courtesy of Dr. John Buscombe, Royal Free Hospital, London)

with ^{123}I- or ^{131}I-MIBG has been useful for characterising a suspicious adrenal gland in a patient with clinical suspicion of a pheochromocytoma and in staging patients with malignant pheochromocytomas where the advent of SPECT-CT allows even small lesions to be identified [10] (Fig. 25.2).

There is also the possibility of treating patients with metastatic pheochromocytomas with high activity ^{131}I-mIBG with good results obtained for both symptom relief and palliation of symptoms [11].

Adrenal Biopsy/Fine Needle Aspiration

With the advent of sophisticated radiological and biochemical investigations, there is a decreasing need for invasive tests such as needle biopsy or fine needle aspiration. If required the procedure is done with the CT guidance. Adrenal biopsy is not recommended unless it is part of staging a known malignancy [12]. Before biopsy, pheochromocytoma should be excluded with biochemical tests [13]. Because of its close proximity with diaphragm and pleura, potential complications include pneumo/hemothorax. Bleeding and infection are other complications.

A major problem in adrenal disease is that the glands frequently become nodular with age, presumably as part of a degenerative process, followed by a regenerative

cycle. This tendency to nodularity is seen commonly in other endocrine glands, classically the thyroid. One task is to separate such natural nodularity from the diseases that require treatment. Another difficulty in adrenal pathology is distinguishing benign from malignant adrenal tumours by histological analysis. This lack of histological certainty means that careful clinical follow-up is often required.

Adrenal Incidentalomas

The term adrenal incidentaloma (AI) is usually defined as an adrenal mass unexpectedly detected through an imaging procedure performed for reasons a priori unrelated to adrenal dysfunction or suspected dysfunction [12]. Autopsy rates indicate a prevalence of incidental adrenal masses of 2–9 % increasing with age [14, 15]. CT scan studies have demonstrated detection rates of adrenal masses of 0.6–4.4 % [16]. Like renal tumours widespread application of abdominal imaging (ultrasound, CT and MRI) has resulted in increased frequency of clinically silent adrenal lesions. The majority are benign and non-functioning, but up to 20 % are functioning or malignant, and are therefore of great clinical significance.

Epidemiology

Prevalence of incidentalomas peaks between the ages of 50–60 years, with a slight female preponderance [17]. Incidentalomas are particularly common in patients with features of the metabolic syndrome (insulin resistance, dyslipidaemia, obesity and hypertension).

Causes of Incidentalomas

The differential diagnosis of adrenal incidentaloma is extensive but most of them are non-secreting cortical adenomas [12] (Table 25.1). Detection rates of incidentalomas on imaging and autopsy are shown in Table 25.2.

History and Physical Examination

A thorough clinical assessment is needed in patients who are diagnosed with incidentalomas. There may be a history of weight gain in patients with Cushing's syndrome or hypercortisolism. In addition, there would be history of centripetal obesity, easy bruising, hypertension, virilisation and fatigue. In patients with pheochromocytoma,

Table 25.1 Differential diagnosis of adrenal incidentaloma

Adrenal cortical tumours	Adenoma, carcinoma, nodular hyperplasia
Adrenal medullary tumours	Pheochromocytoma, ganglioneuroma, neuroblastoma
Other adrenal tumours	Myelolipoma, metastasis, hamartoma, teratoma, lipoma, hemangioma
Infection	Bacterial: abscess, tuberculosis
	Fungal: histoplasmosis, coccidiomycosis, blastomycosis,
	Viral: cytomegalovirus
	Parasitic cysts
Granulomatous	Amyloidosis, sarcoidosis
Cystic	Parasitic, endothelial, degenerative adenoma, haemorrhagic cyst
Organs around adrenal	Renal, pancreatic, splenic, vascular
Technical	Artefacts

Modified from Aron et al. [12]. with permission from Elsevier

Table 25.2 Causes of incidentalomas detected by imaging and autopsy

Pathology	Rate of detection % (n = 267)
Adrenal adenoma (non-functioning)	86
Adrenal adenoma functioning (cortisol-secreting)	8.6
Myelolipoma	3
Pheochromocytoma	2.6
Ganglioneurinoma	1
Adrenocortical carcinoma	0.3
Cysts	0.022
Metastases	0.01
Nodular hyperplasia	0.01
Adrenal adenoma-functioning (aldosterone-secreting)	0.003
Haemorrhage/haematoma	0.003
Adrenal adenoma functioning (androgen-secreting)	0
Other- lymphoma, congenital adrenal hyperplasia	0

Based on data from Ref. [18]

there may be a history of headache, weight loss, anxiety attacks, sweating and cardiac arrhythmias. In aldosteronism the physician has to look for hypertension, fluid retention and history of hypokalaemia [19].

Assessment of Malignant Potential

Evaluation of adrenal incidentaloma has to address two important questions.

(a) Is it a malignant lesion? If malignant, is it primary adrenal or metastatic?
(b) Is it a secretory type (functional lesion)?

Being highly vascular, adrenal glands are likely sites for blood-borne metastasis from other organs most notably breast, lung, gastrointestinal tract, kidney, melanoma and lymphoma. Metastatic disease must be suspected in any patient with a history of cancer; three-quarters of incidental adrenal masses prove to be metastatic in patients with such a history. In patients with no prior history of cancer, two thirds of incidentally found adrenal lesions are reported to be benign.

Computed tomography (CT) scanning is effective in separating benign adrenal disease from malignancy. The main indicator of malignancy is size. For example, adrenocortical carcinoma was detected in 2 % of masses <4 cm in diameter, 6 % of masses 4.1–6.0 cm and 25 % of masses >25 cm [20]. Assessment of CT radiographic absorption (CT attenuation coefficient expressed as Hounsfield units, HU) of adrenal masses suggests that a value of >10 HU is an indicator of malignant potential, with specificity of 96–100 % and sensitivity of 68–79 % [21, 22]. Other radiographic features such as heterogeneous appearance of the gland, irregular border of the mass and involvement of surrounding structures are sinister. For patients who are unable to undergo a contrast-enhanced CT because of renal insufficiency or allergy to iodinated contrast media, chemical shift MRI can be performed as CT and MRI demonstrate similar accuracy in the diagnosis of adrenal masses [13].

The finding of intracellular lipid in a solid adrenal lesion by magnetic resonance imaging (MRI) is suggestive of an adrenocortical adenoma. Pheochromocytomas are characterised by hypointensity on T1-weighted MRI and hyperintensity on T2-weighted MRI. The presence of fat in the lesion may suggest a myelolipoma, which are benign non-functioning neoplasms consisting of mature adipose cells and haemopoetic tissue.

Assessment of Functional Status

The main concern is that an adrenal incidentaloma is secreting cortisol. In this case, adrenalectomy may be more hazardous. Firstly, the contralateral adrenal may be suppressed, and a hypoadrenal crisis and hypotension may occur when the adenoma is removed and the circulating cortisol falls to low levels. Secondly, complications of infection, poor wound healing and haemorrhage are more likely if the high preoperative cortisol levels are not detected and treated prior to operation. An elevated serum cortisol level and suppressed serum adrenocorticotropin (ACTH) or dehydroepiandrostenedione sulphate (DHEAS) are very suggestive of autonomous adrenal cortisol production. However, patients with mild over-secretion may have serum cortisol levels within the normal range and a low dose dexamethasone suppression test is often useful.

Conn's syndrome should be suspected in any patient with hypertension with or without hypokalaemia. As a screening measure, patients should have an assessment of their electrolytes including bicarbonate and measurement of plasma aldosterone concentration and plasma renin activity with assessment of the ratio.

Clinically silent **pheochromocytomas** account for 5–11 % of incidentalomas [4, 23, 24]. These frequently present with no specific symptoms and should be excluded

in any patient with an incidentaloma. Twenty-four hour urinary free catecholamines provide a useful screening tool with 96 % sensitivity and are widely available [25]. Other tests include plasma or urinary metanephrines and fractionated catecholamines, with sensitivity and specificity of around 95 %. Serum DHEAS as levels may be increased in adrenocortical carcinoma. Serum 17-hydroxyprogesterone should be assessed in view of the possibility of congenital adrenal hyperplasia.

Management

Adrenalectomy is recommended for masses greater than 6 cm in diameter. Homogeneous lesions less than 4 cm diameter are considered low risk and may be followed by scanning. Masses, which measure 4–6 cm, or with heterogeneity, may be followed up or excised, although if features of rapid growth or decreased lipid content are present, surgery would be advisable. Over a 10-year follow-up, less than 30 % increase in size and less than 20 % develop biochemical abnormalities [20].

Tumours of the Adrenal Cortex

Benign (Adenomas)

Functioning Adrenocortical Adenomas

Adrenal Cushing's syndrome accounts for approximately 10 % all cases of Cushing's syndrome. The most common cause is a unilateral benign adenoma. In severe, untreated cases it is associated with 50 % mortality at 5 years [26], whilst less clinically obvious cases have a significantly increased morbidity and mortality due to hypertension and secondary diabetes mellitus. Clinical manifestations vary according to the degree of levels of cortisol.

In adrenal Cushing's, the serum cortisol usually remains high throughout the day and night, or pulses up and down with no relation to time of day. The midnight cortisol in adrenal Cushing's syndrome is usually very similar to the morning cortisol. A low dose dexamethasone suppression test in adrenal Cushing's syndrome usually shows no suppression of the serum cortisol. The high circulating cortisol levels suppress the hypothalamo-pituitary axis, resulting in undetectable serum ACTH levels and often mild reductions in LH and TSH levels.

The mainstay of treatment for adrenal Cushing's syndrome is unilateral adrenalectomy. Serum cortisol levels can be lowered with metyrapone for at least 6 weeks before surgery. Ketoconazole may also be used for this purpose but has a slower time of onset and off-set. The anaesthetic agent etomidate provides an effective short-term method of controlling very severe hypercortisolaemia [27]. Hydrocortisone

cover should be administered with the induction of anaesthesia and continued during the peri- and post-operative period due to hypothalamo-adrenal axis suppression. One regimen is a hydrocortisone infusion of 2 mg per hour, or 100 mg i.m. every 6 h until the patient is able to swallow tablets again (usually within 8 h). The oral hydrocortisone is rapidly tapered to a physiological replacement dose of 10 mg on waking, 5 mg at lunch and 5 mg at 1,700-h.

The patient is readmitted about 3 months after surgery to withdraw hydrocortisone and to check the recovery of the hypothalamo-pituitary axis and endogenous cortisol from the contralateral adrenal gland. If the patient is still dependent on hydrocortisone, reassessments are done every 6 months. Most patients recover the function of the contralateral adrenal by about 18 months after surgery, but a small number continue to need hydrocortisone replacement for the long-term. Adrenal adenomas treated successfully by surgery have a good prognosis with a low risk of recurrence.

Conn's Syndrome (Primary Hyperaldosteronism)

Aldosterone is the main mineralocorticoid produced by the zona glomerulosa; the outer portion of the adrenal cortex. Hyperaldosteronism most commonly occurs as a result of a unilateral adenoma or idiopathic hyperaldosteronism (also known as bilateral adrenal hyperplasia). Rare causes include glucocorticoids-suppressible hyperaldosteronism and aldosterone-producing adrenocortical carcinoma.

Many anti-hypertensive drugs interfere with the assessment of hyperaldosteronism; but patients may be controlled on calcium-antagonists or α-adrenoceptor blockers during investigation. Diuretics, β-adrenoceptor antagonists, angiotensin-converting enzyme inhibitors and angiotensin-2 receptor antagonists should be withdrawn for at least 2 weeks prior to investigations. Initial simple investigations include measurement of serum potassium and bicarbonate and urinary potassium; the presence of a hypokalaemic alkalosis and raised urinary potassium of >30 mmol/24 h is highly suggestive of hyperaldosteronism.

The aldosterone: renin ratio (ARR) has been used as the initial test for Conn's syndrome. An aldosterone:renin ratio is suggestive of Conn's syndrome at >800 (when expressed in SI units; aldosterone in pmol/L and renin activity in pmol/L/h) or >67 (when expressed in conventional units: aldosterone ng/dL: renin activityng/ml/h).

Conn's syndrome is unlikely: when the ratio is <300 (in S.I. units) or <24 (in conventional units).

CT or MRI of the adrenal is done to identify whether a single adenoma or bilateral adrenal hyperplasia is present. Further information may be provided by adrenal vein sampling, only available in specialist centres.

Where there is a unilateral adenoma, surgery is the treatment of choice leading to a cure of hypertension in 70 % of cases. Surgery is not advised in cases of idiopathic hyperaldosteronism due to the inability to cure the condition, even with bilateral

adrenalectomy. Medical treatments include the mineralocorticoid receptor antagonists. Spironolactone is used in doses of 200–400 mg/day, but the main limitation to use is gynaecomastia and impotence in men. Epleronone is a newer specific mineralocorticoid receptor antagonist.

Non-functioning Adrenocortical Adenomas

This is a common lesion and usually does not need active treatment. Multiple adrenocortical adenomas are seen in multiple endocrine neoplasia type 1 and the features of parathyroid, pituitary and pancreatic neoplasia should be sought. The investigations, management and follow-up have been discussed in the section on adrenal incidentalomas (above).

Adrenocortical Carcinoma

Epidemiology

Malignant adrenal tumours may be primary adrenocortical carcinoma or secondary metastases to the adrenal from other cancers. Adrenocortical carcinomas are rare tumours accounting for only 0.05–2 % of all cancers. The reported incidence is 2 per million of population per year and there is a female preponderance. Any age may be affected from infants to the elderly, although the peak age of presentation is 30–50 years of age. Approximately 2–10 % are bilateral.

Clinical Presentation

Patients present as a result of the mass itself or from hormone secretion; approximately 50 % present as hormone-secreting tumours.

When presenting as a non-secreting tumour, symptoms are often vague such as abdominal pain, anorexia or as a result of metastatic disease. When functional, patients may present with a range of endocrine conditions: Cushing's syndrome, virilisation or feminisation or Conn's syndrome. Sudden and late-onset virilisation and increase in libido in females may indicate very high circulating testosterone levels from a virilizing carcinoma. Tumours may secrete multiple hormones, a characteristic feature of adrenocortical carcinomas.

Functional Assessment

This involves measurement at 0900-h of serum cortisol, ACTH, aldosterone, plasma renin activity and the androgens (androstenedione, DHEAS, testosterone/SHBG, oestradiol and 17-hydroxyprogesterone). A low dose dexamethasone suppression test is often needed where there is clinical or biochemical evidence of hormonal excess.

Table 25.3 Staging and prognosis of adrenocortical carcinoma

Stage	Size	Lymph nodes	Local invasion	Mets	Survival 5 years (%)
I	<5 cm	–	–	–	60
II	>5 cm	–	–	–	58
III	Any	+	+	–	24
IV	Any	+	+	+	0

Staging Investigations

A CT scan of the abdomen, chest and pelvis should be performed for metastases, invasion of local structures such as kidney and inferior vena cava. Involvement of the inferior vena cava may also be via tumour thrombus via the adrenal vein. MRI may also demonstrate the presence of thrombus in the inferior vena cava. CT and MRI have been shown to significantly underestimate adrenal size by about 20 %. If there is significant distortion of the kidney by the tumour, an isotope renogram (MAG-3 renogram) may help to define differential function of the kidney in case of nephrectomy. An isotope bone scan and plain chest radiograph are also required.

Prognosis: Staging the tumour is by imaging to assess of tumour size, local invasion and lymph node involvement (Table 25.3). High expression of steroidogenic factor-1 (SF-1) in adrenocortical neoplasia carries a poorer prognosis [28].

Treatment

Surgery is the only realistic hope of cure. Radical excision with *en bloc* resection of any local invasion has proven to be the most effective method. A range of palliative chemotherapeutic agents have been tested and are largely ineffective, except when used in combination with mitotane, with response rates (partial and complete response) of 11–46 %. Of these, only 6–7 % demonstrate a complete response [29]. Mitotane is an adrenolytic agent, which in small doses inhibits 11-beta-hydroxylase causing a reduction in cortisol levels; for this it may be used in Cushing's syndrome. It has adrenolytic activity in high doses causing a reduction in all steroid hormones and also alters the extra-adrenal metabolism of cortisol and androgens. It results in an improvement of hypercortisolism in 60 % of patients [30] and has a tumour response (complete and partial) in 13–33 % of cases. At present it is the only and most frequently effective palliative medical therapy. Occasional patients may be well served with cisplatin-based chemotherapy without unreasonable side effects and palliation could last as long as 6–18 months. Mitotane is associated with gastrointestinal side effects and lethargy, neurotoxicity and rashes.

In a Europe wide study of 304 patients with advanced adrenocortical carcinoma were randomly assigned to either mitotane with etopside, doxorubicin and cisplatin (EDP) or mitotane with streptozotocin. Patients who received EDP had significantly higher response than streptozotocin-mitotane combination and had longer progression survival [31].

Adrenocortical Oncocytomas and Cysts

Adrenocortical oncocytomas are rare tumours composed of oncocytes that are large polygonal or round cells with abundant granular and eosinophilic cytoplasm and are packed with mitochondria. Patients of any age may be affected with a slight preponderance of women. Presentation is often vague; abdominal pain and haematuria may occur. Up to a third are detected incidentally and are usually non-functioning. Size may vary from 2 to 20 cm and whilst they are usually non-malignant, there have been cases of local invasion [32, 33].

Adrenal cysts are most frequently benign, but may have features of malignancy and careful assessment should therefore be made. A review of 613 cases of adrenal cysts determined that 7 % are malignant or potentially malignant and there was 1 reported case of malignancy in a cyst originally thought to be benign [34]. If the suspicion of malignancy is low, and the lesion is non-functioning, the adrenal cyst may be managed observation alone. The cyst may be drained percutaneously if it expands. Surgical excision is indicated if the cyst develops solid elements.

Tumours of the Adrenal Medulla

Pheochromocytomas

Pheochromocytomas are catecholamine-secreting tumours that arise from chromaffin cells of adrenal medulla in 90 % of cases; the remaining 10 % arise from extra-adrenal tissue and are termed paragangliomas. They occur in about 0.05 % of hypertensive patients. Autopsy studies suggest a higher incidence; a Mayo clinic autopsy study indicated an incidence of 1,300 cases per million. Of these 61 % were reported retrospectively to have been hypertensive and 91 % had non-specific symptoms that may have been attributable to pheochromocytomas [35].

Pathogenesis and Patho-physiology

Pheochromocytomas occur more frequently on the right than the left. They are bilateral in 10 % of adults and in 35 % of children, usually in association with a genetic disorder. Paragangliomas arise from extra-adrenal chromaffin tissue adjacent to sympathetic ganglia. 85 % are located intra-abdominally; other locations include the bladder and the mediastinum. Extra-adrenal paragangliomas rarely secrete adrenaline; cortisol is required for the induction of the enzyme responsible for the conversion of noradrenaline to adrenaline and the lack of proximity to the adrenal gland precludes this. Catecholamine secretion may be increased by haemorrhage within the tumour or pressure on the tumour. Surgical manipulation of the tumour may cause a hypertensive crisis if appropriate measures are not taken pre-operatively. The rate of

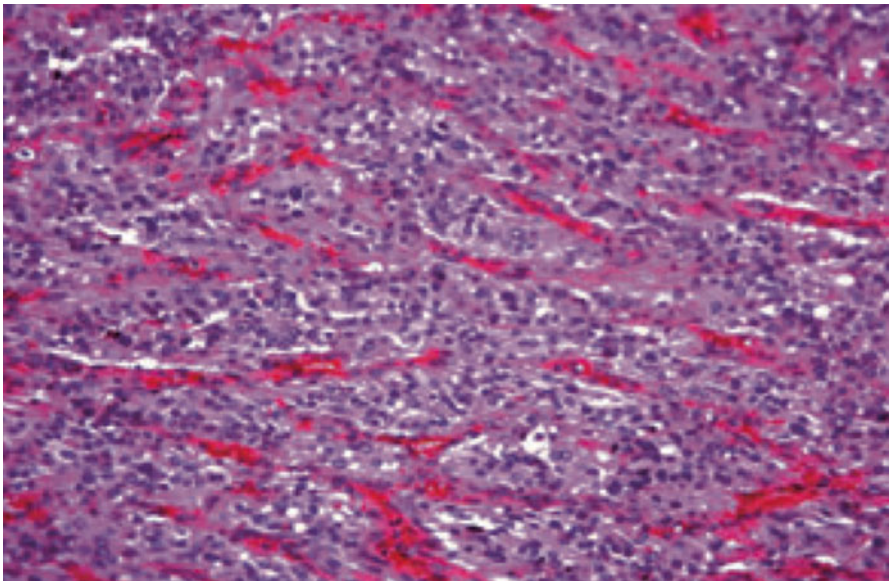

Fig. 25.3 Pheochromocytoma of adrenal medulla (H & E×40)

malignancy is associated with an increased size (>6 cm). They are well-defined tumours and the cut section shows foci of necrosis, haemorrhage and cystic areas. Cells are pleomorphic with nuclei, which are also pleomorphic. The cells are arranged intermingled with thin walled sinusoids with fibrovascular stroma (Fig. 25.3).

Genetics

Approximately 10 % of phaeochromocytomas are associated with autosomal dominant genetic tumour syndromes: multiple endocrine neoplasia type 2A; von Hippel-Lindau disease; familial paraganglioma syndromes. Phaeochromocytomas are seen less frequently in neurofibromatosis type 1, tuberous sclerosis and Sturge-Weber syndrome. Such patients tend to be younger and more often have bilateral or multicentric tumours and may be normotensive. Genetic testing is advisable for any patient with a family history of phaeochromocytomas or paragangliomas, for patients with bilateral phaeochromocytomas or features of any of the associated genetic syndromes, and in patients under the age of 50 years. Such patients should also have the following investigations: clinical thyroid examination; serum calcium; plasma calcitonin, and ophthalmoscopy.

Multiple endocrine neoplasia type 2A includes medullary thyroid carcinoma and hyperparathyroidism, and phaeochromocytomas are found in 50 % of patients. Extra-adrenal tumours are rare. Point mutations in the RET oncogene cause the disease and mutations of the tyrosine at codon 634 is most commonly associated with phaeochromocytomas [36, 37].

Von Hippel Lindau (VHL) syndrome comprises haemangioblastomas in the retina, cerebellum and spinal cord, and renal cell cysts and carcinomas. 10–20 % of patients develop phaeochromocytoma; these mutations tend to be missense mutations in the VHL tumour suppressor gene rather than deletion or frameshift mutation. They typically occur around the age of 28 years and 50 % are bilateral.

Familial paraganglioma syndromes are caused by mutations in the succinate dehydrogenase B or D subunit genes. Multiple paragangliomas may be found in the sympathetic chain from the skull base to the floor of the pelvis.

Clinical Features

The characteristic feature is hypertension with additional symptoms including palpitations, sweating and headaches are commonly reported. Other symptoms include anxiety, tremor, visual disturbance, gastrointestinal symptoms, fever and chest pain. Paroxysms may be induced by any action that causes pressure on the tumour, such as bending over or micturition in bladder paragangliomas. Procedures such as bladder catheterisation, anaesthesia and surgery may also precipitate hypertensive crises. A number of drugs may also cause an increase in catecholamine secretion, in particular unopposed beta blockade, metoclopramide, tricyclic anti-depressants and opiates. Other clinical findings include evidence of cardiomegaly due to left ventricular hypertrophy, cardiac arrhythmias and pallor may present as a result of vasoconstriction. The tumour itself may be detected on palpation of the abdomen in the form as a mass, or a subsequent rise in blood pressure. Approximately 15 % of phaeochromocytomas are malignant and evidence of metastases should be sought in regional lymph nodes, liver, chest and skeleton.

Biochemical Investigations

The initial screening test for phaeochromocytoma is a 24-h urine collection for free catecholamines: noradrenaline, adrenaline and dopamine. Levels may vary according to the intermittent secretion of catecholamines; at least two collections must therefore take place. Plasma or urinary free metanephrines, a metabolite of catecholamines may be more sensitive. A number of medications influence the secretion of catecholamines and must therefore be discontinued whilst investigations are taking place. These are indicated in Table 25.4.

Plasma catecholamines may also prove to be of some benefit in the diagnosis, although levels are only increased periodically in association with paroxysms of symptoms. A normal level does not therefore exclude the possibility of a phaeochromocytoma. Chromogranin A may also prove to be useful as a tumour marker but false positives may occur in renal failure.

Table 25.4 Drugs that affect catecholamine secretion

	Increased	Decreased	Variable
Anti-hypertensives	Alpha blockers	Clonidine	ACE inhibitors
	Beta blockers	Adrenergic neurone blockers	Calcium channel blockers
	Hydralazine		
	Sodium nitroprusside		
Neuro-psychiatric drugs	Levodopa	MAO-I	Levodopa
	Domperidone		Tricyclics
	Metoclopramide		Phenothiazines
			Bromocriptine
Others	Containing catecholamines		
	Decongestants- ephedrine		
	Caffeine		
	Amphetamine		
	Nicotine		
	GTN		

Imaging

Pheochromocytomas have a characteristic high intense image on T2-weighted MRI scans. If an adrenal tumour is not found, further imaging of the whole body should then take place. Radionucleide scanning using 131-iodine metaiodobenzylguanidine is used to confirm the nature of a tumour as it is taken up by uptake channels on chromaffin cells. This scan may also detect any metastases.

High dose 131-iodine metaiodobenzylguanidine therapy may be used as an adjunct to surgery. If imaging proves to be unhelpful in localizing the tumour, venous sampling may localise the lesion.

Management

Surgical extirpation leads to normotension in 75 % of patients. The rate of post-operative complications correlated with the pre-operative hypertension. Once the diagnosis of a phaeochromocytoma is made alpha-adrenoreceptor blockade should be commenced followed by beta-adrenoreceptor blockade 24 h later. Unopposed beta-adrenoreceptor blockade may precipitate a hypertensive crisis and so should not be commenced until adequate alpha-adrenoreceptor blockade has been administered. Oral phenoxybenzamine (20 mg q.d.s.) followed by oral propranolol (80 mg t.d.s.) is commenced with monitoring of blood pressure. To ensure complete alpha-adrenoreceptor blockade pre-operatively, intravenous phenoxybenzamine (0.5 mg/ kg in 250 ml saline over 2 h) is administered daily on day −3 to day-1 days prior to surgery on day 0. Reversal of alpha-adrenoreceptor mediated vasoconstriction may lead to

haemodilution; haemoglobin should be monitored pre- and post-operatively. Careful peri-operative anaesthetic management is vital as multiple complications may arise. Handling of the tumour may cause dramatic changes in blood pressure and arrhythmias. Tumour devascularisation typically causes hypotension requiring volume replacement.

Laparoscopic adrenalectomy may be preferable when the tumour is less than 6 cm and non invasive. Advantages to laparoscopic adrenalectomy include reduced post-operative pain, shorter hospital stays and also hypotensive episodes tend to be less severe and less frequent [38]. A lateral or posterior approach may be used and the phaeochromocytoma should be bagged to avoid fragmentation and spread of tumour cells. Adrenal cortex sparing surgery may be used in patients undergoing bilateral adrenalectomies to avoid the need for lifelong glucocorticoid and mineralocorticoid replacement. There is no anatomical plane between the cortex and medulla, so this approach will leave some medulla behind and has been associated with tumour recurrence in genetic syndromes.

Treatment of malignant phaeochromocytomas involves resection of large metastases, chemotherapy, and external beam radiotherapy to bony or nervous system metastases. If metastases are 131-I-metaiodobenzylguanidine avid on the initial scan, high doses may be administered. In most patients this provides partial remission and symptomatic relief. More rarely complete remission may occur; this tends to be patients with less tumour burden [39].

Prognosis

Benign phaeochromocytomas have a 96 % 5-year survival rate, but this drops to 44 % in malignant phaeochromocytomas. Rates of malignancy are reported to be 10 % for adrenal phaeochromocytomas and 30–50 % for paragangliomas. Neither histological examination nor pre-operative investigations can reliably confirm the presence of malignancy. Features of malignant potential include tumour diameter >6 cm, tumour necrosis, vascular invasion and extensive local invasion. Repeat 24-h urine catecholamines should be checked 2 weeks post surgery; in the case of a benign tumour, levels should drop into the normal range. Patients should be followed up for life as metastases may develop up to 20 years after initial presentation.

Follow up of patients with phaeochromocytoma should involve urinary catecholamines and CT of the adrenal bed in first year for a baseline, and in suspicious cases, annually for 5 years.

Neuroblastoma

Neuroblastomas are tumours arising from sympathetic neuroblasts; a third of which are adrenal in origin. They are found almost exclusively in children. They are rapidly growing tumours, often causing mass effect or may be metabolically active.

Neuroblastomas are associated with a good prognosis with surgery as the mainstay of treatment; curative surgery in stage 1 and 2 disease has a 2-year survival rate of 89 % [40, 41]. Advanced stage tumours require a combination of surgery, chemotherapy and/or radiotherapy to achieve a complete response.

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Chapter 26
Epidemiology, Biology, and Genetics of Adult Male Germ Cell Tumors

Darren R. Feldman and R.S.K. Chaganti

Introduction

Germ cell tumors (GCTs) comprise more than 95 % of testicular neoplasms [1, 2] and account for the most common cancer diagnosis each year among adolescent and young adult (AYA) men in developed countries. Despite being associated with a nearly universal favorable outcome, GCTs display extraordinary diversity in their histologic appearance, clinical presentation, and genetic composition, which relates to their unique biology as the malignant counterpart of a spectrum of tissues involved in human development. Derived from malignant transformation of a germ cell, histologically, GCTs are broadly separated into two histologic subtypes, seminomatous GCT (SGCT) and nonseminomatous GCT (NSGCT). More than 90 % of GCTs originate in the testis, although they can also arise at extragonadal sites, typically midline structures such as the mediastinum, retroperitoneum, and pineal gland. This chapter will review the epidemiology, biology, and genetics of GCTs with a special focus on insights gained over the last decade as well as persistent areas of controversy.

Epidemiology

Since most agencies providing cancer statistics (e.g., American Cancer Society, SEER) report tumor incidence by primary site (e.g., breast, lung, testis, etc.) rather than histologic type, annual crude incidence rates for GCTs must be estimated from

D.R. Feldman, MD
Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

R.S.K. Chaganti, PhD (✉)
Department of Medicine and Cell Biology Program, Memorial Sloan-Kettering Cancer Center, New York, NY, USA
e-mail: changantr@mskcc.org

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knowledge of the annual testicular cancer incidence (8,590 cases per year) [3], the proportion of testicular cancers that are GCTs (>95 %) [1, 4], and the proportion of GCTs that arise outside of the testis (6 %) [5]. Based on these values, we estimate that approximately 9,000 cases of GCT will be diagnosed among men in the United States in 2012. As such, GCTs comprise only slightly more than 1 % of tumors diagnosed in American men each year. The number of cases diagnosed in women is even smaller and is beyond the scope of this review.

It is important to note that while GCTs are rare, they still represent the most common tumor to affect men between the ages of 15 and 34. In addition, the incidence has been increasing by more than 1 % per year over the last few decades [6–8]. The median age at the time of diagnosis ranges from 25 to 29 for NSGCT and from 35 to 39 for SGCT [9]. Similar to histology, primary tumor site also varies by age with pineal gland GCTs nearly always diagnosed before the age of 30 [5]. Incidences also vary by location and ethnic/racial background. For example, the incidence is as high as 10 per 100,000 among men in Scandinavian countries such as Norway compared to approximately 5 per 100,000 among men in the United States and approximately 1 per 100,000 among men in parts of Asia and Africa [6]. GCTs are also significantly more common in Caucasians, compared to African Americans, Hispanic Americans, and Asian Americans [9].

Risk factors for development of GCT are listed in Table 26.1. The most well proven risk factor for testicular GCTs is a history of cryptorchidism. Without surgical

Table 26.1 Germ cell tumor risk factors

Characteristic	Risk estimates or comment [reference]
Disorders of male development	
Cryptorchidism	Five to nine-fold increased risk, 10 % lifetime risk [11, 12]
Disorders of sex development	Variable, depends on specific disorder [14, 109]
Family history	
Brothers	Five to nine-fold increased risk in brothers [21–23]
Fathers/sons	Two to four-fold increased risk in fathers/sons [21–23]
Infertility/subfertility	18–22-fold increased risk (all were seminomas) [13]
GCT history	
Prior history of GCT	2 % of patients in the US with testicular GCT develop contralateral testicular GCT [15]. History of an extragonadal GCT also increases the risk of metachronous testicular GCT [20].
ITGCNU	50 % patients with ITGCNU develop testis cancer within 5 years [19]
Environmental exposures	
Marijuana use	3.5-fold more common among GCT patients vs. controls [29, 30]
Pesticide exposure	Higher levels found in men and mothers of men with testis cancer as compared to controls and control mothers [31, 32]
Genetic abnormalities/changes	
SNP in KITLG	Homozygosity for the dominant allele associated with up to a 4.5-fold increase in risk of GCT [25, 110]
Klinefelter's syndrome	Risk factor for Mediastinal Primary NSGCT, not testicular GCT [33]

Abbreviations: *GCT* germ cell tumor, *ITGCNU* Intratubular germ cell neoplasia of unknown significance, *US* United States, *SNP* single nucleotide polymorphism, *KITLG* KIT ligand, *NSGCT* nonseminomatous germ cell tumor

correction, approximately 5–10 % of cryptorchid patients will develop testicular GCT [10]. While orchiopexy, particularly when performed early in life (and certainly before puberty) [11] can decrease this risk, it does not eliminate it, and these patients also remain at risk for development of contralateral testicular GCTs. Hypospadias, another common male congenital malformation, was also recently demonstrated to increase the risk of testicular GCT development in a Danish cohort study [12].

Infertility and subfertility have been associated with increased risks of developing testicular GCTs. One study found that 0.25 % of men presenting with infertility were subsequently found to have testicular cancer, a rate approximately 20-fold higher than the SEER estimates (0.01 %) of the incidence among men of similar age and race during the same time period [13]. Patients with disorders of sex development, which commonly coexist with male infertility, also appear to be at increased risk of testicular GCT development [14].

A prior history of GCT or its noninvasive precursor lesion, intratubular germ cell neoplasia of unknown significance (ITGCNU) are additional strong risk factors for the development of GCTs. Approximately 2 % of men in the United States with unilateral testicular GCT will eventually develop contralateral GCT during their lifetime [15]. In Scandinavian countries where testicular cancer has a higher incidence, the risk of contralateral GCT may be even greater [16, 17]. If untreated, IGCNU, identified on testicular biopsy, performed for the workup of infertility or in a patient with a diagnosis of GCT in the contralateral testis, portends an extremely high risk of invasive GCT development (≈50 % within 5 years) [18, 19]. A prior history of extragonadal GCT is also associated with an increased risk of a subsequent testicular GCT diagnosis [20].

Family history constitutes another risk factor for GCT, with brothers of patients with testicular GCTs carrying a 5–12-fold increase in risk and sons accruing an approximately two-fold increase in risk [21–24]. Recently, several germ-line DNA single nucleotide polymorphisms (SNPs) were found to increase the likelihood of developing GCTs, possibly explaining a familial predilection. Genome wide association studies (GWAS) performed by two independent groups demonstrated that patients homozygous for a SNP within the *KIT* ligand (*KITLG*/*SCF*) on chromosome 12q22 carried up to a 4.5-fold increased risk of developing a GCT [25, 26]. In addition, SNPs in downstream effectors of *KIT* such as the *SPRY4* gene on chromosome 5q313 were also associated with an increased risk of developing testicular GCTs [25]. Since KIT signaling is known to play an important role in germ cell development and fertility [27, 28], these findings may provide a plausible pathway-based explanation as to why testicular GCTs may be more common in men with infertility or subfertility.

Some environmental exposures have recently been proposed as risk factors for the development of testicular GCTs. Two retrospective case-control studies found frequent and long-term marijuana use to be more prevalent among patients diagnosed with nonseminomatous (but not seminomatous) testicular cancer as compared to age-matched controls [29, 30]. Other environmental exposures, especially those occurring in utero, such as pesticides, have also been proposed to increase the risk of testicular GCT development [31, 32]. Finally, Klinefelter's syndrome has been demonstrated to significantly increase the risk for mediastinal but not testicular GCTs [33]. No other mediastinal GCT risk factors have thus far been identified.

Pathobiology and Histology of Germ Cell Tumors

Germ Cell Development

GCTs have a fascinating biology which relates to the pluripotent nature of their cell of origin, the developing germ cell. A brief review of male gonadal development, spermatogenesis, and embryogenesis can be helpful to understanding the biology and range of histologies seen in GCTs. Arising from the embryonic ectoderm, the primordial germ cell (PGC) is first recognized during gastrulation based on its expression of alkaline phosphatase [34]. PGCs subsequently migrate to the genital ridge, where they further develop into gender-distinct gonads, a process dependent upon the presence (male) or absence (female) of stromal expression of the *SRY* gene, located on the Y chromosome. In males, PGCs in combination with Sertoli cells form seminiferous cords which, along with Leydig cells, subsequently organize into the embryonic gonads by about 2 months of gestational age. PGCs differentiate into gonocytes, which then cease proliferation until after birth. Postnatally, gonocytes begin proliferating again, and mature into undifferentiated Type A spermatogonia by about 3 months of age. Prior to and culminating with the initiation of puberty under stimulation from gonadotrophins, Type A spermatogonia mature into Type B spermatogonia. In AYA men, Type A spermatogonia are postulated to comprise the gonadal stem cells, existing as either Type Ad (dark type), a non-dividing germ cell reserve in case of destruction or loss, or Type Ap (pale type), an actively dividing, possibly self-renewing germ cell population. Following a single mitotic division, Type B spermatogonia become primary spermatocytes, which in turn undergo DNA replication and then two meioses, ultimately resulting in 4 haploid gametes. Spermiogenesis ensues, leading to the formation of mature spermatozoa.

Germ Cell Transformation to GCT and Histologic Differentiation

GCTs arise when developing germ cells undergo malignant transformation. The earliest recognizable abnormal histology during this transformation is ITGCNU which is thought to represent the non-invasive precursor to all GCTs [35]. Upon becoming invasive, GCTs are separated into the two histologic categories, seminoma and nonseminoma.

Seminomas are more similar to ITGCNU than nonseminomas, morphologically resembling undifferentiated spermatogonial germ cells and expressing proteins common to germ cells in early development such as placental alkaline phosphatase (PLAP), KIT, and POU5F1 (OCT3/4) [36–38]. Seminomas typically display low mitotic and apoptotic rates and tend to be clinically diagnosed in Stage I (limited to the testis), often curable with orchiectomy alone [1]. Nonseminomas include four distinct histologies (embryonal carcinoma [EC],

yolk sac tumor [YST], choriocarcinoma [CC], and teratoma [T]), each of which parallels a different stage of embryonic or extraembryonic development and differentiation. Normal germ cells destined to become gametes are subject to inhibitory signaling that prevents them from undergoing differentiation until fertilization with ova is achieved. Thus, nonseminoma formation can be explained by germ cells undergoing reprogramming during malignant transformation resulting in the acquisition of the capacity for embryonic and extraembryonic differentiation, although in a spatially and temporally aberrant manner. *In vitro* evidence supports this view as normal PGCs isolated from the mouse and human can be converted into pluripotent cells (embryonic germ cells) following exposure to KIT ligand (stem cell factor), leukemia inhibitory factor (LIF), and basic fibroblast factor (bFGF) [39]. Epigenetic modifications such as DNA methylation and chromatin acetylation may play a role in the reprogramming process [40]. In contrast, SGCTs lack the ability to initiate differentiation.

Differentiation of EC along embryonic (T) or extraembryonic (YST, CC) pathways leads to the decline of pluripotency of the transformed germ cell paralleling the process in embryonic development. For example, expression of *POU5F1* in EC is downregulated in T, CC, and YST. [41] EC is considered the malignant counterpart of an early embryo and is pluripotent. ECs display the highest mitotic and apoptotic rates of any GCT histology and have been demonstrated to be genetically similar to embryonic stem cells [42]. The normal zygote at this stage is comprised of an inner cell mass surrounded by trophectoderm. The inner cell mass gives rise to the fetal tissues and the extraembryonic endoderm, whereas the trophectoderm gives rise to the placenta, consisting of an outer syncytiotrophoblast layer and an inner cytotrophoblast layer. CC represents malignant transformation of the placenta, and by definition must contain both the syncytiotrophoblast and cytotrophoblast layers. In contrast, malignant syncytiotrophoblast cells that appear in the absence of cytotrophoblast cells are not considered CC and in fact, can occur in combination with seminoma in the absence of any other nonseminoma component; indeed, they are still considered to be pure seminomas. CCs, like the placenta, produce HCG and are highly vascular in nature.

As normal embryological development continues, the morula undergoes repeated cell divisions and eventually the inner cell mass separates into two layers, an outer epiblast, which gives rise to the three fetal tissue layers (ectoderm, mesoderm, endoderm), and an inner hypoblast, consisting of extraembryonic endoderm, which forms the yolk sac. In the embryo, the yolk sac serves as the initial hematopoietic organ as well as a source of protein synthesis and nutrient transport. Differentiation of malignant germ cells along the yolk sac lineage leads to formation of YST, also known as endodermal sinus tumor. YSTs typically express AFP but not HCG in contrast to CCs, which express HCG but not AFP. EC, as a pluripotent neoplasm, is capable of differentiating into either of these tumor types, and can express both HCG and AFP.

Sperger and colleagues demonstrated the genetic similarity between EC and embryonic stem cells (ESCs) by comparing gene expression signatures of human ESC lines, EC cell lines and primary tumors, yolk sac tumor cell lines and primary

tumors, seminomas, somatic cell lines, and normal testis. Upon hierarchical clustering, ESC lines clustered closest with EC tumors as compared to any of the other cell lines or tissues [42]. The original definition of ESCs was based on the expression of specific genes associated with pluripotency regulation including *FGF2*, *POU5F1*, *THY1*, *SOX2*, *EBAF1*, *ZFP42*, and *TDGF1*. Studies from our lab supported the similarity between ESCs and ECs; we demonstrated all of the aforementioned genes to be expressed by ECs whereas seminomas lacked expression of *SOX2*, *FGF4*, *EBAF1*, and *TDGF1* [43, 44]. These data are consistent with the notion that *SOX2*, *FGF4*, *EBAF1*, and *TDGF1* play a specific role in pluripotency. Furthermore, the transcription factors known to be important for maintenance of the undifferentiated state, such as *POU5F1* (*OCT3/4*) and *NANOG*, were upregulated in both ECs and seminomas [43, 44].

Teratomas display somatic differentiation of the three tissue layers of the embryo. Typically, two or three of these layers are represented in a given teratoma. Differentiation can be complete, appearing identical to adult tissue types in the case of mature T, or incomplete, resembling fetal tissue in the case of immature T. Both mature and immature Ts tend to have low rates of mitosis and apoptosis, although this can be more variable in the case of immature Ts. On occasion, Ts can undergo malignant transformation, developing into a secondary somatic malignancy derived from a particular T tissue type. Common secondary somatic malignant histologies include rhabdomyosarcomas, adenocarcinomas, and primitive neuroepithelial tumors (PNET). Tumors that recur after prolonged remissions, known as late relapses, and mediastinal primary nonseminomas tend to have a higher propensity to undergo malignant transformation.

The most frequent nonseminomatous histology is a mixed form, comprised of more than one component (e.g., EC plus T) or a combination of a nonseminoma component with a seminoma [1, 9]. The most common pure nonseminoma histology is EC [1, 9]. Regardless of histologic subtype, a hallmark of all seminomas and nonseminomas is the presence of increased copies of 12p, usually as an isochromosome, (i[12p]) [45].

Debate Over the Cell of Origin of GCT

Although it is widely agreed that GCTs arise from malignant transformation of germ cells along their development, there is disagreement over the precise time point at which this occurs. Two models have been proposed. One, proposed by Skakkebaek and colleagues [46], postulates that PGCs or gonocytes, while still *in utero*, but after reaching the genital ridge, initiate abnormal cell proliferation under the direction of KIT pathway activation, leading to ITGCNU. This premalignant lesion remains dormant until puberty when, under stimulation from gonadotrophins, undergoes further transformation, acquires extra copies of 12p, and evolves

to an invasive GCT. As such, this theory supposes that ITGCNU precedes acquisition of i[12p] and is supported by common expression patterns between PGCs/gonocytes and ITGCNU, of genes such as *PRDM1*/*BLIMP1* and *PRMT5*, as well as the observation that not all ITGCNU may contain extra copies of 12p [47, 48]. In addition, epidemiologic data and the characteristics of germ cells in developmental abnormality syndromes that predispose patients to GCT such as testicular feminization and testicular dysgenesis, are cited in support this hypothesis. Another model, proposed by Chaganti and Houldsworth [49], suggests that the zygotene/pachytene spermatocyte with a 4n DNA content is the cell of origin. The error-prone homologous recombination at this stage of germ cell development allows acquisition of increased 12p copy number, which leads to aberrant gene expression, increased mitosis, re-establishment of pluripotentiality, and genomic instability that support malignant transformation to GCT. Evidence supporting this theory includes the shared chromosomal aneuploidy between GCTs and zygotene/pachytene spermatocytes and the abundant expression of wild-type p53, a hallmark of germ cells and GCTs. However, neither hypothesis has been experimentally validated.

Debate Over the Origin of Extragonadal GCTs

Adult GCTs and testicular cancer have become synonymous since more than 95 % of testicular cancers are GCTs and more than 90 % of GCTs originate in the testis. Nevertheless, 5–10 % of GCTs arise from extragonadal locations, with the most common sites including the mediastinum, retroperitoneum, and the pineal gland. With the exception of tumors that arise in the pineal gland and show a predominance of seminomatous histology (often referred to as germinomas), the majority of extragonadal GCTs are nonseminomas [5]. The concept of retroperitoneal primary tumor remains controversial as many believe these cases to represent metastatic lesions from testicular tumors that were not able to be identified by ultrasound or at orchiectomy. Changes in the testicular parenchyma where a tumor has undergone spontaneous regression are referred to as having a “burnt out” appearance and could explain the failure to identify a gonadal primary tumor in some cases of solitary retroperitoneal GCT masses [50, 51].

Two mechanisms have been proposed to explain how GCTs of extragonadal primary sites other than the retroperitoneum arise. The conventional hypothesis suggests that PGCs or gonocytes get “left behind” while migrating through the embryo to the genital ridges and eventually transform. While this model is easy to conceptualize, misplaced germ cells at the PGC or gonocyte stage have never been identified in developing human embryos. Such cells have been observed in mouse embryos but are not viable due to a predilection to rapid apoptosis [52]. Finally, extragonadal GCTs have been identified to have chromosomal changes highly similar to gonadal GCTs

with increased 12p copy number and aneuploidy [45]. These alterations are thought to be acquired later in GC development (meiosis of primary spermatocytes) than during the migratory stage of gonocytes, raising doubt to this theory and instead supporting a common cell of origin for gonadal and extragonadal GCT. An alternative explanation involves the potential of transformed germ cells to undergo reverse migration to the mediastinum or pineal gland, where stromal environments left over from embryological development could remain fertile for transformed germ cell proliferation. At present, this remains an open area of controversy.

Genetics of Germ Cell Tumors

Gain of Chromosome 12p

GCTs are one of only a handful of malignancies (e.g., CML, GIST) that contain a pathognomonic genetic abnormality, present in nearly all cases. In GCT, this abnormality is the i(12p), which was first described in 1982 by Atkin and Baker during karyotyping of metaphase chromosomes from cases of GCTs [53]. Subsequently, several studies have documented approximately 85 % of GCTs to contain this chromosomal abnormality, and in cases where i(12p) was absent, extra copies of part or all of 12p occur as tandem duplications *in situ* or within other chromosomes [54]. As such, this assay has provided diagnostic utility for poorly differentiated midline tumors of unknown histogenesis, allowing the diagnosis of GCT to be made, and permitting administration of potentially curative chemotherapy [55]. Several studies have indicated that i(12p) is evident as early in GCT neoplasm development as ITGCNU, yet others have indicated that the appearance of this marker is associated with tumor invasion out of the tubules [48, 49, 56, 57].

Regardless of whether or not chromosome 12p gain is present only in fully malignant GCT or also ITGCNU, its omnipresence in invasive disease strongly suggests a role in the pathogenesis of GCT. Initially, it was thought that aberration of a single gene within 12p would be found responsible for GCT pathogenesis/progression. However, with more than 400 genes located on chromosome 12p and no overwhelming evidence to support one gene in particular, conventional wisdom now asserts that multiple genes on 12p, possibly in conjunction with other chromosomal anomalies, enable invasive GCT development. One gene of particular interest is cyclin D2 (*CCND2*), whose protein product is involved in regulation of DNA replication at the G1/S transition of the cell cycle. Overexpression of this protein leads to increased cell cycling and has been identified in ITGCNU, seminoma, and EC [58]. In contrast, normal spermatogonial cells in the adult testis rarely express cyclinD2, although expression of this protein has been observed in neonatal spermatogonial cells of the mouse.

Additional genes of interest have been identified through gene expression profiling, including a group of stem cell associated genes all mapping to a 200 Kb region at 12p13.31. These genes include *STELLAR*, *NANOG*, and *GDF3*, all of which

demonstrate elevated expression in seminomas and embryonal carcinomas [44]. The overexpression of these genes through gain of 12p may be responsible for the undifferentiated phenotype observed in these two GCT histologies. Furthermore, exposure of EC cell lines to differentiating agents such as all-trans retinoic acid (ATRA) or bone morphogenic protein 2 (BMP2) lead to downregulation of these genes and resultant loss of pluripotency [44, 59, 60].

Evaluations of chromosomal changes within GCTs, primarily seminomas, by comparative genomic hybridization (CGH) revealed the frequent presence of a high-level amplification of the 12p11-12.2 region in addition to gain of the entire short arm of chromosome 12 [61, 62]. However, attempts to identify the specific target gene within this amplicon using molecular cytogenetic studies and global genomic screening have not been conclusive [63–65].

Chromosomal Changes Other Than 12p

In addition to i[12p], conventional karyotype analyses have demonstrated that GCTs are aneuploid in DNA content, typically hypertriploid or tetraploid. Specific chromosomal abnormalities have been identified as recurrent across GCTs, some correlating with particular histologic subtypes [66, 67]. For example, breakpoints at 1p32-36 and 7q11.2 have been associated with teratoma whereas breakpoints at 1p22 correlated with yolk sac tumor histology [67]. Deletion or rearrangement of 12q and deletion of 6q13-25 constitute other frequently observed chromosomal changes in GCTs [66].

Interrogation of ITGCNU demonstrated frequent gain of portions of chromosomes 1, 5, 7, 8, 12p, and X and loss of DNA content from chromosome 18 [48, 56]. Adjacent invasive tumors also exhibited many of these changes but in addition, frequently had gains of portions of chromosomes 2, 3, 4, 6,13q, 14q, 17q, 18q, 20, and 21 and losses of portions of chromosomes 1p, 4, 6q, 9, 11, 13q, and 19 [48]. In the case of 17q gain, *GRB7* and *JUP* were identified as potential target genes through microarray analysis [46].

Potential tumor suppressor genes involved in GCT pathogenesis have also been identified, primarily through loss of heterozygosity (LOH) studies [68, 69]. These studies demonstrated GCTs frequently contain loss of regions including the known tumor suppressor genes, *RB1*, *DCC*, and *NME*. In addition, loss of heterozygosity was demonstrated in regions where other proposed tumor suppressor genes are located (1p, 3p, 5q, 10q, 11p, 11q, and 17p) as well as new sites not previously identified as containing tumor suppressor genes (1q, 2q, 3q, 5p, 9q, 12q, 18p, and 20p). Epigenetic modifications such as promoter methylation might also contribute to loss of heterozygosity for tumor suppressor genes involved in GCT histopathogenesis. For example, seminomas have been demonstrated to contain lower levels of promoter methylation than nonseminomas. In addition, methylation of *MGMT* correlated with loss of its expression [70, 71]. However, methylation changes and expression of other genes have not correlated well in other studies [72].

Mutations

In contrast to most malignancies, GCTs are believed to contain relatively few driver mutations. However, mutations in *KRAS* [73], *KIT* [74, 75], and *SMAD4* [76] have been identified in some GCTs and have been proposed as important in germ cell transformation. *KIT* is perhaps the most well studied of these genes. In one series, activating *KIT* mutations were found in a large proportion of bilateral GCTs, particularly bilateral seminomas [74]. However, other studies did not support this claim [77, 78]. As discussed earlier, aberration of *KIT* signaling was also recently identified as increasing susceptibility to GCT development [25, 26]. More recent efforts by our group and others have identified additional mutations within a subset of GCTs, particularly those that demonstrate cisplatin resistance [111].

Genetics and Pathobiology of Chemosensitivity and Resistance

The introduction of cisplatin in the late 1970s radically changed the outlook for post-pubertal men with advanced GCTs, increasing the complete remission rate from approximately 25 % to nearly 80 % [79]. Subsequently, GCTs have become a model for the curable malignancy and for investigations into platinum sensitivity. With the activity of cisplatin, albeit to a lesser extent, against a number of malignancies, there has been great interest in understanding the biological basis of the platinum sensitivity of GCTs as well as the mechanisms of resistance.

The transformation from a platinum-sensitive to a platinum-resistant phenotype likely depends on changes in several intracellular pathways including those involved in cellular response to DNA damage, apoptosis, differentiation, and cell growth (Table 26.2). Several studies have demonstrated differences in immunohistochemical staining of markers of cell proliferation and apoptosis between different GCT histologies [80–82]. For example, in one study, ECs were demonstrated to have the highest rate of apoptosis and negative staining for BCL2 in contrast to mature Ts which had very low levels of apoptosis and positive staining for BCL2 [82]. However, these investigations did not identify any markers specific to platinum resistance. In order to more specifically identify resistance markers, studies were carried out within pure EC specimens, demonstrating improved outcomes for ECs with higher rates of proliferation (Ki-67) and lower rates of spontaneous apoptosis [83].

Differentiation and Resistance

Several pieces of evidence suggest an association between differentiation and development of chemotherapy resistance. For example, Ts, which represent somatic differentiation of malignant germ cells, are highly chemoresistant with surgical resection comprising the mainstay of treatment [84]. While Ts are thought to lack the ability to metastasize, they can nonetheless be problematic through local

Table 26.2 Proposed mechanisms to explain the typical extreme sensitivity of GCT to cisplatin and development of resistance

Cellular process	Mechanism
DNA repair	GCTs are proposed to have an innate DNA repair defect that forces apoptosis in response to DNA damage rather than cell cycle arrest with DNA repair. Cisplatin resistance in GCT may result from upregulation of DNA repair proteins.
Apoptosis	GCTs typically display a brisk upregulation of apoptosis upon exposure to DNA damaging agents such as cisplatin. Defects along the apoptotic pathway could lead to platinum resistance.
TP53	*TP53* is typically wild type in GCT vs. frequently mutated in other tumors. GCT resistance to cisplatin is associated with *TP53* mutations, possibly through inability to activate apoptosis.
p21	GCT usually have low levels of cytoplasmic p21 and high levels are associated with cisplatin resistance. p21 is a CDKI responsible for inducing cell cycle arrest at the G1/S checkpoint to allow for DNA repair.
Differentiation	The most common GCT histologies exist in an undifferentiated state such as seminoma and embryonal carcinoma. Differentiation such as to teratoma leads to platinum resistance.
Driver mutations	*BRAF* mutations has been proposed but not validated as being associated with cisplatin resistance. p53 mutations are associated with resistance as per above. Few other driver mutations have been identified in GCT that associate with cisplatin resistance although mutations in *KRAS*, *HRAS*, *PIK3CA*, and *AKT* were recently also identified within a subset of resistant GCT.

Abbreviations: *CDKI* cyclin-dependent kinase inhibitor

uncontrolled growth leading to compression of important structures, or differentiation along the lines of a secondary somatic malignancy [85]. *In vitro* studies support the concept of differentiation leading to chemotherapy resistance. For instance, the pluripotent and undifferentiated EC cell line NT2/D1 undergoes rapid apoptosis upon exposure to cisplatin. In contrast, upon exposure to the differentiating agent ATRA, NT2/D1 cells become relatively resistant to cisplatin with a marked attenuation in apoptosis [86]. Other studies have demonstrated that loss of expression of *POU5F1*, a stem cell marker involved in maintenance of pluripotency, also correlates with development of cisplatin resistance [87].

DNA Repair Proficiency and Resistance

Since the mechanism of action of cisplatin involves the formation of DNA adducts which lead to apoptosis, a long held belief has been that a decreased proficiency in DNA repair underlies the unique sensitivity of GCT to platinum-based chemotherapy. One study suggested that certain high mobility group (HMG) domain proteins specific to germ cells could allow shielding of cisplatin-DNA adducts, preventing effective DNA repair from taking place and increasing cisplatin sensitivity [88]. GCTs have also been demonstrated to contain decreased levels of the xeroderma pigmentosum complementation group A (XPA) protein, which is involved in repair

of DNA adducts and UV radiation-induced photoproducts, providing another possible explanation for the platinum sensitivity of this tumor type [89, 90]. However, another study found conflicting results, demonstrating that sensitive GCT cell lines containing low levels of XPA remained capable of efficient DNA repair. In addition, overexpression of XPA did not confer cisplatin resistance [91]. As such, there remains no convincing evidence to support the defective DNA repair hypothesis as the underlying Achilles heel of GCT exposed to cisplatin.

Mutations and Resistance

As previously mentioned, GCTs have historically been regarded as a malignancy associated with relatively few driver mutations and instead, characterized by more global changes in chromosomal content (aneuploidy, and large region chromosomal gains and losses). However, inactivating mutation or deletion of the tumor suppressor gene, *TP53*, a critical regulator of the cellular response to DNA damage and induction of apoptosis, has been demonstrated to correlate with GCT platinum-resistance [92]. Some investigators have proposed that the rare (<5 %) incidence of *TP53* loss in GCT as compared to the more frequent (≈50 %) aberrations in other malignancies [93, 94] may explain why the vast majority of GCTs are sensitive to cisplatin. However, not all *TP53* mutant GCT cell lines have been found to be platinum-resistant [95], suggesting that *TP53* mutation might not be sufficient by itself to induce resistance in some cases.

More recently, the V600E mutation in *BRAF* was reported to be associated with resistant GCT. Honecker and colleagues found that 9 (26 %) of 35 resistant GCTs harbored V600E *BRAF* mutations as compared to only 1 (1 %) of 100 unselected cases. These authors also reported an increase in microsatellite instability among resistant GCT tumors as compared to unselected cases [96]. However, these results contrast with those of other groups [97, 98] and have not been confirmed. Our group recently attempted to validate the findings of Honnecker within 46 cisplatin-resistant and 24 cisplatin-sensitive GCTs. Using a Sequenom approach, no BRAF mutations were identified in any of the tumors. However, mutations in *KRAS*, *HRAS*, *PIK3CA*, or *AKT1* were observed in tumors from 9/46 (20%) patients with resistant GCT as compared 0/24 patients with sensitive GCT [111].

It is possible that with more sensitive next generation sequencing techniques, an increasing number of mutations may be identified within GCT that correlate with resistance.

Apoptotic Pathway Proficiency and Resistance

In addition to mutations in *TP53*, aberrations in other parts of apoptotic signaling could also lead to cisplatin resistance [99]. For example, a cell line with inability to activate caspase-9 maintained cisplatin resistance, independent of whether *TP53* was wild-type or mutant [100]. Another study found that upon exposure to cisplatin, sensitive GCT cell lines displayed an increase in expression of FAS and recruitment of FADD and caspase-8 to FAS, whereas resistant GCT cell lines did not [101].

Recent work has further implicated aberrations in the p21-*CDK2* pathway to also lead to cisplatin resistance. Koster and colleagues found sensitive GCT cell lines to have decreased cytoplasmic staining for p21 as compared to resistant cell lines. Furthermore, silencing of p21 or manipulations to increase p21 shuttling from the cytoplasm to the nucleus increased apoptosis and restored the cisplatin sensitivity of the resistant GCT cell lines. Finally, these authors demonstrated that phospho-AKT is responsible for phosphorylation of p21 that prevents shuttling to the nucleus; inhibition of AKT led to decreased cytoplasmic AKT and increased apoptosis upon cisplatin exposure of cisplatin-resistant cell lines, an effect that was reversed by silencing of *CDK2* [102, 103]. Our recent work demonstrating the presence of *PIK3CA* and *AKT1* mutations in cisplatin-resistant but not sensitive GCT [111], lends support to activation of this pathway as a possible mechanism of escape from cisplatin-induced apoptosis.

Apart from the pluripotency and differentiation hypothesis, the common premise to all of the aforementioned mechanisms underlying cisplatin sensitivity and resistance is that GCTs appear to have an innate response to DNA-damaging agents that causes rapid initiation of multiple cell death pathways. In many but not all cases, this response appears to be dependent upon *TP53*. In contrast, exposure of other malignant cell types to cisplatin results in halting of the cell cycle, allowing DNA repair and avoidance of apoptosis, followed by re-entry into the cell cycle and active proliferation. An improved understanding of the factors that lead to the rapid upregulation of apoptosis in GCT could have major implications to identifying and overcoming the mechanisms of cisplatin resistance in other neoplasms.

Utility of GCT Genetics to Predict Patient Outcome

Investigations into GCT biology and molecular pathogenesis offer not only the potential to increase our understanding of these tumors but also to enhance patient outcome prediction beyond current systems which rely solely on clinicohistologic factors. For example, following orchiectomy, patients with Stage I seminoma, the most commonly encountered GCT stage-histology combination, have an approximately 20 % risk of recurrence. In one study, the presence of specific pathologic factors such as tumor size >4 cm and rete testis involvement increased the recurrence rate from 12 % (for patients with neither factor) to 32 % (for patients with

both factors) [104]. Yet, even in the highest risk cases, the majority of patients remain relapse-free without any further treatment. As such, based on the emerging appreciation of the long-term risks of radiation (e.g., secondary malignancies) as well as the nearly 100 % survival for patients treated at recurrence, adjuvant radiation therapy, once the universal treatment for Stage I seminoma, has fallen out of favor over the last several years. It would be highly beneficial if intratumoral molecular markers that predict recurrence could be identified, aiding in the selection of patients for adjuvant therapy as well as intensity of follow-up.

For advanced disease, a clinicopathologic prognostic system is currently in use, known as the International Germ Cell Cancer Collaborative Group (IGCCG) risk model [105]. This classification system takes into account histology (seminoma vs. nonseminoma), primary tumor site (mediastinal vs. gonadal/retroperitoneal), tumor marker (HCG, AFP, and LDH) levels, and sites of metastases (non-pulmonary visceral metastases). Based on these factors, patients are classified into good-, intermediate-, and poor-risk groups, with 5-year survival rates of approximately 90, 75, and 50 % respectively [105]. Therefore, for patients in the poor-risk group, the probability of survival is predicted no better than the flip of a coin. It would certainly be of great value to be able to predict which of these patients will be cured with standard chemotherapy so that more intensive or novel strategies could be applied to the remaining patients. Similarly, it would be very helpful if we could predict which 10 and 25 % of patients with good- and intermediate-risk disease, respectively, are destined to fail conventional therapy.

In general, the molecular markers of cisplatin resistance discussed above could all represent potential prognostic factors for patients with advanced GCT, since cisplatin sensitivity is crucial to the efficacy of first-line therapy in advanced GCT. However, most of these markers have not been validated. Furthermore, even those that are well established, such as mutations in *TP53*, occur only rarely among resistant cases and are not universally predictive of poor outcome, limiting their clinical utility [92, 93, 95]. As discussed above, *BRAF* mutations and microsatellite instability were recently reported in a retrospective study to be found in more than 25 % of cisplatin-resistant GCT as compared to only 1 % of unselected cases [96]. While these results are interesting, they have not yet been independently validated, or studied in a prospective manner.

Several studies have focused on the association of DNA copy number changes with outcome in GCT. Early chromosomal comparative genomic hybridization (CGH) studies revealed gains of genetic material at multiple sites other than 12p in 5 of 17 cisplatin-resistant cases as compared to none of the cisplatin-sensitive cases [62]. More recently, another CGH study demonstrated gains of an 8.7 Mb region in chromosome 6q and loss of 0.3 Mb region in chromosome 10q to be present in 3 cisplatin-resistant GCT cell lines that were derived from repeated cisplatin exposure of their cisplatin-sensitive parental clones [106]. However, these findings have not been duplicated among additional GCT samples taken from patients with cisplatin-resistant disease.

Our group performed an array-based CGH (aCGH) on a larger set of tumor specimens (n = 53) with known outcome to cisplatin-based chemotherapy and identified 16 regions of DNA gain or loss that were associated with 5-year overall survival.

Using expression data from this same cohort, we identified 75 probe sets within these 16 regions that demonstrated >2-fold differences in expression as compared to tumors with normal copy numbers or >3 fold differences in expression as compared to normal testis tissue. These data were used to build a model predictive of outcome based on expression of these 75 probe sets, which was then applied to an independent set of 54 tumors for which we had gene expression profile data but not aCGH data. The model predicted 5yOS with 75 % accuracy and this could be increased to 80 % when including probes from regions that were predictive of 2-year disease-specific survival. Importantly, on multivariate analysis, the model's prognostic capability was independent of the IGCCCG risk classification (Unpublished data).

Tumor gene expression patterns have recently been studied in multiple malignancies as predictors of outcome. In particular, the OncotypeDx® (Genomic Health) assay [107] has been commercialized for predicting the likelihood of recurrence in hormone-receptor positive breast cancer patients with localized lymph node negative disease treated with adjuvant hormonal therapy. Patients with a high risk of recurrence on the OncotypeDx assay are offered adjuvant chemotherapy prior to starting hormonal therapy whereas those with a low risk of recurrence are treated with adjuvant hormone therapy.

Based on the success of this approach in other tumor types, we have recently completed an evaluation of differential gene expression as a predictor of outcome in GCT. We conducted whole genome microarray analysis on fresh frozen tumor specimens from 74 NSGCTs and used the prediction analysis for microarray (PAM) software to identify genes associated with favorable and unfavorable outcomes. In total, 170 probe sets corresponding to 135 genes had a significant association with 5-years OS. When the PAM classifier was applied to an independent validation set of 34 NSGCTs, it correctly predicted 5-years OS with 90 % accuracy. On multivariate analysis, the PAM classifier was independent of the IGCCCG classification model, serving as proof of concept that in GCTs, like other malignancies, gene expression-based modeling can enhance outcome prediction [108]. We further categorized the prognostic genes into defined groups using the GOMINER algorithm. Interestingly, overexpression of genes with an immune function (immunoglobulin and T-cell related genes) was associated with a favorable outcome, whereas overexpression of genes involved in differentiation, particularly into a neural lineage was associated with a poor outcome [108].

Conclusions

GCTs encompass a fascinating group of neoplasms with diverse clinical features, histologic appearance, protein and gene expression patterns, and differentiating capability. This vast biologic spectrum relates to the derivation of GCT from malignant transformation of a developing germ cell, existing in an undifferentiated state and with capability to acquire pluripotentiality. Despite their diversity, these tumors are uniquely sensitive to the DNA damaging agent, cisplatin, and therefore, in advanced disease, have among the most favorable prognosis of any metastatic

neoplasm. An improved understanding of the biology of these tumors likely will provide invaluable insight into gametogenesis, embryology, stem cell biology, and mechanisms of cisplatin sensitivity and resistance.

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Chapter 27
Pathology of Testicular Tumors

Sohail Ibrahim Baithun and Abigail Lee

Approximately 94–96 % of testicular tumors are of germ cell origin (germ cell tumors- GCT), with sex cord stromal tumors and lymphomas comprising the remaining few [1]. The GCTs are classified histologically into seminomatous and nonseminomatous GCTs (NSGCT). More than 50 % of the germ cell tumors consist of more than one cell type. The recommended pathological classification is based on the modified WHO classification (Table 27.1) [2].

Serum Tumour Markers

Testicular cancer markers assist in diagnosis, staging, monitoring the treatment, recurrence detection and in the assessment of prognosis. They are measured prior to orchidectomy. Table 27.2 outlines the tumour markers that are useful in the management of testicular cancer. Pure seminomas do not have any specific markers although some have associated elevated levels of hCG. When seminomas are associated with raised AFP, these are considered and treated as non-seminoms. In NSGCTs the degree of tumour marker elevation after orchidectomy is considered as one of the predictors of prognosis [3].

S.I. Baithun, MB, FRCP (✉)
Department of Histopathology, King Howard University, Busaiteen, Bahrain
e-mail: siabaithun@yahoo.co.uk

A. Lee
Department of Morbid Anatomy,
The Royal London Hospital, Barts Health NHS Trust, London, UK

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Table 27.1 Recommended pathological classification

Germ cell tumors
Intratubular germ cell neoplasia, unclassified type (IGCNU)
Seminoma (including cases with syncytiotrophoblastic cells)
Spermatocytic seminoma (mention if there is sarcomatous component)
Embryonal carcinoma
Yolk sac tumour
Choriocarcinoma
Teratoma (mature, immature, with malignant component)
Tumours with more than one histological type (specify percentage of individual components).
Sex cord/gonadal stromal tumours
Leydig cell tumour
Malignant Leydig cell tumour
Sertoli cell tumour
lipid-rich variant
Sclerosing
Large cell calcifying
Malignant Sertoli cell tumour
Granulosa cell tumour (adult and juvenile types)
Thecoma/fibroma group of tumours
Other sex cord/gonadal stromal tumours (incompletely differentiated, mixed
Tumours containing germ cell and sex cord/gonadal stromal (gonadoblastoma).
Miscellaneous non-specific stromal tumours
Ovarian epithelial tumours
Tumours of the collecting ducts and rete testis
Tumours (benign and malignant) of non-specific stroma.

Modified from Albers et al. [2]. With permission from Elsevier

Table 27.2 Tumour markers for testicular cancer

Marker	Association with types of testicular cancer	Other non-testicular tumours
Alpha-fetoprotein (AFP)	Yolk sac cells	Gastrointestinal and hepatic tumours; nonmalignant conditions of liver
	Embryonal carcinoma	
Beta-chorionic gonadotrophin (hCG)	Choriocarcinoma, embryonal carcinoma	Gastrointestinal malignancies, lung, breast, kidney and bladder
	Some seminomas	
Lactic dehydrogenase (LDH)	Nonspecific for GCTs	Muscle injury, some lymphomas
	Indicate bulkiness of the tumour	

Intratubular Germ Cell Neoplasia (ITGCN, Carcinoma *In Situ* CIS)

Testicular carcinoma *in situ* is known as the precursor of germ cell cancers of the testis [4] with the exception of spermatocytic seminoma seen commonly in older men, and infantile tumours (yolk sac tumor and mature teratoma) [5]. There is a substantial body of evidence to suggest that ITGCN is a precursor of testicular germ cell tumors (TGCTs) during intrauterine life, remaining dormant until the age of puberty. Thereafter, under the influence steroids and gonadotropins and environmental and lifestyle factors, ITGCN becomes an invasive seminomatous or non-seminomatous germ cell tumor [6]. The risk of ITGCN is also increased in the contralateral testis of patients with testicular carcinoma [7]. It is believed that ITGCN originates from gonocytes [8].

ITGCN is likely to develop into invasive malignancy in 50 % of patients within 10 years and 70 % within 7 years [7] and the most common type is a seminoma [9]. The cells of ITGCN have a number of similarities to embryonic germ cells, such as their positivity for alkaline phosphatase, increased glycogen content, and the presence of stem cell factor receptor (c-KIT). Based on immunohistological findings, Jørgensen et al. [10] have suggested that the cell of origin of ITGCN is present in the gonad around the 7th to 10th week of intrauterine life. In 5 % of cases with unilateral seminoma or nonseminoma there is a contralateral ITGCN, indicating major events taking place even before primordial germ cells reach the left and right gonadal blastema [11]. Known risk factors for ITGCN include contralateral testicular malignancy, cryptorchidism, atrophic testis, infertility and true hermaphroditism [12].

Histopathological Features

The diagnosis of ITGCN requires testicular biopsy and the specimen should be placed in Bouin's or Stieve's solution, as formalin causes shrinkage artifacts. The cells are larger than normal spermatogonia with abundant cytoplasm and hyperchromatic nuclei, which have prominent nucleoli (Table 27.3).

Table 27.3 WHO criteria for the diagnosis of carcinoma in situ of the testis (see Fig. 27.1)

Larger than normal spermatogonia
Clear or vacuolated cytoplasm rich in glycogen
Nuclei: large, irregular, and hyperchromatic
Nucleoli: one or more large and irregular
Abnormal mitoses
Basally located cells
Spermatogenesis commonly absent
Segmental involvement of tubules

Based on data from Ref. [13]

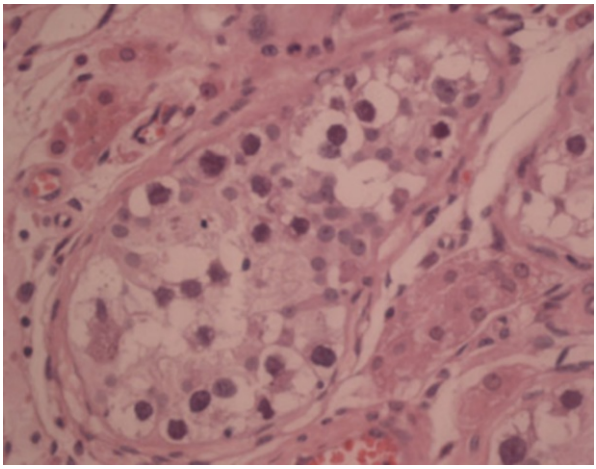

Fig. 27.1 Testicular carcinoma in situ (H & E ×40)

The cell margins are conspicuous and cytoplasm is abundant and the basement membrane is frequently thickened [14]. ITCGN is seen within seminiferous tubules surrounding invasive carcinomas in the majority of cases [15] (Fig. 27.1).

A wide variety of histological markers are used in the diagnosis of ITGCN. The most widely used marker is placental alkaline phosphatase [16]. Another most specific recent marker is Oct¾ [17]. They are also associated with positive CD117 [18].

Seminoma

Seminoma is the most common germ cell tumour accounting for almost half of all cases [19]. Patients with seminoma typically present between the ages of 35–45 years and the majority of patients present with testicular enlargement [1]). Macroscopically, seminomas are usually well-circumscribed, firm and homogenous tumours.

Microscopically (Fig. 27.2), the tumour is composed of sheets of large monomorphic cells with copious clear cytoplasm, a definite cell membrane and a single nucleus with prominent nucleoli. Thin fibrous septa are present which divides the tumour into lobules. Numerous lymphocytes are typically present and a granulomatous reaction can often be seen. In a proportion of cases, syncytiotrophoblastic cells can be observed scattered through the tumour [20]. A seminoma is typically positive for PLAP, OCT4 [21] and CD117 [22]. In cases where syncytiotrophoblastic giant cells are present within the tumour, these cells can be highlighted using immunohistochemistry for human chorionic gonadotrophin (HCG) [23]. The most common cytogenetic abnormality in seminoma is the presence of the isochromosome 12p [24].

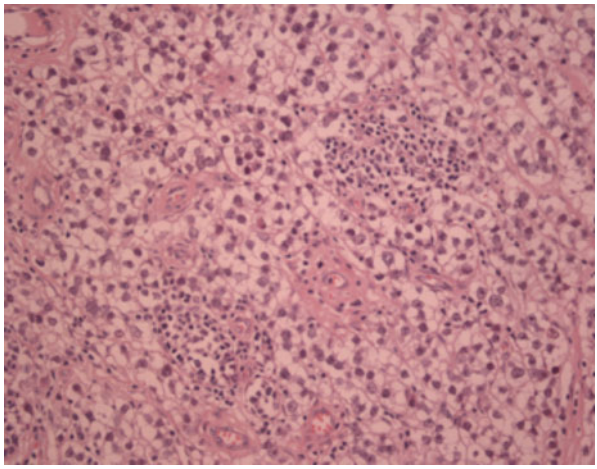

Fig. 27.2 Seminoma (H&E ×40)

Spermatocytic Seminoma

This is an uncommon germ cell tumour which typically occurs in men over the age of 50 years and demonstrates indolent clinical behaviour. Patients typically present with testicular enlargement [25]. Macroscopically, the tumour is soft and friable [25]. Microscopically, the tumour is composed of three cell types: large, medium-sized and small cells. The large cells have copious cytoplasm and can be either single or multinucleate. The nuclei are usually round but can show size variation. The medium-sized cells have round nuclei with granular cytoplasm and eosinophilic cytoplasm. The small cells have a similar appearance to lymphocytes.

Spermatocytic seminomas are not associated with other neoplastic germ cell components or with classical seminoma [25]; however a small percentage of cases can be associated with high-grade sarcoma. The presence of high-grade sarcoma correlates with aggressive clinical course [26]. The immunohistochemical markers, PLAP and OCT4, which are positive in classical seminoma are negative in spermatocytic seminoma [27]. CD117 is typically positive in spermatocytic seminoma [28].

Nonseminomatous Germ Cell Tumors

These tumors have embryonic elements and differentiate along embryonic lineage (embryonal carcinoma, teratoma, teratocarcinoma) or extraembryonic tissue components (yolk sac tumor and choriocarcinoma).

Choriocarcinoma

It is a rare but highly aggressive tumour that typically occurs in young men in the second and third decade. It is rarely presents in a pure form [19] however, it is often found as a component of NSGCT. Patients often present with a raised serum hCG level and symptoms of metastatic disease [1]. Macroscopically, the tumour has a necrotic haemorrhagic appearance. Microscopically, the tumour is composed of syncytiotrophoblasts and cytotrophoblasts usually arranged in solid sheets [29]. Syncytiotrophoblastic cells are large multinucleated giant cells with dark eosinophilic cytoplasm; cytotrophoblasts are medium sized polygonal cells with clear cytoplasm. These cells can be difficult to distinguish from embryonal carcinoma cells or seminoma cells, however their proximity to syncytiotrophoblastic cells helps identify them. Syncytiotrophoblastic cells often wrap around the cytotrophoblast and form villous structures [1]. Immunohistochemistry demonstrates the syncytiotrophoblastic tumour cells are strongly positive for HCG, cytokeratin is positive in both syncytiotrophoblastic and cytotrophoblastic cells [29].

Yolk Sac Tumour (Endodermal Sinus Tumour)

The pure form of yolk sac tumour is rarely seen in adults and is usually seen admixed with other germ cell tumours. Patients often present with high serum alpha-fetoprotein (AFP) [30] and rapid testicular enlargement [1]. Yolk sac tumour is a common tumour of infants, more than 75 % of testicular tumours in childhood are yolk sac tumours and are typically found in the pure form [31]. Macroscopically, the testis contains a poorly defined lobulated tumour which may contain cystic areas or areas of haemorrhage and necrosis. Microscopically, the tumour can demonstrate numerous patterns with the most common being a reticular-microcystic pattern (Fig. 27.3). This is composed of anatomizing channels lined by cuboidal cells forming loose cystic spaces. The microcystic pattern contains small cystic spaces with clusters of cells projecting into the lumen. Several other patterns are also seen but with reduced frequency. The definitive feature of YST is the formation of

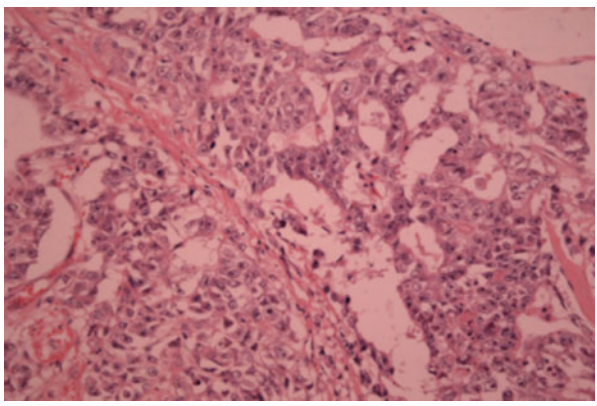

Fig. 27.3 Embryonal cell carcinoma (H & E ×40)

Schiller-Duval bodies, these are fibrovascular cores surrounded by malignant cells, which are set within a cystic space lined by flat epithelial cells. Intracellular hyaline globules are also characteristic of yolk sac tumour [1]. immunohistochemistry demonstrates the tumour cells are positive for AFP [30] and CEA, and are negative for HCG [32].

Embryonal carcinoma. It comprises approximately 15–30 % of pure testicular germ cell neoplasms and typically occurs in patients between the ages of 15–34 years. The majority of patients have metastatic disease at presentation with half have distant metastases. Despite the inherent tumour aggressiveness overall 5-year survival rate is over 80 % although survival correlates with disease extent at diagnosis [33].

Macroscopically, embryonal carcinoma is often a small tumour which is poorly circumscribed and contains areas of haemorrhage and necrosis. One fifth of embryonal carcinomas show extension beyond the testis at the time of operation. Microscopically, embryonal carcinoma can demonstrate solid, tubular or papillary patterns with areas of necrosis or haemorrhage. The cells are large and pleomorphic with large irregular nuclei, abundant cytoplasm and numerous mitoses.

Frequent nuclear overlapping is present and giant tumour cells can also be seen [1]. Immunohistochemistry demonstrates the tumour cells are positive for PLAP [34], CD30 [35] and OCT4. AFP and HCG are usually negative, occasional syncytiotrophoblastic giant cells may stain positively with HCG.

Polyembryoma. The pure form of polyembryoma is an extremely rare germ cell tumour often found as a component in a mixed GCT. Polyembryomas are composed of embryoid bodies, which are formed by an embryonic plate of embryonal carcinoma overlying the cystic structure of yolk sac tumour cells. The pattern resembles an early embryo [36]. Microscopically, numerous embryoid bodies surrounded by a loose myxoid stroma are present. The embryoid body consists of amniotic cavity, embryonic disk, yolk sac and the myxoid extraembryonal mesenchymal tissue [1].

Teratoma

Teratomas are GCTs that have components of three cell layers of developing embryo namely ectoderm, mesoderm and endoderm. There are three types of teratomas: mature, immature and teratoma with malignant transformation. This differentiation in prepubertal teartomas is not required because of their similarities [37].

Mature Teratoma

This variety is uncommon as a pure tumour but is commonly present as a component of malignant germ cell tumours. The tumour typically occurs in the first two decades of life and is the second commonest tumour of childhood. In prepubertal patients mature teratomas typically are benign [1]. Pure testicular teratoma in adults is rare and malignant with metastatic potential [38]. These tumours rarely spread to the surrounding or distant tissues.

Macroscopically, the tumour is well circumscribed and if often multicystic, bone and cartilage may be observed. Microscopically, the tumour is composed of a mixture from all three cell line; endoderm, mesoderm and ectoderm. Any mature component can be represented however typically epidermis, neural tissue, gastrointestinal mucosa, respiratory mucosa and bone and cartilage are the most common [1].

Immature Teratoma

These are less well-differentiated tumours, which are malignant and therefore have potential to spread. As with the mature form of teratoma, in adults the pure form of immature teratoma is rare although these tumours are a common component of NSGCT. In children immature teratoma occur predominantly below the age of 7 years with most presenting in infancy; in early childhood the behaviour is similar to mature teratoma [39]. An immature teratoma is one in which the tissue either resembles fetal tissue or cannot be recognized as normal tissue. Usually the immature forms are mesenchymal spindle cells although immature neural and other elements including peripheral neuroectodermal tumour can also be seen [1, 40].

Mixed Germ Cell Tumours

They are the second most common following seminoma [41]. The most common combination is teratoma and embryonal carcinoma (25 %) followed by embryonal carcinoma and seminoma and teratoma and embryonal carcinoma and seminoma (both 15 % each). Rarely the combination of seminoma and yolk sac tumour is seen. Forty percent of mixed germ cell tumours contain foci of yolk scat tumour [1].

Macroscopically, the testis is often entirely replaced by tumour, which shows both solid and cystic areas. Identification of the differing components cannot be observed grossly although the presence of haemorrhage and necrosis may suggest choricarcinoma or embryonal carcinoma [1].

Microscopically, many different germ cell elements are present and can be identified by the architecture. Usually, the elements are randomly distributed throughout the tumour [1]. The application of the appropriate immunohistochemical antibodies can identify the relevant areas of tumour.

Non-germ Cell Tumours

Leydig Cell Tumour

Leydig cell tumours account for approximately 1–3 % of all testicular tumours [41]. The age range for these tumours is wide ranging from infancy to late adulthood with an average age of presentation at approximately 46 years. Typically patients present with testicular swelling, which is usually unilateral; some patients also have

gynaecomastia. In infants and young children the presenting complaint may be isosexual pseudoprecocity. Macroscopically, the tumours are well circumscribed with a diameter ranging from between 0.5 and 10 cm with an average size of 3 cm. Microscopically, the tumour cells are large and polygonal with eosinophilic granular cytoplasm. The most common pattern is diffuse but other patterns such as trabecular, insular and ribbon-like are also seen. Reinke crystals are present in approximately 35 % of tumours.

In a few cases spindle shaped cells are observed [42]. Nuclei are typically round with a single nucleolus and occasionally nuclear grooves [1]. Generally mitoses are rare however numerous mitotic figures can be observed in occasional cases [42]. The tumours can show malignant clinical behaviour in approximately 10 % of patients; metastasis is the only criteria to determine malignancy [1]. The pathological features which are more common in tumours with malignant outcome are large size with infiltrative margins, nuclear atypia, vascular invasion, necrosis and high mitotic rate athough none of these features are diagnostic [42]. Immunohistochemistry demonstrates the tumour cells are positive for inihibin and chromogranin and are negative for S100. Keratins can be focally positive [43].

Sertoli Cell Tumour

Setoli cell tumours comprise less than 1 % of all testicular tumours [41]. The age range for these tumour is wide however approximately 30 % occur in the first decade of life. Patients usually present with a unilateral testicular mass with approximately 20 % of patients also having gynecomastia [44]. Sertoli cells tumours also show an association with Peutz-Jeghers syndrome [45] and testicular feminization [46]. As with Leydig cell tumours, the majority of Sertoli cell tumours are benign with approximately 10 % being malignant [47]. The malignant variants typically metastasise to the iliac an para-aortic lymph nodes [47, 48]. Macroscopically; the tumours are small, solid and well defined [44]. Microscopically; there are two variants of Sertoli cell tumour. The classical type is composed of uniform cells arranged in nests, tubules or cords with fibrous stroma surrounding the tumour cell islands [1]. The sclerosing Sertoli cell tumours show thin cords, large aggregates and simple and anastomosing tubules composed of medium sized cells with pale cytoplasm and round or vesicular nuclei in a prominent collagenous background [49]. Tumours with malignant outcome are more likely to be large with necrosis, nuclear pleomorphism, vascular invasion and increased mitotic activity [50].

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Chapter 28
Testicular Cancer- Clinical Features, Staging and Surgical Management

Axel Heidenreich

Clinical Features

Although the majority of patients present with a painless testicular swelling, testicular pain might be present in nearly 30 % of the patients often labelled as epididymitis or epididymo-orchitis. This may be an acute or chronic episode but a high index of suspicion is essential. Acute pain indicates intratumoral or intratesticular haemorrhage. Rare symptoms include haematospermia, gynaecomastia and sudden enlargement of atrophic testis. Testicular cancer patients can also present to other specialities due to its ability to have widespread metastatic potential. These include chest and neurological symptoms; backache, abdominal pain, erectile dysfunction (Retroperitoneal and pelvic masses), haemoptysis, cough or dyspnoea (lung metastases), supra-clavicular mass due to enlarged lymph glands. Patients may present with atypical neurological symptoms from brain metastases or spinal cord compression.

It is important to assess for testicular cancer risk factors, which include contralateral testicular cancer, undescended testis, infertility and history of testicular tumour among blood relatives, particularly in the father and/or brothers.

The delay in diagnosis has a direct impact on the extent of the disease. In a study of 335 patients, Bosl et al [1] showed a time delay of 75, 101, and 134 days in patients with clinical stage I, II and III disease, respectively. There also seems to be difference in clinical course between seminomatous and nonseminomatous germ cell tumours. Seminomas tend to have a long and indolent clinical course while nonseminomatous tumours present much earlier than seminomas. In a study from Sheffield, UK the tumor specific mortality rose from 8 to 16 % if the treatment was initiated later than 6 months when compared to the treatment given in the first 6

A. Heidenreich, MD, PhD
Department of Urology, University Hospital Aachen, Aachen, Germany
e-mail: aheidenreich@ukaachen.de

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months [2]. Delay may be caused in patients who ignore symptoms for a considerable period of time or by clinicians who fail to recognise the problem by misdiagnosing a testicular mass as epididymitis or back pain from retroperitoneal disease due to vertebral disc problems. Another rare finding is presence of 'scar tissue' indicating a "burnt out" testicular tumour. The diagnosis may not be possible even after excision of the tissue.

Clinical Assessment

Mandatory clinical examination includes systematic testicular palpation without unduly pressing the testis for the fear of dissemination. The tumour is usually felt hard with variable consistency. Abdomen is examined for masses and neck area for any lymph nodes. Importance of considering any acute or subacute intrascrotal swelling as a testicular tumour unless otherwise proved cannot be overemphasized. Other conditions, which are likely to mislead include epididymo-orchitis, torsion, hydrocoele, haematocoele, spermatocoele, large epididymal cysts, hernia gumma and trauma to the testis. Amongst these conditions the two, which can mimic testicular tumour, are acute torsion and epididymo-orchitis. Syphilitic and tuberculous lesions of the testis may also present with painless testicular swelling.

Investigations and Staging

When a testicular lesion is suspected, initial investigations include estimating the serum tumour markers α-fetoprotein (AFP), ß-human chorionic gonadotropin (β-HCG) and lactic dehydrogenase (LDH) [3, 4] (Table 28.1). Ultrasound of the testes with an appropriate transducer (7.5–10 MHz) capable of performing Doppler studies is carried out [4]. Typically, solid, hypodense intratesticular lesions are identified and these might be distinguished from intratesticular cysts, epidermoid cysts, and extratesticular lesions (Fig. 28.1). Other imaging procedures, such as magnetic resonance or positron emission tomography of the testis, are not routinely be used as their results do not alter the clinical management. The details of ultrasound assessment are discussed in the chapter on radiology (Chap. 5).

Computerized Tomography (CT)

Contrast enhanced (oral and intravenous) CT of the chest, abdomen and pelvis is required as an initial staging investigation [5, 6]. For the evaluation of the lungs and mediastinum, chest CT scan is much more sensitive than a plain chest X-ray [7, 8].

Table 28.1 Diagnosis and staging of germ cell cancer

Tumour markers m*andatory:*
AFP: seen in 40–60 % nonseminomas and AFP is absent in seminoma; Even if raised in seminoma, the tumour is considered as mixed GCT
β-HCG: raised levels found in 10–15 % of stage I pure seminoma. Nearly 40–50 % NSGCTs have elevated levels of β-HCG
LDH: both SGCT and NSGCT show elevation of LDH.
Imaging:
Testicular ultrasound (7.5 MHz transducer)
CT-scan of abdomen and pelvis
Chest CT-scan (not mandatory for seminoma stage I)
Magnetic resonance imaging (MRI) of chest and abdomen: only if there is a contraindication for CT-scan (e.g. allergy to contrast media)
Bone scan: only if symptoms
Positron emission tomography (PET)-scan: to identify viable tissue in residual lesion ≥3 cm in advanced seminoma if determined ≥8 weeks after chemotherapy
Head CT may be required when indicated where cerebral metastasis are suspected.
Fertility investigations (should be offered):
Semen analysis; serum estimations of total testosterone, luteinising hormone (LH), follicle stimulating hormone (FSH), sperm banking (this may require screening tests for hepatititis and human immunodeficiency virus (HIV)

Based on data from Ref. [9]

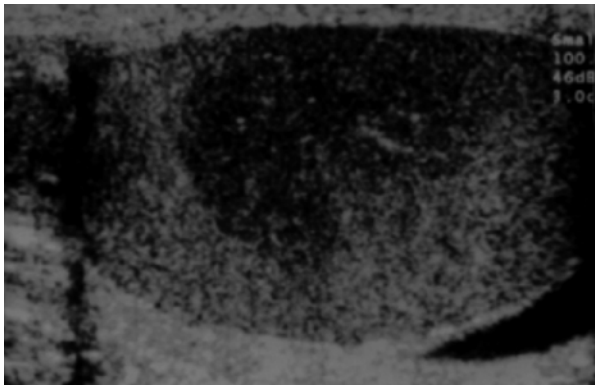

Fig. 28.1 Ultrasound of testis showing seminoma

However, it should be noted that pulmonary/pleural nodules of <1 cm can represent a false positive finding in CT scans [8]. Furthermore, CT scans of the abdomen and pelvis might give false-negative results in up to 30 % of cases due to difficulties in the interpretation of lymph nodes based on morphology and size alone [5]. Therefore, the differentiation between clinical stages I and IIA by CT might be unreliable. A detailed description of the location, number and size of lymph nodes should be provided in the radiology report. Magnetic resonance imaging (MRI) scans of the abdomen and pelvis do not provide additional information and should be restricted

to those patients in whom intravenous contrast media is contraindicated [9]. Based on available data, PET has not conclusively demonstrated to improve sensitivity over CT staging alone [10, 11]. Even in high-risk stage I patients PET scan was not sensitive enough to predict early metastatic disease in a statistically significant proportion of patients. PET scans are therefore not recommended outside the clinical trials as a part of routine initial staging procedures.

Staging of Testicular Cancer

Clinical staging of a patient with a testicular germ cell tumour is done according to the TNM classification (Table 28.2) [12]. In order to verify clinical stage I disease markers need to be followed until normalization after orchidectomy. Those patients who do not have marker normalization after orchidectomy obviously have metastatic disease. Patients with metastatic disease are categorised according to the classification devised by the International Germ Cell Cancer Collaborative Group (IGCCCG) [13] which includes histology, location of primary tumour, location of metastases and pre-chemotherapy levels of AFP, HCG and LDH as prognostic markers to categorise patients into 'good', 'intermediate' and 'poor' prognosis groups (Table 28.3). The individual treatment strategy is based on both the TNM classification and the IGCCCG-prognostic factor-based classification.

Table 28.2 TNM Staging American Joint Committee on Cancer (AJCC) and Union Internationale Contre le Cancer (UICC) [12]

Primary tumour pT	
pTX	Primary tumour cannot be assessed
pT0	No evidence of primary tumour (e.g. histological scar in testis
pTis	Intratubular germ cell neoplasia (carcinoma in situ)
pT1	Tumour limited to testis and epididymis without vascular/lymphatic invasion: tumour may invade tunica albuginea but not tunica vaginalis
pT2	Tumour limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica albuginea with involvement of tunica vaginalis
pT3	Tumour invades spermatic cord with or without vascular/lymphatic Invasion
pT4	Tumour invadas scrotum with or without vascular/lymphatic invasion
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis

Table 28.2 (continued)

N1		Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension		
N2		Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, any one mass more than 2 cm but not more than 5 cm in greatest dimension		
N3		Metastasis with a lymph node mass more than 5 cm in greatest dimension		
Pathologic (pN)				
pNX		Regional lymph nodes cannot be assessed		
pN0		No regional lymph node metastasis		
pN1		Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension		
pN2		Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence or extranodal extension of tumour		
pN3		Metastasis with a lymph node mass more than 5 cm in greatest dimension		
Distant metastasis (M)				
MX		Distant metastasis cannot be assessed		
M0		No distant metastasis		
M1		Distant metastasis		
M1a		Non-regional lymph nodes(s) or lung		
M1b		Other sites		
Serum tumour markers (S)				
Sx		Serum marker studies not available or not performed		
S0		Serum marker study levels within normal limits		
	LDH (U/l)	**hCG (mlU/ml)**	**AFP (ng/ml)**	
S1	<1.5 × N and	<5,000 and	<1,000	
S2	1.5–10 × N or	5,000–50,000 or	1,000–10,000	
S3	>10 × N or	>50,000 or	>10,000	
[N indicates the upper limit of normal for the LDH assay]				
Except for pTis and pT4, where radical orchiectomy is not always necessary for classification purposes, the extent of the primary tumour in classified after radical orchiectomy; see pT. in other circumstances, TX is used if no radical orchiectomy has been performed.				
Substages of stage I testicular cancer:				
Stage IA	pT1	NO	MO	S0
Stage IB	pT2, pT3 or pT4	NO	MO	S0
Stage IS	Any pT/TX	NO	MO	S1-3

Table 28.3 IGCCCG prognostic grouping classification

Prognosis	5-year-survival (%)	Non-seminoma	Seminoma
Good	90	Testis or primary extragonadal retroperitoneal tumour	Any primary localisation
		And low markers	Any marker level
		AFP <1,000 ng/ml,	And no non-pulmonary visceral metastases
		And ß-HCG <1,000 ng/ml (<5,000 IU/l)	
		And LDH <1.5× normal level	
		And no non-pulmonary visceral metastases	
Intermediate	75	Testis or primary extragonadal retroperitoneal tumour	Any primary localisation
		And intermediate markers	And presence of non-pulmonary visceral metastases (liver, CNS, bone, interstitium)
		AFP 1,000–10,000 ng/ml	Any marker level
		And/or ß-HCG 1,000–10,000 ng/ml (5,000–50,000 IU/l)	
		And/or LDH 1.5–10× normal level	
		And no presence of non-pulmonary visceralmetastases	
Poor	50	Primary mediastinal germ cell tumour with or without testis or	–
		Primary retroperitoneal tumour	
		And presence of non-pulmonary visceral metastases (liver, CNS, bone, intestinum)	
		And/or "high markers"	
		AFP >10,000 ng/ml,	
		And/ or ß-HCG >10,000 ng/ml (50,000 IU/l)	
		And/ or LDH >10× normal level.	

Based on data from Ref. [13]

Spread of Testicular Tumor

The testicular tumors have a specific mode of spread, with the metastases occurring through lymphatic and vascular routes. Local spread is limited by the tunica albuginea of the testis. The lymphatic spread is a common form of metastasis in all histological types. Haematogenous spread occurs to the lungs, liver and brain. As testes develop in the retroperitoneum in the abdomen, their lymph drains to paraaortic and other lymph nodes in the infrarenal region. The lymphatics from the epididymis drain into testicular lymphatics. These lymphatics join lymphatics from the tunica albuginea in rete testis and proceed to the spermatic cord [14].

The lymphatics initially accompany testicular vessels. After crossing the ureter they spread out to join retroperitoneal lymph nodes anterior to the lumbar vessels [15, 16]. The right testicular vein drains into the anterior aspect of the inferior vena cava and the left testicular vein drains into left renal vein.

Right-sided tumors metastasize to the infrarenal aortocaval, precaval, right paracaval, and retrocaval lymph nodes. Left-sided tumors spread to the left paraaortic and preaortic lymph nodes. The echelon lymph nodes are lateral to the paracaval and paraaortic lymph nodes in the region between the first and third lumbar vertebra on the iliopsoas muscle, which can get involved particularly in cases with relapse [17]. When the anatomy of the inguinoscrotal region is disturbed by surgical procedures like orchidopexy or scrotal exploration, there is likely to be a direct spread to the iliac or inguinal lymph nodes, which normally drain scrotal skin.

Surgical Management

Radical Inguinal (High) Orchidectomy (RIO)

As a rule radical inguinal orchiectomy is a standard treatment and performed prior to any therapy [5]. This is performed through the inguinal approach with isolation the spermatic cord up to the level of internal inguinal ring followed by ligation/transfixation at that level and division of the cord. Testicular tumour markers are done before and repeated after the orchidectomy. The only exception to this rule is when patients present with a life-threatening metastatic disease and an unequivocally elevated AFP or β-hCG. In such cases, orchidectomy is done after the completion of chemotherapy [18–20]. The operation is performed through an inguinal incision. The tumour-bearing testicle is excised along with the spermatic cord to the level of the internal inguinal ring. In patients with negative serum tumour markers or small equivocal possibly benign tumours, histological analysis of a frozen section may be desirable prior to proceeding to orchiectomy or to allow organ sparing surgery, particularly if a benign tumour is found [21, 22].

Organ Preserving Surgery

In patients with synchronous bilateral tumours, metachronous contralateral tumours or solitary testicles with normal preoperative testosterone levels, organ-preserving surgery is an alternative procedure to orchiectomy and should be discussed with the patient. If organ preserving surgery is considered, the patient should always be treated at a tertiary referral centre with an experience in the management of testicular cancer [23–25]. When organ preserving surgery is performed, adjuvant radiotherapy is strongly recommended according to the management strategy for testicular intraepithelial neoplasia (TIN) in unilateral tumours [25]. Adjuvant

radiotherapy may be delayed in patients who wish to father children. In patients who have non-obstructive azoospermia, sperm samples can also be retrieved at the time of surgery.

Fertility Preservation

All patients with established diagnosis of malignant testicular tumours should have pre-treatment option of semen preservation for future fertility treatment. It is also advisable to carry out an reproductive endocrine profile consisting of serum levels (Table 28.1) of follicle stimulating hormone (FSH), luteinising hormone (LH), testosterone (T) and semen analysis before orchidectomy [26]. The testis is easily affected by chemotherapy or radiotherapy and the effects are long-lasting and in some cases irreversible. Testicular toxicity affects spermatogenesis more than it affects testosterone production by Leydig cells [27]. The topic of fertility concerns may not be discussed at all by patients due to variety of factors: patients may be overwhelmed by the diagnosis of cancer diagnosis, they may be unaware that potential fertility loss could occur, or they may be concerned that pursuing fertility preservation might delay their cancer treatment leading to increased morbidity and mortality [28]. In such cases the onus is on the clinician to initiate the discussion on fertility preservation when it is applicable.

Diagnosis and Treatment of Testicular Intraepithelial Neoplasia (TIN) or Carcinoma in situ (Cis) or Intratubular Germ Cell Neoplasia (ITGCN)

The pathological aspect has already been discussed in detail in the pathology section. Nearly 70 % of all TIN will progress to an invasive GCT within a 7 years period if left untreated and followed by surveillance [29, 30]. ITGCN cells are typically located within the seminiferous tubules and usually there is no active spermatogenesis in the TIN bearing tubules (Fig. 28.2). These cells populate in numerous seminiferous tubules in the peritumoral parenchyma and basically all TGCT have at least some ITGCN cells in the adjacent parenchyma. They spread along the seminiferous tubules (Fig. 28.2) sometimes invading the rete testis; in some cases they may proliferate locally by filling a tubule by several layers (Fig. 28.3). As mentioned earlier, the cells are characterized by an overexpression of intracytoplasmic placental alkaline phophatase (PLAP) on immunohiostochemistry (IHC) (Fig. 28.3). According to recent recommendations, IHC for PLAP is mandatory for the adequate diagnosis of ITGCN [4, 31]. Besides ITGCN, only seminomas and embryonal carcinomas overexpress PLAP in similar abundance. About 10 % of ITGCN cells may not express PLAP at all and it might be helpful to stain with the 43–9 F [32].

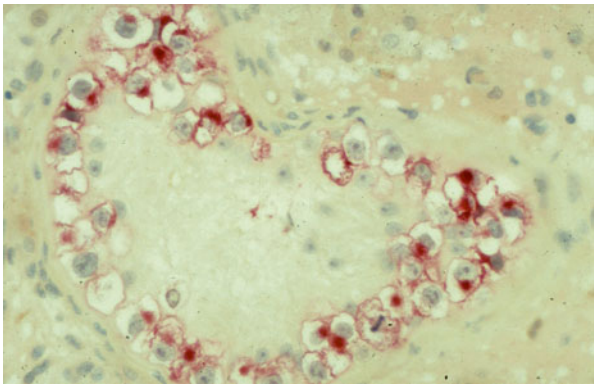

Fig. 28.2 Typical morphology of TIN cells: large cells with abundant glycogen, thickened basal membrane, no active spermatogenesis, overexpression of PLAP

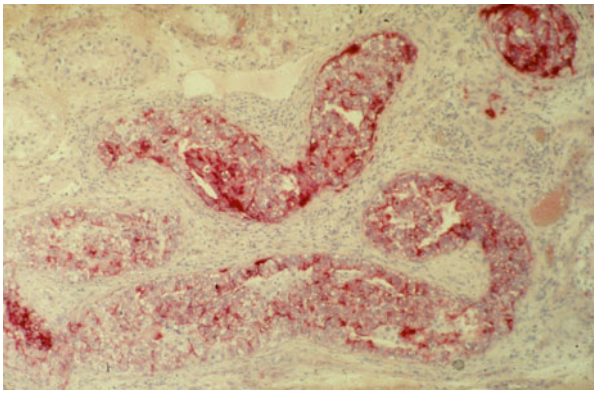

Fig. 28.3 Multifocal spread of TIN populating numerous seminiferous tubules; TIN cells proliferate locally and fill the tubules in several layers

Currently, surgical testicular biopsy is the most reliable method for diagnosing ITGCN [33]. The biopsy should be taken in the craniolateral region of the testicle where the risk to damage intratesticular vessels is minimal. Damage to the specimen should be avoided. Dieckmann et al [33] in their prospective study of 2,318 testis cancer patients have shown that a two-site biopsy is significantly more sensitive to detect ITGCN than a single site biopsy [33]. A total of 119 (5.1 %) exhibited ITGCN in contralateral testis with a discordance rate of 31 % of the biopsies. The discordance was more frequent in patients with normal testicular volume and unimpaired spermatogenesis.

A critical analysis of the available data on contralateral testicular biopsy in patients with untreated testicular cancer does not support the idea of routine testis biopsy in all cases [34, 35]. Contralateral testis biopsy might be offered to high risk patients (testis volume <12 ml, history of cryptorchidism, age <30 years, table 28.4) [35], however, this procedure does not result in improved survival rates nor in decreased treatment associated toxicity in secondary testicular germ cell tumors.

Table 28.4 Clinical risk factors for contralateral TIN in patients with unilateral testicular germ cell tumors

Risk factor	Relative risk	95 % confidence interval
Testicular atrophy (<12 ml)	4.3	2.83–6.44
History of cryptorchidism	2.1	1.21–3.63
Age <30 years	1.7	1.17–2.6
Family history of testis cancer	2.2	1.25–12.3
Infertility	1.6	1.10–10

Based on data from Ref. [35]

Management of Seminoma

The role of surgery in pure seminomas is limited mostly to the radical orchidectomy. Post-orchidectomy management for stage I disease involves surveillance, with treatment reserved for patients who have relapse, or adjuvant treatment with either radiotherapy or chemotherapy [36] and this aspect of management is described later. Retroperitoneal lymph node dissection is not recommended.

Primary RPLND is not an option stage I seminoma even after relapse and for stage II seminomas; RPLND has been replaced largely by chemotherapy and/or radiotherapy [37]. In a retrospective study comparing radiotherapy and RPLND in stage I and II seminoma, Warszawski et al [38] observed in their 161 subjects treated between 1975 and 1991 (98 patients received radiotherapy and 63 patients underwent RPLND) a higher relapse rates after RPLND (9.5 % Vs. 2.0 %).

Post-chemo RPLND (PC-RPLND) in seminomas: The original recommendation was to resect tumours >3 cm diameter. However viable seminoma is found in less than 20 % of patients after chemotherapy. Also pure seminoma is a different entity compared to NSGCT. There is a higher degree of desmoplastic reaction than NSGCT and there is relatively higher grade of poor tissue planes. Most often the excision of residual masses cannot be completed in a safe manner with nearly 40 % of patients requiring additional operative procedures [39]. Overall RPLND does not seem to have any therapeutic benefit even when undertaken as a technically challenging procedure.

Low Stage NSGCT

Clinical Stage I

Definition

Clinical stage I is defined by negative imaging studies of the chest, the abdomen and the pelvis. Furthermore, in order to verify clinical stage I disease elevated markers should be followed up in the post-orchidectomy period until normalization. Patients

who fail to normalize after orchidectomy or those in whom markers do not decline according to their half life after orchidectomy do not have stage I disease.

The standard treatment options of patients with clinical stage I disease remains controversial since patients have an excellent survival rates with all forms of treatment including retroperitoneal lymph node dissection (RPLND), active surveillance and primary chemotherapy [4]. The controversy has remained over the last two decades as nearly 30 % of these patients would harbour occult microscopic retroperitoneal lymph node metastases, which cannot be reliably detected by modern imaging studies, tumour markers or molecular approaches. With RPLND the staging process becomes more reliabe and accurate; however, nearly 70 % are operated unnecessarily and 10 % will develop systemic metastases with a need for salvage chemotherapy. With primary chemotherapy alone approximately 50–70 % of the patients are overtreated and might be exposed to unnecessary long-term complications. Active surveillance on the other hand is clearly indicated in low risk disease which has a recurrence rate of only 15 %. In patients with a high risk disease the relapse rates vary between 35 and 55 % and makes intensive salvage chemotherapy necessary.

Prognostic Risk Factors

Lymphovascular infiltration (vascular invasion, VI) by the primary tumour is one of the most important prognostic indicators for occult metastases and must be assessed in all patients [40–44]. Without adjuvant treatment 48 % of the patients with VI would develop metastases while only 14–22 % of those without metastasis relapse. Based on these data, VI alone does not represent a valuable prognostic risk factor for a risk-adapted approach as it is likely to result in an unnecessary overtreatment rate of about 50 %. The proliferation rate and the percentage of embryonal carcinoma (EC) present in relation to the total tumour volume are further prognostic indicators [42, 43]. The combination of absence of VI and a percentage of EC <45 % correctly identified 91.5 % of all patients with true pathological stage I disease [42]. On the other hand, the presence of VI and a percentage of EC >80 % correctly predicted pathological stage IIA/B disease in 88 % of the patients. Based on these data, the German Testicular Cancer Study Group performed a prospective study in which 200 patients with clinical stage I NSGCT were assigned to RPLND and risk factors were assessed prospectively [43]. The combination of absence of VI, percentage of EC <50 % and a MIB-1 proliferating index <20 % correctly identified pathological stage II disease with 86.5 % accuracy. If none of the prognostic risk factors were present, the risk of occult retroperitoneal disease was 16 % and patients were classified as low risk. The risk of lymph node metastases was 65 % if at least VI and percentage EC >50 % were present and the patients were classified high risk. In another small prospective evaluation, Perotti et al [44] tested a prediction model in which patients with a percentage of EC >80 % and/or the presence of VI were assigned to a high risk of occult metastatic disease. The authors correctly predicted final pathological stage II disease in 67 % when only one prognostic factor was present.

The combination of imaging studies, histopathological evaluation and immunhistochemical techniques is likely to improve the prediction of the final pathological stage of the disease. Localization and size of lymph nodes in conjunction with a low volume of embryonal carcinoma, absence of vascular invasion and a low MIB-1 proliferation rate might give important information with regard to the probability of lymph node metastases. In a retrospective analysis of 91 clinical stage 1 NSGCT patients using a combined approach with quantitative immunohistochemical, histopathologic, and radiologic assessment who underwent nerve-sparing RPLND, Liebovitch et al [45] found 40 out of 41 patients were correctly classified as low risk tumours for metastases. They concluded Patients with lymph nodes <1 cm diameter which are located in the primary landing zone, a low volume of embryonal carcinoma harbour a risk of <10 % of occult retroperitoneal lymph node metastases and might be best managed by active surveillance.

Treatment of Patients with Non-seminoma Clinical Stage I NSGCT

If the correct treatment were to be executed, the cure rate for patients with CS I NSGCT should be 99 % regardless of the treatment chosen. Basically, three treatment options, which have similar cure rates but significantly differing in frequency and type of treatment-associated toxicities, might be offered to these patients: (i) active surveillance; (ii)primary chemotherapy with 1–2 cycles PEB and (iii) Nerve-sparing RPLND. When choosing a risk–adapted approach in clinical stage I NSGCT, the clinician has to reflect that all the patients are expected to be long-term survivors and there that long-term side effects of treatment would be minimal or non existent. It is therefore the aim of ongoing clinical research to minimize the modalities of treatment and their toxicities without compromising therapeutic efficacy. The European Germ Cell Cancer Consensus Group Conference (EGCCCG) recommends low risk patients that they should be primarily offered active surveillance [4], whereas systemic chemotherapy with 2 cycles PEB represents the treatment of choice for high risk patients.

Active Surveillance

Active surveillance encompasses a treatment strategy with the aim of detecting retroperitoneal or systemic relapses and to treat only those patients with documented metastatic disease thereby decreasing the risk of unnecessary overtreatment. During the initial post-treatment phases of follow-up, regular clinical examinations, monitoring of serum tumour markers and imaging investigations are carried out. The frequency and type of examinations are dependent on the estimated risk of relapse and the time that has elapsed since completion of therapy and should be modified

according to these risks. However, only limited information about the optimal follow-up strategy exists.

When recommending active surveillance for low risk or in certain scenarios also for stage I high risk NSGCT, two major important aspects have to be considered: (1) risk of secondary malignancies due to the repetitive radiation exposure of the imaging studies and (2) more intensive treatment in case of relapse (3 cycles PEB ± post-chemotherapy RPLND) as compared to primary active therapy (1 cycle PEB).

In patients who were on active surveillance for CS I with a low risk NSGCT, the relapse rate was 27–30 % on a long-term follow up of ≥20 years [41, 46, 47]. Relapses occur in the retroperitoneum in 54–78 % of patients, in the lungs in 13–31 %, but are rarely seen in more than one visceral organ. With this approach 78–86 % of patients do not need any further treatment after orchiectomy [41, 43, 46–48]. If a patient under surveillance relapses, the administration of chemotherapy will result in a cure rate close to 100 %. When the surveillance is not suitable, adjuvant chemotherapy with two cycles of BEP is recommended. Nerve sparing retroperitoneal lymph node dissection (RPLND) is a feasible option at high-volume centers [43]. A randomized phase III trial of one cycle BEP versus RPLND in 382 unstratified patients with clinical stage I disease (plus adjuvant chemotherapy for those who were to be pathological stage II after RPLND) suggested a significantly reduced recurrence rate using adjuvant BEP as compared to surgery (1.1 % versus 7.5 %, respectively [43].

Patients with a low risk of relapse (no VI) for follow up should be managed by surveillance according to the EGCCCG recommendation. This requires at least 5 CT scans performed at 0, 3, 12, 18 and 24 months [4]. This follow-up protocol with extensive imaging studies, however, might lead to a high radiation exposure with significant long-term consequences for the patients.

In a recent study, Tarin et al. [49] estimated the risk of secondary cancer associated with CT imaging related radiation during the surveillance of stage I NSGCT patients. In their analysis they evaluated surveillance protocols recommending about 16 CT scans over a 5-year period and they took into consideration a 64-slice CT scanner obtaining images of the abdomen and pelvis with and without inclusion of the chest. For calculation of organ specific radiation doses a standardized, phantom male patient was employed using the Monte Carlo simulation techniques. With a 5-year surveillance protocol the lifetime cancer risk ranged from 1 in 52 (1.9 %) for an 18-year old to 1 in 63 (1.2 %) for a 40-year old patient. If chest CTs were also obtained the risk increases to 1 in 39 (2.6 %) and 1 in 58 (1.6 %), respectively. The relative risk of a secondary malignancy with surveillance compared to a single scan after RPLND is approximately 15.2.

Various studies have been designed to reduce the number of CT scans during the surveillance strategy. Atsü et al [50] analysed the outcome of 140 CS I NSGCT who were followed with only 2 CT scans at postoperative months 6 and 12 with no CT scans thereafter. All patients underwent serial measurements of the serum tumour markers, abdominal ultrasonography and chest X-rays at variable frequency depending on the time intervals between orchidectomy and follow-up. Relapses developed in 32 (24 %) patients and they were detected within a median of 5 (2–23) months.

28 relapses developed during the first year and only 4 relapses occurred during the second year of surveillance. All patients were salvaged by systemic chemotherapy combined with postchemotherapy RPLND in 7 cases. In their study, the presence of any EC in the orchiectomy specimen resulted in a 3.7-fold increase of the relapse risk. In order to reduce the number of CT scans during follow-up, the prospective randomized Medical Research Council Trial (MRC, UK) TE08 was initiated which compared the diagnostic efficacy of 2 versus 5 CT scans during the first 2 years of follow-up to detect the number of patients who relapse with intermediate and poor prognosis disease at relapse [51]. 247 patients and 167 patients were randomized to the two-scan and the five-scan group, respectively. Besides CT scans all patients underwent follow-up assessments at various time intervals: clinical examination, evaluation of serum tumour markers AFP, ß-hCG and LDH as well as chest X-ray With a median follow-up of 40 months, 37 (15 %) relapses had developed in the two-scan and 33 (20 %) relapses occurred in the five-scan group. None of the patients had a poor prognosis disease at the time of relapse, but 2 (0.8 %) patients and 1 (0.6 %) patient had intermediate prognosis disease. There were, however, some other statistically significant differences between the two groups with regard to the indicators of relapse. The proportion of patients in whom elevated tumour markers were the first indicators of relapsing disease was 21.6 and 6.1 % in the two-scan and the five-scan group, respectively. Interestingly, 16 patients had normal markers at time of their orchidectomy but elevated markers at time of relapse underlining the importance of serum tumour markers measurements in every patient with CS I NSGCT who undergoes active surveillance. In the two arms combined a total of 11 patients developed lung metastases with 7 of them being tumour marker negative. The following conclusions can be drawn from this large prospective randomized trial: (a) fewer CT scans reduce the radiation exposure and costs without harming the patient, (b) regular measurements of tumour markers ß-hCG, AFP and LDH together with chest X-ray and two abdominal CT scans are necessary for a surveillance program, and (c) it is unclear if this approach of reduced imaging studies can be applied for high risk patients since only 10 % of the recruited NSGCT demonstrated vascular invasion with a relapse rate of 32 %.

In this scenario, Kakiashvili et al. [52] reported on the largest experience of nonrisk adapted surveillance in 371 patients with clinical stage I NSGCT. With regard to outcome measurements, patients were stratified into two cohorts based on the time of diagnosis with group 1 being diagnosed between 1981 and 1992 and group 2 being diagnosed between 1993 and 2005. The median follow-up is 6.3 years and the median time to relapse was 7.1 months. Presence of vascular invasion and pure embryonal carcinoma were identified as independent predictors of relapse in both cohorts. Forty-two percent and 27.6 % of both cohorts were high risk patients and 54.5 and 49.2 % of those patients relapsed as compared to only 18.7 and 14.2 % in the low risk group. Interestingly, the number of high risk patients decreased over time which might be as a result of improved diagnostic modalities and due to precise definition of high risk disease. This non-risk adapted surveillance strategy resulted in a 5-year disease specific and overall survival rate of 99.2 and 98.2 %, respectively. This approach will spare unnecessary treatment in 50 % of high risk patients and it will thereby reduce the overall treatment burden

in these young men. The retropetitoneum was the relapsing site in 75 % of the patients, in another 10 % of the patients relapse was only diagnosed by a tumour marker rise.

In another retrospective study, 223 clinical stage I NSGCT underwent surveillance independent on their prognostic risk profile [53]. Vascular invasion was present, absent or unknown in 66, 27, and 7 %, respectively. After a median follow-up, 59 (26 %) patients relapsed with good prognosis disease and all were salvaged by systemic chemotherapy, 8 % of the patients needed to undergo postchemotherapy RPLND. Only half of the relapsing patients demonstrated vascular invasion in their orchiectomy specimen. Furthermore, recent studies have questioned the high recurrence rate of close to 50 %. In the retrospective study from Divrik et al [54] the relapse rate was only 35.9 % in CS I NSGCT with only 1 risk factor which was defined as either presence of vascular invasion or percentage of embryonal carcinoma >50 %. Rustin et al [51] reported a 32 % 2-year relapse rate among patients with vascular invasion. Also, Stephenson et al [55] described a progression rate of only 33 % in patients with CS I NSGCT who would undergo surveillance based on their studies on primary nerve sparing RPLND. Based on these findings some authors offered surveillance even to patients with high risk CS I NSGCT with excellent outcome. Al-Thourah et al. [56] retrospectively evaluated 107 CS I patients with predominant embryonal carcinoma who underwent active surveillance or nerve sparing RPLND. With a median follow-up of 4 years 33 % in the surveillance group experienced relapse and were salvaged with chemotherapy and postchemotherapy RPLND. In the RPLND group 18 (56 %) patients had pathological stage I and 14 (44 %) had pathological stage II disease. 4 patients experienced a systemic relapse outside the boundaries of resection and all were cured by chemotherapy. Comparing both therapeutic approaches, 33 % of patients in the surveillance group and 46 % of patients in the RPLND group needed systemic chemotherapy. Patients with both embryonal carcinoma and VI experienced systemic relapse in 59 and 57 % of the cases in the surveillance arm and the RPLND arm, respectively whereas patients with none of the risk factors were cured in 65 % by either treatment. Based on these findings active surveillance might be an option even in high risk CS I NSGCT but it is associated with a high risk of recurrence. Nevertheless, systemic chemotherapy with 2 cycles PEB and potential long-term toxicity could be spared in 33 % of the patients.

Based on the results presented, active surveillance might be used in both, low and high risk clinical stage I NSGCTs. Whereas it represents the standard approach in low risk patients with an expected relapse rate of 12–15 %, high risk patients and physicians who follow the surveillance strategy have to be informed about the 50 % relapse risk and the urgent need to adhere to strict follow-up schedules in order to maintain the high cure rate.

Primary Chemotherapy

A detailed account of chemotherapy is discussed later in Chap. 29.

Retroperitoneal Lymph Node Dissection (RPLND)

According to the European Germ Cell Cancer Consensus Group (EGCCCG), patients unwilling to undergo a surveillance strategy or adjuvant chemotherapy, nerve sparing lymphadenectomy (NS-RPLND) may be performed [4]. Primary RPLND is still widely in practice in the United States for highrisk patients although less so in Canada and Europe. Regional surgical therapy (in this case RPLND) could be justified because the retroperitoneum is the usual site of relapse in more than 80 % of patients with CS I NSGCT [57–59]. RPLND provides accurate staging information regarding retroperitoneal lymph node status. With proper selection of patients for RPLND, two-thirds have a low burden pathologic stage (pS) II disease, and almost 90 % will be cured by surgery alone [57–59]. The rationale for primary nerve sparing RPLND for patients with CS I NSGCT is based on the evidence that it represents the primary metastatic site in more than 80 % of patients and that it is also the most frequently involved site of chemoresistant mature teratoma which holds the potential of malignant transformation and late relapse if left unresected [60–62] Virtually all patients who relapse after primary RPLND are chemotherapy naive and eventually cured by usually 3 cycles of cisplatin-based chemotherapy. Only a minority of CS I NSGCT harbours occult systemic metastatic disease and might be better managed by inductive systemic chemotherapy. RPLND simplifies follow-up for the patient. Subsequent retroperitoneal recurrence is rare, and abdominal imaging can be restricted to one baseline CT a few months after surgery.

With the introduction of nerve-spearing technique (Fig. 28.4) along with various modified templates, antegrade ejaculation rates 90–100 % have been reported, with significantly reduced morbidity and virtually unknown mortality (60–62).

However, critics of nerve sparing RPLND argue that up to 75 % of patients with CS I NSGCT managed by primary RPLND will undergo unnecessary invasive procedure. However, this only holds true if a non-risk adapted strategy is chosen in every single CS I patient. Recently, patients' selection factors on outcome after primary RPLND have been reported and the application of these parameters might allow a risk-adapted indication RPLND [55]. The authors analysed a cohort of 453 patients with CS I to IIB NSGCT who underwent RPLND between 1989 and 2002. Of those, 308 (68 %) and 122 (27 %) presented with CS I and CS IIA disease, respectively. Interestingly the frequency of clinical stage I patients increased significantly over time from 65 to 76 % ($p=0.03$) in the years 1989–1998 and 1999–2002, respectively, which might be the result of improved imaging studies. Whereas the frequency of mature teratoma remained fairly constant in the two time periods (22 % vs 21 %) the number of patients with low volume disease (pN1) increased significantly from 40 to 64 % ($p=0.01$) so that adjuvant chemotherapy could be spared in more patients. 217 (70 %) patients of the 308 CS I NSGCTs demonstrated true pathological stage I disease after RPLND. The 4-year progression-free probability in this cohort was 97 %; the risk of systemic progression decreased from 14 % before 1999 to 1.3 % after 1999 suggesting an improved risk stratification for systemic disease based on the selection criteria developed after critical analysis of the first patient cohort being treated between 1989 and 1999.

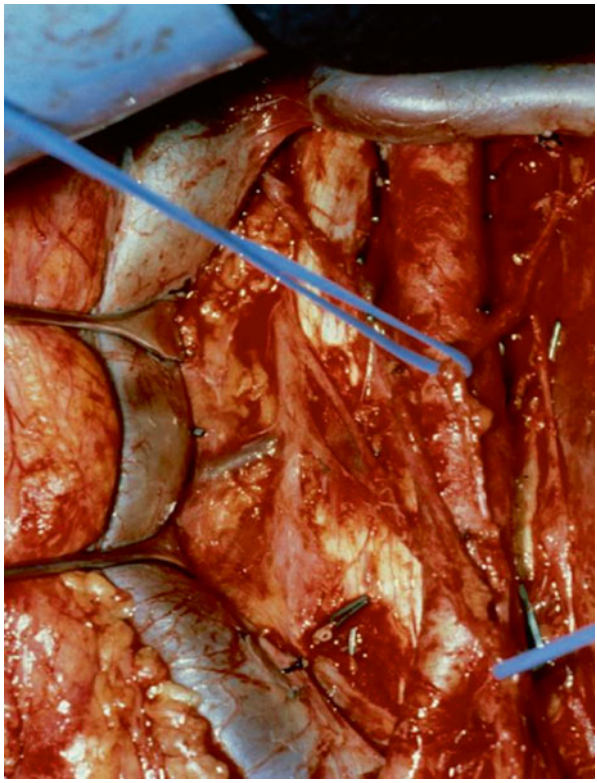

Fig. 28.4 Nerve-sparing RPLND in a patient with Clinical Stage I NSGCT

For CS I NSGCT elevated post-orchiectomy tumour markers appear to be associated with a significantly increased risk of progression, which was as high as 72 %. The question, however, remains if patients with embryonal carcinoma predominance and/or lymphovascular invasion should undergo RPLND or primary chemotherapy due to an anticipated high risk of systemic relapse following locoregional surgical treatment. Stephenson et al [57] analysed the outcome of 267 patients with CS I and CS IIA NSGCTs with one or two of the aforementioned risk factors who underwent nsRPLND. ECA and VI were present in 31 % of the patients and ECA without VI was identified in 10 % whereas 58 % demonstrated VI without ECA. 129 (66 %) patients with CS I and 26 (37 %) with CS IIA had pathological stage I disease. 112 patients demonstrated lymph node metastases and 60 (54 %9 and 52 (46 %) demonstrated pN1 and pN2 disease, respectively. The presence of both risk factors was associate with a significantly higher risk of retroperitoneal metastases (54 % versus 37 %, $p=0.009$), however the risk to harbour pN2 disease was not significantly increased. Patients with pathological stage I were followed actively and did not receive adjuvant chemotherapy whereas 22 and 83 % of patients with pN1 and pN2 disease received adjuvant cytotoxic treatment with 2 cycles, respectively. All patients remained disease-free during the complete follow-up period. 16 % of pathological stage II patients had teratoma in the retroperitoneum which

would not have been eliminated by primary chemotherapy. 211 patients did not receive adjuvant chemotherapy and 26 (12.3 %) patients experienced relapse with 4 recurrences developing in the retroperitoneum due to a modified template resection. The 5-year progression-free survival probability including a full bilateral template would be 90 %. All relapsing patients could be salvage by 4 cycles EP chemotherapy. Summarizing the data of the total cohort of 267 patients, 80 (29.9 %) CS I/IIA high risk patients received either adjuvant or salvage chemotherapy. If only high risk CS I NSGCT are considered an estimated 89 % would have been free of progression 5 years after chemotherapy.

In a similar approach, Nicolai et al [63] reviewed their experience of primary RPLND with no adjuvant chemotherapy in a cohort of 322 consecutive CS I NSGCT who were followed for a median time of 17 years. 262 (81.4 %) patients were staged as pathological stage I whereas 41 (12.7 %) and 19 (5.9 %) patients demonstrated pathological stage IIA and IIB, respectively. 50 patients (15.5 %) developed a recurrence with 96 % occurring the first 2 years of follow-up. The majority of relapses (n = 44) were located outside the retroperitoneum, whereas 6 and 4 relapses developed in the retroperitoneum and in the contralateral testis. 271 (84.1 %) patients of the total cohort did not experience relapsing disease including 68.3 % of the patients with pathological stage IIA/B. Based on multivariate analysis, presence of vascular invasion, percentage of embryonal carcinoma >50 %, presence of lymph node metastases increased the probability of relapses by the factor 2.7, 3.5 and 2.9, respectively.

Rassweiler et al [64] assessed the role of laparoscopic RPLND in the management of CS I NSGCT reviewing the literature comprising a total of more than 800 patients. Whereas no significant differences with regard to complications could be observed when compared to open RPLND, it became evident that more than 90 % of patients with positive lymph nodes underwent adjuvant chemotherapy reducing laparoscopic RPLND to just a staging surgical procedure. However, the laparoscopic approach is feasible is highly specialized centres, the curative potential of this approach still has to be evaluated.

Although rare with an incidence of only 2–5 %, clinical stage I mature teratoma of the testis harbours a risk of about 16 % [65, 66] for retroperitoneal lymph node metastases. The majority of these patients would demonstrate teratomatous elements in the retroperitoneal lymph node metastases, so that nerve sparing RPLND represents the treatment of choice.

When discussing nerve-sparing RPLND as primary treatment option in patients with CS I NSGCT, potential surgery-related complications have to be considered. Quite recently, the German Testicular Cancer Study Group evaluated the outcome of 239 CS I NSGCT who underwent nerve sparing RPLND [67]. Minor and major complications were observed in 14.2 % and in 5.4 %, respectively. Antegrade ejaculation could be preserved in 93.3 % of the patients and the frequency of ejaculation correlated significantly with the experience of the single surgeon. 14 (.8 %) patients developed relapses with the majority (n = 11) being located in the extraperitoneal areas.

Summary of Treatment Options for Clinical Stage I NSGCT

According to the current guidelines, active surveillance, primary chemotherapy and nerve sparing RPLND represent 3 treatment options with the same high cure rate of about 100 % but significantly with different long-term complications. As demonstrated, active surveillance can be performed in low risk and in high risk NSGCT with an anticipated relapse rate of about 15 and 50 %. The majority of patients will relapse with good and intermediate prognosis tumours which have to be treated with 3 to 4 cycles chemotherapy. About 25–30 % of these patients will have to undergo postchemotherapy RPLND for residual masses. Primary chemotherapy with 1–2 cycles PEB is a therapeutic option for high risk clinical stage I NSGCT associated with a recurrence rate of only 2–3 % and a minimal acute and long-term toxicity rate. Nerve sparing RPLND, if performed properly, will cure about 85 % of all high risk patients with clinical stage I NSGCT without the need for chemotherapy.

Although armchair calculations of the odds of cure and toxicity associated with the various treatment options can be performed, recommendations about the most optimal therapy in clinical stage I NSGCT remain controversial. There seems to be a consensus that active surveillance is the treatment strategy of choice for CS I low risk patients. However, there is no clear cut recommendation in high risk patients. Each treatment has its own advantages and disadvantages which have to be discussed thoroughly with the patient. If, however, the positive results of 1 cycle of PEB can be validated, it will become the standard cytotoxic approach for clinical stage I NSGCT.

Management of Clinical Stage II GCTs

IIA/IIB Seminomas (SGCT)

In many centres radiotherapy is the standard treatment. This is discussed in Chap. 30. Overall survival rates are almost 100 % [67].

Clinical Stage IIA NSGCT

The cure rate for CS IIA and IIB non-seminoma is close to 98 %. The vast majority of patients with marker elevations of AFP, HCG and/or LDH in CS IIA/B are treated according to the algorithms for patients with advanced disease, according to IGCCCG recommendations [13].

Only a few patients without marker elevations but with retroperitoneal lymph nodes 1–2 cm, suspected to be CS IIA, represent a particular problem. Some of these

patients will have benign lymph node enlargement. Some of them, however, will have teratoma, pure embryonal carcinoma or mixed tumours. Therefore, patients with pure embryonal carcinoma in the primary should undergo primary chemotherapy immediately or after a period of surveillance [67–69]. In patients with teratoma or mixed tumours in the primary two options can be considered: staging RPLND or surveillance. With RPLND the pathological stage can be verified immediately; if surveillance is chosen, one follow up after 6 weeks is indicated to document whether the lesion grows, remains stable or shrinks. A shrinking lesion is likely to be not of malignant origin and should be further observed. A stable or growing lesion indicates either teratoma or undifferentiated malignant tumour. If the lesion grows without corresponding increase of the tumour markers AFP or HCG resection of the lesion should be performed by an experienced surgeon because of suspected teratoma. Patients with a growing lesion and an concommitant increase of the tumour markers AFP or HCG should not be operated, but require chemotherapy with BEP according to the treatment algorithm for patients with metastatic disease and IGCCCG recommendations [13]. There is no proven role for PET-scans in this situation.

When RPLND is performed this should be done using a nerve-sparing technique ([59–61, Fig. 28.5) wherever possible. However, depending on the experience of the surgeon, RPLND may result in retrograde ejaculation in 5–32 % of patients despite a nerve-sparing approach [59–61, 67). Other morbidity related to surgery may occur in up to 10 % of patients. Surgical exploration at the time of RPLND will reveal a

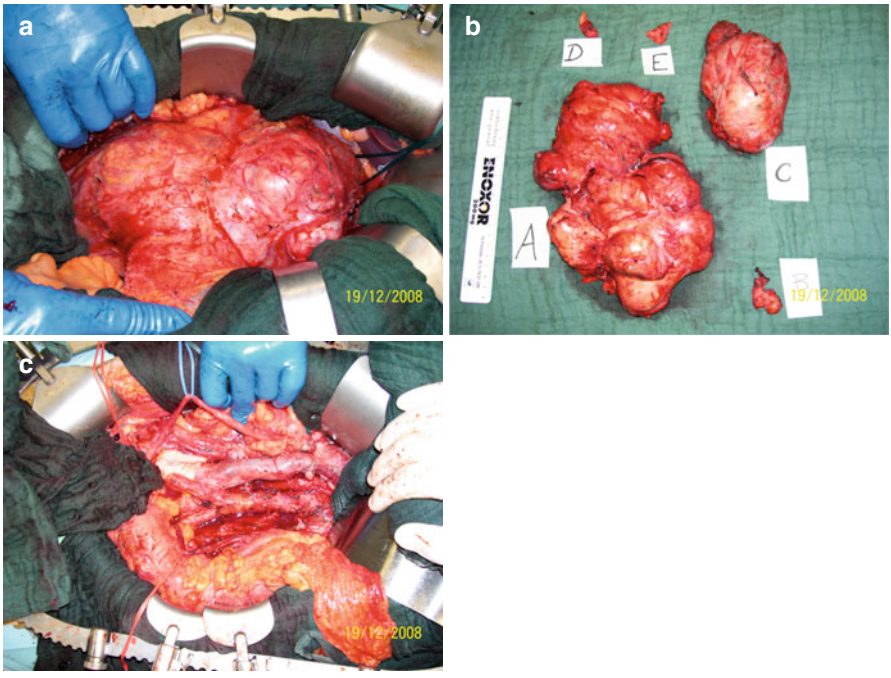

Fig. 28.5 (**a**) Large retroperitoneal mass resembling a growing teratoma syndrome. (**b**) Resected specimens. (**c**) Intraoperative site after complete resection of the mass. *A–D* residual retroperitoneal lymph node metastases

pathologic stage (PS) I in 12–13 % of patients, the remaining 87–88 % of patients will have PS IIA/B. In the PS IIA/B patients, further options after PRLND are surveillance or adjuvant chemotherapy [4, 70–77]. Surveillance after RPLND has a risk of relapse in about 30–50 % patients, who will then require three to four cycles of BEP. Relapses occur almost exclusively outside the retroperitoneum. Adjuvant chemotherapy in all PS IIA/B patients after RPLND reduces this risk of recurrence to about 0–7 %. Yet, adjuvant chemotherapy represents an overtreatment in 50–70 % of radically operated PS IIA/B patients with the resulting treatment-related toxicity and possible late sequelae.

Postchemo – RPLND (PC-RPLND)

Surgical resection of postchemotherapy residual retroperitoneal lymph node masses or residual visceral metastatic deposits represents an integral part of the multimodality treatment for patients with advanced testicular cancer [78]. The rationale for PC-RPLND is to remove persistent disease that may contain mature teratoma in approximately 30–40 % and vital cancer in about 10–20 % of the patients. In NSGCT, PC-RPLND is only indicated in men with normalized or plateauing serum tumour markers **and** residual disease.

PC-RPLND in Small Residual Lesions

In patients with residual lesions <1 cm, the role of PC-RPLND is discussed controversially based on the finding that up to 20 and 8 % of patients will harbour mature teratoma and vital cancer. However, this approach has been challenged by recent retrospective studies from 3 groups. Kollmannsberger et al [79] analysed 276 patients who underwent systemic chemotherapy for metastatic NSGCT. 161 (58.3 %) achieved a complete remission (residual lesions <1 cm) and all patients were followed without surgical resection. After a mean follow-up of 40 (2–128) months relapses were observed in 6 % and none of them died after appropriate salvage therapy. 94 % of the patients belonged to the IGCCCG good prognosis group. Ehrlich et al [81], [80] evaluated 141 patients who were observed after systemic chemotherapy and residual lesions <1 cm. After a mean follow-up of up to 15 years 9 % of the patients relapsed and 3 % of the patients died due to testis cancer. IGCCCG risk group classification predicted the outcome best: recurrence-free survival and cancer specific survival were 95 and 99 %, respectively in men who belonged to the good risk group whereas it dropped to 91 and 73 % in the intermediate and poor risk group. The German Testicular Cancer Study Group (GTCSG) analysed the outcome of 392 patients who underwent PC-RPLND for residual lesions of any size (94). 9.4 and 21.8 % of the men with residual lesions <1 cm harboured vital cancer and mature teratoma, respectively. These numbers increased to 21 and 25 % in patients with residual lesions of 1–1.5 cm and to 36 and 42 % in men with lesions larger than 1.5 cm.

Considerations for the Most Appropriate Surgical Strategy

PC-RPLND requires detailed knowledge of the retroperitoneal anatomy, familiarity with surgical techniques of the vascular and intestinal structures as well as profound experience in the management of patients with testicular cancer. Depending on the size and the extent of the residual lesions, the surgeon has to modify his surgical approach to the retroperitoneal space. An abdominal midline incision can be used in most patients with unilateral and infrahilar disease, whereas a Chevron incision might be more suitable in those men with bilateral and suprahilar disease. Retrocrural disease is best approached by a thoracoabdominal incision.

In patients with residual masses at multiples sites, an individual decision should be made regarding the number and extension of resections based on the risk of relapse and on quality-of-life issues [82]. Resection of residual tumours outside the abdomen or lung should also be considered on an individual basis, since discordant histology is found in 35–50 % of patients. Pulmonary or mediastinal residual masses harbour necrosis/fibrosis in 90 % if the retroperitoneal masses did not contain mature teratoma or viable cancer [83]. Management for liver lesions at post-chemotherapy retroperitoneal lymph node dissection must be individualized. Observation may be warranted for liver lesions requiring complicated hepatic surgery regardless of retroperitoneal pathology [84]. The concordance between retroperitoneal and liver histology was 49 % overall, including 94 % for necrosis, 26 % for teratoma and 36 % for cancer. Liver necrosis alone was found in 94, 70 and 50 % of patients with retroperitoneal necrosis, teratoma and cancer, respectively.

Special Preoperative Imaging Studies

Imaging studies should allow an adequate assessment of the large retroperitoneal vascular structures since involvement of the inferior vena cava (IVC) and the abdominal aorta can be expected in about 6–10 % and 2 %, respectively [82, 85]. Magnetic resonance imaging represents the most appropriate imaging technique to predict infiltrations of the vessel wall and the presence of an intracaval tumor thrombus. Infiltrations of the IVC wall or IVC thrombi should be completely resected since about two thirds of the patients harbour vital cancer or mature teratoma in the infiltrating masses. The necessity for aortic replacement is rare and usually accompanied by large residual masses involving additional adjacent structures and making additional surgical procedures necessary.

Timing of PC – RPLND

PC-RPLND should be initiated within 6–12 weeks after chemotherapy. Hendry et al. retrospectively analysed the outcome of 443 patients undergoing either immediate or elective PC-RPLND once progression of the residual masses was

demonstrated [86]. A significant benefit with regard to progression-free survival (83 % versus 62 %, p=0.001) and cancer-specific survival (89 % versus 56 %, p=0.001) was identified for the immediate surgical approach.

Extent of PC-RPLND

Early retrospective and single-centre studies indicate that a modified PC-RPLND might be a safe approach in men with limited retroperitoneal disease and right/left primary tumours with no evidence of teratoma or viable cancer on frozen section analysis. (Fig. 28.6) However, application of the modified unilateral template to

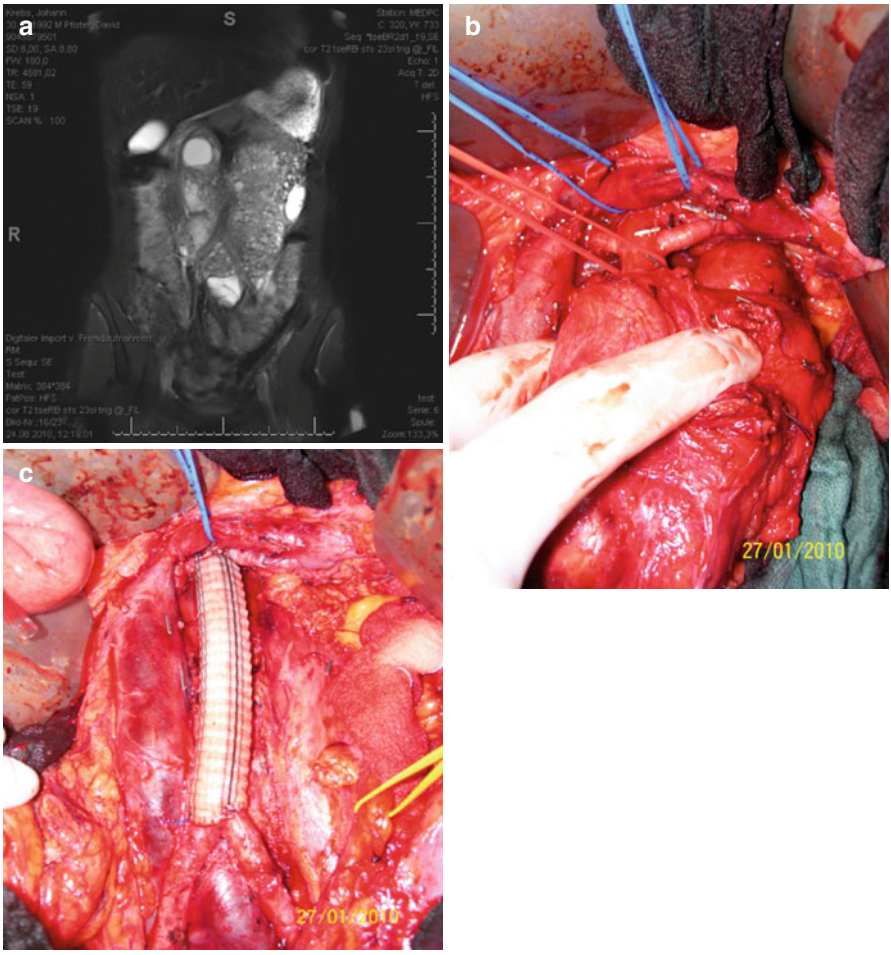

Fig. 28.6 (**a**) Large retroperitoneal mass encasing the abdominal aorta. (**b**) Complete mobilisation of the mass after careful preparation of the abdominal aorta, renal arteries and renal veins. (**c**) Complete resection of the mass and the abdominal aorta, and placement of an aortic prosthesis

PC-RPLND still is discussed controversially based on the 3–8 % incidence of mature teratoma or viable cancer in the contralateral landing zone. 2 experienced groups reported their experience on modified unilateral template PC-RPLND. The group at Indiana University has performed a limited PC-RPLND in 100 men with low-volume retroperitoneal disease (<5 cm) confined to the primary landing zone of the primary tumour [87]. After a mean follow-up of 32 months only 4 patients relapsed, all outside the boundaries of the modified and even of the bilateral template. The 2-year and 5-year disease free survival was 95 %.

The GTCSG assessed the oncological necessity of full bilateral retroperitoneal PC-RPLND in 152 patients [88]. If patients exhibited a well defined lesion ≤2 cm modified PC-RPLND was performed, lesions >5 cm were always treated by a full bilateral PC-RPLND. Lesions 2–5 cm in diameter were approached dependent on the site of the primary and the location of the mass: interaortacaval residuals were always approached with a full bilateral PC-RPLND, whereas as paraaortic and paracaval lesions were treated by a modified PC-RPLND if the metastatic site corresponded to site of the primary. There was a significant difference with regard to postoperative morbidity with more complications in patients undergoing extended surgery ($p < 0.001$). Antegrade ejaculation was preserved in 85 % of patients undergoing modified PC-RPLND whereas it could not preserved in 75 % of the cases undergoing full bilateral PC-RPLND. 8 (5.2 %) recurrences were observed after a mean follow-up of 39 (6–105) months: 1 in-field relapse following modified PC-RPLND and 7 recurrences even outside the boundaries of full bilateral PC-RPLND. 2-year disease free survival was 78.6 and 92.8 % for bilateral and modified PC-RPLND, respectively.

PC-RPLND After Salvage Chemotherapy or Previous Retroperitoneal Surgery

Patients who have undergone salvage chemotherapy, prior primary or PC-RPLND, those judged to be unresectable and those with disease progression prior to retroperitoneal surgery are at high risk for both a poor therapeutic outcome and an increased frequency of surgery – associated complications. The presence of anyone of these poor prognostic parameters increases the risk of relapse from 12 to 45 %.

Repeat RPLND itself represents a poor risk factor associated with a significantly lower 5-year survival rate of only 55 % as compared to 86 % in the group of patients undergoing adequate PC-RPLND [89–91]. Whereas the cure rate for those with mature teratoma only approaches 100 %, it decreases significantly to 44 % and 20 % in the presence of viable cancer and teratoma with malignant transformation, respectively.

Desperation PC-RPLND

According to the data of various groups, the 5-year overall survival is 54–67 % so that surgery might be indicated in well selected subset cohort of patients [92, 93]. Increasing preoperative ß-hCG, elevated AFP, redo RPLND and incomplete

resection have been identified as negative risk factors associated with a poor survival. Despite elevated serum tumour markers about 45–50 % of all patients harbour mature teratoma or necrosis/fibrosis in the surgical specimen resulting in a high cure rate. If patients undergo desperation surgery all residual masses should be completely resected; it will be necessary to resect adjuvant visceral and vascular structures in 25–30 % of the cases.

Growing Teratoma Syndrome

The term growing teratoma syndrome (GTS) was coined by Logothetis et al. [95], [94] to describe a rare entity among patients with NSGCTs, characterized by enlarging metastatic masses despite appropriate systemic chemotherapy and normalized serum markers. Histology of those resected lesions revealed benign mature teratomatous elements with no components of viable germ cell tumour (Fig. 28.5).

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Chapter 29
Chemotherapy for Testicular Cancer

Jonathan Shamash

Introduction

Cytotoxic chemotherapy has been the mainstay in the management of metastatic germ cell tumors. These have long been known to be chemo-sensitive, with single agents able to produce many transient responses and the occasional cures. The development of combination chemotherapy lifted the response and subsequent cure rates. Combining vinblastine and bleomycin lead to a rise in the cure rate from 5 to 25 %. However, it was the combination of cisplatin with vinblastine and bleomycin (PVB) by Einhorn in 1977 that lead to a dramatic improvement in the cure rate to over 80 % [1]. The observation by Peckham that etoposide had activity in relapsed germ cell tumours lead to the development of BEP (cisplatin, etoposide and bleomycin), a regimen which appeared better tolerated than PVB [2]. In 1985, the randomised trial of this against PVB confirmed the superiority of this regimen in more advanced metastatic disease and has led to this combination becoming the reference regimen to which other combinations have been compared [3]. Over the years sequential randomised studies have looked at the doses of the individual drugs and it has been shown that reducing the dose of etoposide and bleomycin leads to inferior results [4], as does the omission of bleomycin [5], although a further cycle of cisplatin and etoposide may compensate for this if etoposide is given at a dose of 500 mg/m^2 [6]. It has become clear that maintenance chemotherapy beyond the initial four cycles has proved unnecessary as has giving more than four cycles [7]. The substitution of carboplatin for cisplatin in non-seminomatous germ cell tumours has led to poorer overall survival by around 5 % and it is no longer a drug of first choice [8].

J. Shamash, MD, FRCP
Medical Oncology, St. Bartholomew's Hospital, London, UK
e-mail: jonathan@jshamash.demon.co.uk

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Efforts have concentrated in several main areas- defining the role of adjuvant therapy in the management of stage 1 disease, stratifying untreated patients into risk groups with similar outcomes so that studies may be performed on more homogenous populations and developing salvage strategies for those in whom initial chemotherapy fails. This has allowed treatment duration to be shortened in those patients with good prognosis metastatic disease and allowed studies of dose intensification to be performed in those with higher risk disease. It has become clear that seminomas are inherently more chemo and radiosensitive than their non- seminoma counterparts allowing differing treatment approaches to be used in this patient subgroup.

The long-term side effects of combination chemotherapy are becoming better appreciated – the increased risk of vascular disease, long term neuropathy, and the overall metabolic effects are all being increasingly scrutinised and may well lead to further attempts at refining current therapy [9, 10].

Cytotoxic Drugs Used in the Treatment of Testicular Germ Cell Tumors

Combination chemotherapy normally requires the combining of drugs with different side effect profiles in the hope that there will be a synergistic or at least additive effect against the tumor. Normally drugs are given in repeating cycles of 2–4 weeks. In many cancers it is difficult to show that delay or dose reduction of drugs carries a worse outcome, however, this is not the case for germ cell tumors where the aim is to give dugs at full dose on time where possible. If delays occur these should be minimised. Often we do not wait for full bone marrow recovery before starting the next cycle.

Platinum Complexes

These drugs are based on the metal platinum. The simplest, – cisplatin is the most efficacious and toxic of the series. Kidney and nerve damage may be dose limiting; nausea and vomiting are severe but can be reduced by appropriate anti-emetics. Ototoxicity is common and usually irreversible – the effect on bone marrow is relatively mild. There are two sister drugs- carboplatin and oxaliplatin. Carboplatin is more myelosuppressive with reduced nausea, neuro and nephrotoxicity. It is less active and is normally used where cisplatin is contra-indicated or in high dose chemotherapy where myelosuppression is less important. Oxaliplatin- is much less commonly used but there is increasing evidence for its efficacy in relapsed patients – resistance to cisplatin does not necessarily overlap. It causes peripheral sensory neuropathy but is not nephrotoxic though moderately emetogenic.

Etoposide is a topoisomerase 2 inhibitor and its main side effects include myelosuppression, sore mouth and alopecia. The inclusion of etoposide in combination chemotherapy has been responsible for improving survival –particularly in patients with more advanced disease. Etoposide is normally combined with cisplatin and bleomycin (BEP) [3] or cisplatin and ifosfamide (VIP) [11]. It is often used as part of high dose chemotherapy regimens.

Bleomycin is a polypeptide which causes breaks in DNA strands. It causes little myelosuppression but can cause pneumonitis which can progress to pulmonary fibrosis – this may be fatal. This side effect is more common in patients with pre-existing lung damage (e.g due to smoking) and in the presence of renal impairment. In combination with cisplatin and etoposide it forms the regimen BEP. It is usually given weekly regardless of blood count at that time. A maximum dose of 300,000 units has been suggested to reduce the risk of lung damage. If it is dropped from the combination then cure rates fall- this may be offset by giving a 4th course of cisplatin and etoposide.

Ifosfamide is an alkylating drug which produces myelosuppression. It also causes hemorrhagic cystitis; this can be reduced markedly by the addition of mesna (2-mercaptoethanesulfonate Na), which combines with toxic metabolites rendering them harmless. It can cause a reversible encephalopathy and is emetogenic. Ifosfamide causes renal tubular damage. The addition of ifosfamide to cisplatin forms the backbone of salvage strategies; in combination with etoposide it can replace bleomycin as the third drug with cisplatin. In high dose chemotherapy, combination with carboplatin and etoposide is possible but as significant dose intensification is not possible, the sister drug cyclophosphamide is more often used [12] – the triple drug combination may have a high response rate but toxicity is greater than with carboplatin and etoposide alone. Ifosfamide and cyclophosphamide both tend to cause gonadal toxicity, which tends to lead to irreversible oligospermia and azoospermia in the case of cyclophosphamide.

Thiotepa is an alternative alkylating drug which is often used in high dose strategies; it has been used successfully in combination with carboplatin and cyclophosphamide, etoposide or topotecan. Its limited ability to cause mucositis as well as its good penetration of the blood-brain barrier and its safety in renal impairment makes it an attractive choice in the high dose setting [13–15].

Vinblastine (and vincristine) is used in relapse cases with cisplatin and ifosfamide. It causes metaphase arrest by binding to the microtubules and as such in the doses it is used it is neurotoxic. The sister drug vincristine has been used in some salvage approaches; however, it is more neurotoxic but causes less myelosupression [16].

Paclitaxel is a microtubular binding drug that causes accumulation of microtubule in cells. It is most commonly is used with cisplatin and ifosfamide in salvage therapy (TIP- paclitaxel, ifosfamide and cisplatin). On its own its response rate is poor, only 11 %, but in combination it is quite effective. Efficacy may be enhanced by giving it weekly [17].

Methotrexate is a dihydrofolate reductase inhibitor with a rapid onset of action. It crosses the blood-brain barrier making it potentially useful in patients

with brain metastases. Large doses than normal may be given followed by folinic acid rescue 24–32 h later, which limits mucositis and myelosuppression. It has been used in several regimens in combination both in the untreated setting and on relapse [18].

Gemcitabine is a deoxcycitidine analogue is well tolerated with schedule dependent myelosuppression as its main dose limiting side effect. It has a response rate of 15 % in heavily pretreated patients and its activity is therefore similar to paclitaxel [19]. The combination with paclitaxel leads to an improved response rate of 21 % [20]. Interestingly, if used post high dose chemotherapy in patients who have not received these agents prior to high dose chemotherapy a 31 % response rate is seen – 12 % complete response (CR) – two thirds of these were durable [21]. Similar responses are seen when gemcitabine is combined with oxaliplatin [22].

Topotecan and irinotecan are two topoisomerase-1 inhibitors that have shown little activity as single agents; however, in combination synergy has been seen when the drugs have been combined with platinum complexes with responses in the 40 % range [23]. Irinotecan causes dose-limiting diarrhoea and topotecan dose-limiting myelosuppression. Topotecan, like methotrexate crosses the blood-brain barrier.

Actinomycin-D is a polypeptide antibiotic and when used as a single agent it has a curative potential. It is used in a number of regimens in the untreated and relapse setting – it causes mucositis, liver function abnormalities and myelosuppression. In combination with methotrexate and etoposide it has shown non-cross resistance with cisplatin [24].

Administration of Chemotherapy

Most chemotherapy regimens are given on a cyclical basis with the treatment repeating every 3 weeks. The drugs are invariably given intravenously as even in those where oral formulations are available variable absorption remains a problem. Often white cell growth factors (filgrastim, lenograstim) are used to ensure neutrophil recovery and avoid treatment delay as there is evidence that significant dose delay or dose reductions lead to inferior outcomes. The administration of prophylactic antibiotics e.g. levofloxacin, a 5-aminoquinolone derivative, has been shown to reduce the frequency of neutropenic sepsis [25]. Some drugs are given more frequently because they are less myelosuppresive- e.g. cisplatin, bleomycin and vincristine. Most combination regimens used in germ cell tumors are very myelosuppressive and carry a higher risk of infection. Whilst keeping such patients in hospital has not lead to any reduction in mortality, they still need to be closely monitored. Advances in supportive care have lessened some feared side effects of chemotherapy; in particular, nausea and vomiting and the shortening of treatments has reduced morbidity. Tumor markers should be measured at least on weekly basis during chemotherapy to monitor for response, a sequential rise in markers beyond the first 3 weeks of treatment may well indicate early relapse.

Stage 1 Disease

As awareness of testicular cancer has increased there has been an increasing proportion of patients presenting with stage 1 disease and indeed the size of the tumors being diagnosed has been falling over the last 20 years [26]. Management of this group has therefore become more important.

Seminoma

The main treatment options consist of surveillance, adjuvant chemotherapy and adjuvant radiotherapy. Surveillance has been getting wider acceptance. It requires patients to come to regular appointments, the follow up schedule recommendations have varied. Relapse can occur later in patients offered surveillance and follow up for 10 years is recommended. Patients can be stratified by – tumour size and the presence of rete testis involvement. Tumors less than 40 mm in diameter and lacking this have the lowest risk of recurrence – 12 %, the presence of either raises it to around 25 % and the presence of both to 31 % [27]. A risk- adapted strategy may be followed by reserving adjuvant therapy for those with the highest risk. This reduces the number of men requiring adjuvant treatment but has involved giving those deemed at highest risk two courses of carboplatin [28]. Patient willingness to attend for follow up appointments is important.

Carboplatin has increasingly become the preferred adjuvant option – recurrence rates in an unselected stage 1 population fall to 4 %. Late relapses do not seem to be an issue. The reduction in the development of contralateral tumours from 2 to 0.5 % is a secondary benefit although it is unlikely that intraepithelial germ cell neoplasia can be prevented [29]. As with all adjuvant strategies many who receive treatment will not need it, although the long-term safety profile of carboplatin seems reassuring. Optimal dosing of carboplatin should use a formally measured estimation of glomerular filtration using ethylenediamine tetra acetic acid (EDTA) rather than using a formula based on serum creatinine. As the relapse rate is much lower in this patient group – follow up may be less frequent with a consequent reduction in the number of follow up CT scans.

Non-seminoma

As in seminoma the choice is between surveillance and adjuvant therapy. Risk stratification is important in making these decisions. The presence of embryonal carcinoma and vascular invasion raises the risk of recurrence to greater than 40 %. The absence of these features means the risk is less than 20 %. Adjuvant chemotherapy is favoured in Europe with two cycles of BEP (etoposide 360 mg/m^2) being standard with a reduction in risk of recurrence down to 2 % [30]. This has been recently

challenged with the description of 1 cycle of BEP (etoposide 500 mg/m^2) achieving reduction in an unselected population (41 % having vascular invasion) down to 1 % [31]. Clearly, if this is accepted, then the toxicity and health economic assessment will be more favourable to this approach. It remains unclear how best to treat patients who relapse after this single treatment – in particular whether retreatment with further cycles of BEP would be appropriate. The third alternative strategy is to perform an elective nerve sparing retroperitoneal lymph node dissection – the rate of relapse seems higher– and patients who have microscopic stage-2 disease are often given two cycles of BEP.

Metastatic Disease- Prognostic Assessment

In the last 20 years, a lot of effort has gone into developing a method of assessing prognosis of patients with germ cell tumors. It has long been recognised that patients with high volumes of disease tend to do less well than those with smaller volumes; in addition the sites of metastases seem to be important, in particular the presence of lung, brain and bone metastases seem to carry a poorer prognosis. The realisation that high tumor markers are associated with slower decline compared to that predicted by half-life has also been developed into prognostic models. The most widely accepted of these is that developed by the International Collaborative Germ Cell Cancer Group (IGCCCG) who developed a validated model, which split patients into 3 groups: good, intermediate and poor prognosis [32]. The groupings depended on whether the primary was a seminoma or non-seminoma, the level of the 3 tumor markers namely, lactate dehydrogenase (LDH), alphafetoprotein (AFP) and human chorionic gonadotropin (hCG), the sites of disease – nodal or pulmonary metastases *vs* non-pulmonary visceral metastases (most commonly liver, brain or bone but also any other site e.g. kidney). The *good prognosis group* included those with low tumor markers and no non-pulmonary visceral metastases. The *intermediate group* included those with higher tumor markers but no adverse anatomical sites (non-seminoma) or seminomas with non- pulmonary visceral metastases. The *poor risk group* included all non-seminoma cases with very high markers, or adverse anatomical sites or those with mediastinal primaries. In the good prognosis group 92 % could expect to be cured with current first line therapy, in the intermediate group this fell to 75–80 % and in the poor group this fell to 42 %. More recent data has suggested that the outcome for the poor prognosis group has improved with time with many randomised studies seeing cure rates in the region of 60 %. A summary is shown in Table 28.3.

IGCCCG- Good Prognosis Disease

A series of randomised controlled trials has defined the current standard regimen to be 3 cycles of bleomycin, etoposide and cisplatin (BEP). The doses used have been the subject of various studies. Cisplatin has been given at 100 mg/m^2 and increasing

the dose has not been shown to improve outcome. The dose of etoposide at 500 mg/m^2 has been shown to be optimum and reducing it to 360 mg/m^2, the previous standard dose in many European versions of this regimen, has been associated with a reduction in overall survival that cannot be compensated by the addition of a 4th cycle [4]. Likewise the reduction in bleomycin from 90,000 units per cycle also has been accompanied by poorer survival [5]. It would appear that a similar survival rate with the omission of bleomycin whilst maintaining the doses of the other two agents might be achieved by giving a 4th cycle [6]. Cisplatin and etoposide doses may be given over 3–5 days whilst 3 days regime is more convenient if a 4th cycle of cisplatin is given as there is evidence that ototoxicity is lessened by giving the cisplatin over 5 days although efficacy remains unchanged [33].

If bleomycin is contra-indicated, either because of poor existing lung function, or because lung function needs to be maintained, (for example in a sportsmen) then the alternative to four courses of cisplatin and etoposide would be to replace bleomycin with ifosfamide. This combination has shown to produce similar results in patients with more advanced disease [11].

IGCCCG – Intermediate Prognosis Disease

Currently the standard treatment consists of 4 cycles of BEP. The substitution of ifosfamide 6 g/m^2 over 5 days for bleomycin (etopside, ifosfamide and cisplatin-VIP) is a reasonable alternative, for the reasons described above. Ifosfamide is associated with greater marrow suppression and reduced fertility although at the doses used – the effect on fertility seems less than previously thought. A recent study adding paclitaxel to BEP (T-BEP) has been reported and has shown an improvement in progression-free survival in eligible patients which was statistically significant (82.7 vs 70.1 %, $p = 0.03$); the study, however, did not recruit the intended number of patients and was closed early because of this, however this is the first time such an improvement has been noted in a multicenter trial in this group of patients over standard BEP [34].

IGCCCG- Poor Prognosis Disease

In this group the standard chemotherapy is four cycles of BEP with four cycles of VIP being an alternative. As the outcome in this group of patients is much less satisfactory various attempts have been made to intensify therapy either by the addition of other agents and/or the use of high dose chemotherapy with stem cell transplantation. Most studies have not shown any improvement in overall survival, however for many of these studies the degree of improvement the study was powered for was probably set to high. There are a number of phase 2 studies which appear to give better overall survival rates than those expected with BEP. Although most of the studies are non- randomised, the difference in improvement is difficult to ignore.

When interpreting these studies it is important to look at the entry criteria- getting pathological diagnosis and formal GFR assessments all can take time and often leads to the exclusion of the sickest patients, which is likely to give improved results. Regimens that have been associated with improved outcome include POMB/ACE-cisplatin, vincristine, intermediate dose methotrexate and bleomycin alternating with actinomycin-D, cyclophosphamide and etoposide [18]. C-BOP/BEP- a weekly induction treatment using, cisplatin, vincristine and infusional bleomycin, followed by three cycles of low dose bleomycin, etoposide and cisplatin [35] and GAMEC-filgrastim, actinomycin-D, etoposide and high dose methotrexate (8 g/m^2) delivered over 10 weeks [24]. All seem to be associated with overall survival of between 70 and 80 %. These results still seem better than the 50–60 % currently seen in the most recent poor-prognosis randomised controlled trials.

One alternative approach has been to start patients with BEP and use the speed of tumour marker decline to guide the treatment. A randomised study is addressing this issue. Patients who appear to appear to be responding well continue to receive a total of 4 cycles of BEP while those who do not have their treatment intensified [36].

The use of high dose therapy has been addressed in many single center studies and the durable remission rate is very similar to that seen with intensive non-stem cell requiring regimens. There has been one randomised study to date in this setting. It compared 4 cycles of BEP chemotherapy to two cycles of BEP followed by two cycles of high dose carboplatin, etoposide and cyclophosphamide – no survival advantage was seen, however, the study included patients with intermediate prognosis as well and therefore had improved survival anyway. The study was powered to show an absolute improvement in complete remission at 1 year from 30 to 50 % – this was probably too ambitious – it is therefore quite possible that there was benefit in this approach and this is supported by the fact that those within the study who had an unsatisfactory marker decline, 61 % had a durable complete response compared to 34 % who received BEP [37].

The Ill Patient with a Metastatic Germ Cell Tumor

In patients with advanced bulky disease – particularly those with intermediate or poor prognosis several situations can lead to problems in administering standard therapy – these are briefly covered below.

1. Para-aortic lymph node obstruction of ureters leading to impaired renal function: It is usual practice to arrange a nephrostomy or ureteric stent for such patients which may not be necessary if the estimated eGFR is above 60 ml/min. Many patients will obtain rapid relief from chemotherapy and therefore obstruction may be relieved without intervention. A low dose induction treatment e.g. baby BOP- cisplatin 50 mg/m^2, vincristine 2 mg and bleomycin 30,000 units with the aim of starting definitive treatment 7–10 days later [38].

An alternative is to give low dose cisplatin (20 mg/m^2) and etoposide (60 mg/m^2) on days 1–3.

2. Inferior Vena Cava Thrombosis: This is not an infrequent finding in patients with large volume para-aortic disease. A therapeutic dose of low molecular weight heparin should be started as the risk of subsequent pulmonary embolism often rises in the subsequent 1–2 weeks particularly if the para-aortic nodes are causing vena caval obstruction and then the chances subsequently regress. This is also a situation where low dose induction treatment may be appropriate as it avoids early thrombocytopenia, which would otherwise increase the risks associated with anticoagulation.
3. Symptomatic Brain Metastases: Patients requiring anti-epileptic drugs cause particular problems. Some of the enzyme inducing drugs e.g phenytoin, carbamazepine may lead to lower levels of cytotoxics e.g etoposide- and this may lead to a reduction in efficacy. On a theoretical basis at least it would be best to avoid these agents. Levetiracetam has broad anti-epileptic activity and may be particularly suitable in such cases as it neither induces nor inhibits liver enzyme activity and therapeutic levels can be achieved rapidly. Many of these patients will be on corticosteroids and the aim is to wean these off over the period of 2–4 weeks. Asymptomatic brain metastases do not necessarily mean that a patient need start an anti-epileptic drug. Whether cranial irradiation be required at the end of chemotherapy or not, remains an ongoing debate. In series where methotrexate has been used, it has generally been felt that this is unnecessary as the drug crosses the blood-brain barrier [18, 24].

Monitoring of Disease Response

Tumor Markers

The use of AFP and β-hCG has proved extremely useful in monitoring response and identifying relapse in germ cell tumors. Not all patients' tumors express them but a vast majority of patients particularly those with non-seminomatous germ cell tumors do. It is frequently the case that markers rise in the first 10 days after therapy begins; they often then plateau, before falling. They are also normally falling after the start of the second cycle. Based on established half-life decline for these markers (7–10 days for AFP and 2–4 days for hCG) it should be possible to identify which patients are responding well to therapy and which are not. A change in therapy on the basis that marker levels are not declining according to predicted half-life is not justified outside a trial on current evidence although some trial evidence supports a change on the basis of this. It should be realised that over 30 % of patients with raised hCG at the end of four cycles of BEP chemotherapy will subsequently be cured without resorting to further chemotherapy as the marker will slowly decline although at a much slower rate than predicted [39]. In the case of mediastinal tumours with raised

AFP which does not normalise but plateaus, a serious consideration should be given to early surgery, particularly if there were no distant metastases at progression as these tumours seem less likely to respond to further chemotherapy and often may undergo somatic transformation [40].

Generally speaking, a sequential rise in tumor markers is indicative of a relapse although there are several caveats to this. AFP rises could follow any damage to the liver that includes various cytotoxics (actinomycin-D, methotrexate) as well as various antibiotics and other hepatic insults including sepsis. Sometimes it is possible to infer a non-malignant cause for a rise in AFP levels, for example if the tumor did not produce it initially. Sometimes it is more difficult as AFP production from the tumor may drop but a hepatic cause leads to the markers falling, then rising and plateauing. HCG may induced by exposure to cannabis products and an enquiry in to the history of use of such substances should be sought if there is a rise in this marker. A CT scan performed at the time of a rise in tumor markers may not be that helpful as the lesions may well have shrunk compared to the previous scan. The development of new lesions, however, is indicative of progression.

Choosing a Second Line Treatment – How Bad Is the Relapse?

A rise in tumor markers and/or the development of new sites of disease often is indicative of relapse. The choice of strategy in managing this situation has been guided by phase 2 non-randomised studies. Until recently it was usual practice to manage relapses in a similar way. In the last few years there has been increasing evidence that the site of the primary, the speed of recurrence, as well as the quality of response to first line therapy affect the subsequent response to further therapy. A recent analysis of patients treated at first recurrence with cisplatin-based conventional therapy identified the following factors as being important [41]:

(a) Histology- pure seminoma was favorable, as was a gonadal primary.
(b) Adverse factors included: extragonadal primaries especially mediastinal primaries (non-seminomatous), progression-free interval of less than 3 months, an elevated AFP, a raised hCG of >1,000IU/l and the presence of liver, brain or bone metastases. The more of these adverse factors the worse the outcome and it proved possible to put patients in to one of 5 prognostic groups- with progression free survival ranging from 5.6 to 75 % (see Tables 29.1 and 29.2). Most of the patients received cisplatin and ifosfamide-based salvage therapy on a 3 weekly basis. Whether the same outcomes occurred if different salvage strategies were used was unclear although there are suggestions that this may not be the case. In addition, the use of LDH so often indicating a poorer prognosis was not an independent factor identified in this prognostic system. Others have found it to be important [42]. The development of this prognostic system will allow interpretation of phase 2 data to be more objective and will aid in stratification for proposed randomized studies.

Table 29.1 IPFSG criteria (International Prognostic Factors Study Group) predictive scoring of outcome to conventional salvage chemotherapy

Variable	0	1	2	3
Primary site	Gonadal	Retroperitoneal		Mediastinal
Response 1st line	CR/PRm-	PRm+/SD	PD	
PFI	>3 months	≤3 months		
AFP at salvage normal	<1,000	>1,000		
LBB at salvage	No	Yes		

Core sum (values from 0 to 10)
Regroup score sum into categories: (0) = 0, (1 or 2) = 1, (3 or 4) = 2, (5 or more) = 3
Add histology score points: pure seminoma = −1; nonseminoma or mixed = 0
Final prognosis score (−1 = very low risk, 0 = low risk, 1 = intermediate risk, 2 = high risk, 3 = very high risk)
LBB liver, brain or bone metastases

Table 29.2 Survival rates according to prognostic categories

Prognostic category	2-year PFS	3-year OS
Very low	75.1	77.0
Low	51.0	65.6
Intermediate	40.1	58.3
High	25.9	27.1
Very high	5.6	6.1

PFS progression-free survival, *OS* overall survival

Conventional Second Line Salvage Options

The realisation that patients relapsing after cisplatin-based initial therapy could be salvaged using further chemotherapy was first made over 20 years ago. It was realised that removal of bleomycin and adding instead ifosfamide 6 g/m^2, was capable of curing around 25–30 % of patients. It was initially suggested that those originally treated with BEP should receive cisplatin 100 mg/m^2, ifosfamide 6 g/m^2 and vinblastine 0.11 mg/kg on day 1 and 2 of each 3 week cycle (VeIP) whilst those who received PVB first should then receive the same regimen but with etoposide 375 mg/m^2 replacing the vinblastine (VIP or PEI) with etoposide often given at the relapse regardless of initial therapy as it is thought to be less toxic, particularly in terms of neurotoxicity [43, 44]. More recently the identification of paclitaxel as an active drug in heavily pre-treated patients has led to the adoption of this regimen; TIP with a dose of paclitaxel replacing either etoposide or vinblastine at a dose of 250 mg/m^2. Whilst the outcome with TIP appears numerically superior the results in fact are likely to be due to patient selection [45]. It is usual to give four cycles of salvage therapy.

Other treatment approaches have used dose dense cisplatin i.e. cisplatin delivered weekly or every 2 weeks. This has been combined with other drugs that often are not particularly myelosuppressive e.g vincristine, bleomycin and methotrexate. Durable responses are seen in around 30 % of cases. Both actinomycin-D and methotrexate have shown activity when combined with etoposide in cisplatin refractory

disease [46]. These drugs have been combined with cisplatin in the dose dense regimen GAMEC [24]. Approximately 40 % of patients have been salvaged using this approach; however myelosuppression and mucositis were problematic particularly in older patients (over 35) and those with poor renal function. As this regimen contained methotrexate in high dose it was used in patients with cerebral metastases and was able to lead to complete remissions. Anthracyclines e.g epirubicin have shown significant activity when combined with cisplatin when given to chemosensitive relapse [47].

Non Cisplatin – Based Salvage Strategies

Many agents including gemcitabine (11 % response rate) [19], oxaliplatin (13 % response rate) [48], paclitaxel (11 % response rate) [17] have shown activity in relapsed germ cell tumors. Combinations of these agents have shown higher response rates (30–40 %); for example, oxaliplatin and gemcitabine, oxaliplatin and paclitaxel, gemcitabine and paclitaxel. Paclitaxel may be particularly important when treating relapsed mediastinal germ cell tumors as there do not seem to be survivors if this drug is omitted. The drug irinotecan, a semisynthetic analogue of the natural alkaloid camptothecin, is unusual in that it showed no activity when used as a single agent in a heavily pre-treated cohort [49], however in combination with cisplatin or oxaliplatin much higher response rates were seen (30–40 %) [23]. The combination of oxaliplatin, irinotecan and paclitaxel has been associated with a response rate of 71 % [15]. One of the reasons why response rates seem so variable in these settings is that the patient population varies with some studies having a high proportion of very refractory patients. The advantage of all these treatments is that they can be used in patients with poor renal function.

High Dose Chemotherapy – Principles of This Approach –Stem Cell Collection/Which Drugs to Include/One, Two or Three Cycles?

The inherent chemo-sensitivity of germ cell tumors and the ability to salvage relapse has led to the development of high dose chemotherapy (HDCT) in the hope that this may circumvent resistance. In order to attenuate the effect of marrow suppression stem cells are collected to re-infuse after high dose therapy has been given. Normally this is done by giving chemotherapy, often cisplatin and ifosfamide-based followed by filgrastim. When the peripheral CD34 count (a marker for hemopoetic stem cells) reaches a threshold (>10/μl), patients have these cells collected using a cell separator. Sometimes high dose filgrastim is given alone particularly if marrow reserve is expected to be good. Many factors have been looked at to stratify the

Table 29.3 Prediction of survival post high dose chemotherapy

Variables	Score
PD before HDCT	1
Mediastinal primary	1
Refractory disease before HDCT	1
Absolutely refractory disease before HDCT	2
HCG >1,000 before HDCT	2
Good risk	0
Intermediate risk	1–2
Poor risk	>2

Risk category	PFS 1 year (%)	PFS 2 years (%)	OS 1 year (%)	OS 2 years (%)
Good	56	51	73	61
Intermediate	28	27	50	34
Poor	5	5	19	8

Definitions of cisplatin sensitivity: better than stable disease. No progression within 4 weeks of last chemotherapy.
Refractory: at least stable disease. Progression within 4 weeks of last chemotherapy
Abs refractory: progressive disease without attaining stable disease for 28 days.
PFS progression-free survival, *OS* overall survival

response to high dose therapy, in particular the site of the primary, the response to the last cisplatin based therapy and the tumour marker level at relapse. A prognostic score has been established for a single high dose therapy based on 5 factors. These include: the presence of progression prior to high dose treatment, a mediastinal primary tumor, refractory disease to cisplatin (progression within 4 weeks of treatment having been at least stable during therapy), absolute refractory disease to last cisplatin-based therapy (progression on therapy), and an hCG of over 1,000 IU/l. These factors were weighted to provide an overall score (Table 29.3) [50].

Patients proceed to receive HDCT once an adequate number of stem cells have been collected. In some protocols this follows some conventional chemotherapy to assess chemo-sensitivity and collect stem cells while in others patients proceed directly to HDCT. The drugs used in the preparative regimen have varied. The use of carboplatin is standard. The dose varies from 1,200 to 2,200 mg/m^2. Increasingly carboplatin is dosed using a formula based on renal clearance e.g the Calvert Formula – Dose in mg = AUC × (A × GFR + B) [AUC: a figure that reflects the concentration of drug in the body that is to be achieved; GFR: glomerular filtration rate; A is the ratio of GFR to how quickly the kidneys get rid of carboplatin; and B is the rate at which the body gets rid of carboplatin in other ways than through the kidneys]. On this basis a dose of between AUC 15- AUC 30 is selected. The reason for this is that the correlation between effect and dose is much more closely linked with renal clearance than a dose based on body surface area. Carboplatin is most often combined with etoposide in a dose of 1,500–2,200 mg/m^2 [52]. Other drugs have been used most commonly cyclophosphamide (6 g/m^2) or thiotepa [13, 14].

Thiotepa has an advantage in that it has very good brain penetration. Other drugs used have included ifosfamide, melphalan and topotecan [15, 51]. The most popular regimen is carboplatin and etoposide and this has predictable toxicity with mucositis being the most troublesome side effect. The number of cycles of HDCT has varied. Increasingly several cycles are preferred. Two cycles of high dose carboplatin and etoposide is commonly employed [52] and in some protocols three cycles have been used although the doses chosen have tended to be rather lower [53]. At present there is no reason to prefer three over two cycles. The time between two cycles of high dose therapy is generally 4–6 weeks.

There has been one randomized study of high dose chemotherapy in relapsed disease and this showed no advantage over standard second line therapy; the study, however, was small. One study comparing three cycles of VIP and one high dose carboplatin, etoposide and cyclophosphamide to one cycle of VIP and 3 cycles of high dose carboplatin and etoposide showed that the multicycled high dose approach produced better overall survival (49 % vs 39 % $p=0.06$) but this was mostly due to reduced treatment related deaths in that arm. The single cycle of high dose therapy using cyclophosphamide, etoposide and carboplatin had a much higher treatment related death rate (16 % vs 4 %, $p<0.01$) and this is the main cause in the difference in overall survival [54]. A recent overview from a database looking at the management of first relapse showed that the prognosis seemed much improved in those who received high dose chemotherapy. In addition patients who received sequential high dose chemotherapy had an improved overall survival (60.6 *vs* 46.3 %, $p=0.001$) [55].

Currently on the basis of the non-randomised data presented the largest series to date has used 1 cycle of induction cisplatin and ifosfamide –based therapy followed by two cycles of high dose carboplatin and etoposide, followed in many patients by 3 months of oral etoposide although the value of this 3 month oral therapy remains unclear. Relapsed metastatic seminoma seemed to do particularly well using this approach with up to 90 % being cured [52].

Should High Dose Chemotherapy be Given on First or Second Relapse?

This remains a difficult question. Essentially patients who have responded well to initial therapy and do not relapse too early will do well with conventional salvage treatment. These patients can be spared an unnecessary therapy if they were treated with conventional salvage regime rather than proceeding to high dose therapy. Consequently, should they relapse they will have a poorer outcome with high dose therapy and this patient group will have been put through a larger amount of total treatment which tends to lead to increased toxicity when high dose treatment is given. On average only 20–30 % patients will have a durable remission when high dose treatment is used in this setting [56]. A pragmatic approach might be to reserve high dose therapy on first relapse for older patients, and those where current conventional salvage approaches seem less appropriate.

Brain Metastases at Relapse

Brain metastases may occur at presentation, and as an isolated relapse site after completion of chemotherapy or as part of a multi-site relapse. The prognosis declines with each situation with those who relapse during chemotherapy having the worst prognosis with a survival as low as 5 % [57] . Whilst initial therapy may treat them successfully there is much less data on the optimal way to approach them on relapse. The role of surgery and/or radiotherapy then becomes important. An isolated relapse occurring after the completion of chemotherapy may be resected and this may be followed by irradiation. Alternatively, chemotherapy may be given with an agent that crosses the blood brain barrier; e.g. high dose methotrexate. Ideally surgical resection post treatment allows the histological response to be elucidated. If the tumor is completely necrotic, there is probably no need to add additional therapy. If however surgical resection is incomplete or not possible, then many would advocate radiotherapy following the completion of chemotherapy. If such patients are going on to receive high dose chemotherapy there is a rational argument to use a regimen that includes drugs that cross the blood brain barrier e.g thiotepa.

Extragonadal Presentations

Germ cell tumors may present without any evidence of a testicular primary. One site that deserves a specific mention is mediastinum. If the presenting tumor is seminoma the outlook seems to be good; however, the non-seminomas are automatically categorised as poor prognosis in their initial staging. In some cases there is an isolated mediastinal mass without any obvious metastases. These cases are managed with chemotherapy in the first instance with surgery being attempted at the end of chemotherapy in cases despite tumor markers failing to normalise. Somatic transformation is not uncommon in these tumors and thus surgery is very important in achieving cure. Mediastinal tumors that relapse seem to do badly with this site being recognised as an adverse prognostic factor [50]. Some series automatically exclude these patients from high dose therapy reports because of their poor outcome, although recently those regimens including a taxane as part of the treatment have shown durable cures in perhaps 25 % or so of patients [53].

Chemotherapy Beyond High Dose Chemotherapy – Always Palliative?

Overall this carries a very poor outcome with perhaps only 5 % being cured. It is often picked up as a rise in tumor markers following the end of treatment. Patients who have completed high dose therapy should have as many residual masses removed as possible. If relapse occurs and the sites of radiological relapse are amenable to surgery

this should be considered. The regimen of gemcitabine and paclitaxel used in this setting seems to give a higher relapse free survival of 14 % [21]. It should be remembered that these patients did not receive either drug prior to high dose chemotherapy. The combination of cisplatin and epirubicin has also been used in the setting of relapsing disease. It is clearly active and the regimen seems well tolerated it is clearly an option in patients who do not have disease that is absolutely refractory to cisplatin [58]. Oral etoposide has been used in this setting, easy to administer but with unpredictable toxicity. The management of these patients is inevitably more subjective-patients will tend to be given dugs that they either did not receive to date or have shown significant activity at relapse. It is likely that these patients should receive either surgery or perhaps radiotherapy to these known sites following chemotherapy if this is practical. Chronic oral etoposide has been recommended by some as it is easy to administer but has a limited activity in this setting; in addition, as its absorption is variable toxicity can be unpredictable, nevertheless durable remissions have been seen when therapy is consolidated by surgery or irradiation [59]. In this setting clearly some degree of chemo-sensitivity is maintained but in the absence of either surgery or radiation long term remission seems unlikely. For patients where this is not possible treatment is palliative in intent and therefore it is best to avoid toxic regimens.

Late Relapse of Germ Cell Tumors

The definition of late relapse is relapse that occurs greater than 2 years from initial chemotherapy. It is an important subgroup of patients occurring in between 1 and 3 % of cases. It is less common in seminomas than non-seminomas. The importance lies in its relatively poor outcome. Surgery has a very important role and indeed is the treatment of choice in patients with resectable disease. Until recently it was reported that cases were relatively un- responsive to chemotherapy, however, more recent publications have suggested an improved outcome. Paclitaxel, ifosfamide and cisplatin has been suggested in this situation with 7 out 14 having durable responses when followed by surgery. Similar results have been reported with GAMEC (5/9) indicating that the improved results are not due to paclitaxel [47]. In the absence of rising markers the question of somatic transformation is raised. The role of re-biopsy in guiding therapy is complex but in those with primitive neuroectodermal transformation then tissue specific chemotherapy has been suggested. In patients with multi site relapse then high dose chemotherapy can be considered. It is unlikely that in the absence of surgical excision of masses remaining at the end of chemotherapy that long term survival will be possible.

New Agents in Germ Cell Tumors

The responsiveness of these tumors to cytotoxic chemotherapy has tended to mean that newer agents particularly the targeted therapies have had little impact in this condition. Seminomas express CD117 (c-KIT) and this would encourage the use of

imatinib in this condition. This has been tried although overall the responses have been disappointing. Successful use has usually been with chemotherapy at the same time [60]. Sunitinib has been explored in chemo-refractory cases post high dose therapy and in late relapse. Toxicity was moderate with a limited efficacy, a response rate of 12 % was seen [61]. Bevacizumab has been used in case reports. Interestingly its successful use in surgically unresectable growing teratoma syndrome has been described [62].

Conclusion

Chemotherapy in germ cell tumors is becoming more refined. At each point in the disease it is becoming possible to risk stratify with the result that for any patients the exposure to chemotherapy is being lessened. The refining of chemotherapy together with the timely use of surgery to remove residual masses have all been helpful in improving the prognosis of this disease. To date newer targeted drugs have failed to make a major impact in this disease leaving cytotoxic drugs to dominate the field. Future studies are likely to require much greater cooperation between institutions to allow further refinement of treatment.

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Chapter 30
The Role of Radiotherapy in Testicular Cancer

Sophie D. Fossa and Jan Oldenburg

Of the two principal histological types of testicular germ cell cancer, seminoma and non-seminoma, the former type is extremely radiosensitive. Most cases of non-seminoma are considered to be radio-resistant, and radiotherapy has no place in the treatment of the overwhelming majority of patients with non-seminoma.

During the last three decades the treatment of stage I seminoma has evolved remarkably. To understand today`s role of radiotherapy in the management of seminoma, one has to be aware of the malignancy`s natural course. As many as 80 % of the patients present with stage I disease, i.e. they have no detectable metastases by clinical, radiological, or biochemical examination. However, between 15 and 20 % of these patients harbor micro-metastases, which will gradually progress if left untreated. Relapses are commonly located in the retroperitoneal lymph nodes and occur most often in patients with so called high-risk tumors (primary tumor size >4 cm in diameter and invasion of the rete testis) [1]. Salvage treatment (chemotherapy, radiotherapy) will cure almost all of these relapsing patients. This background indicates that treatment of all patients with stage I seminoma would confer "overtreatment" for the vast majority of them.

As far as metastatic seminoma is concerned, one has to be aware that maximally 50 % of those diagnosed with retroperitoneal lymph node metastases are cured by radiotherapy alone as opposed to almost 90 % by primary chemotherapy, the size of the lymph node metastases being strongly related to the cure rate [2].

S.D. Fossa, MD, PhD (✉)
Department of Oncology, Oslo University Hospital, Montebello, Oslo, Norway
e-mail: s.d.fossa@medisin.uio.no

J. Oldenburg, MD, PhD
Department of Oncology, Oslo University Hospital, Oslo, Norway

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Stage I Seminoma

For more than 50 years patients with seminoma stage I have received adjuvant radiotherapy to the retroperitoneal lymph nodes. Radiotherapy was also used as definitive treatment in patients with metastases, eventually combined with chemotherapy. Traditionally, up to the 1990s the target dose for stage I seminoma had been 30–40 Gy, applied to a so called dog-leg field covering the para-aortic and ipsilateral lymph nodes. Two randomized studies with long-term follow-up data have demonstrated that radiotherapy to the paraaortic lymph nodes is sufficient, and that the target dose can be lowered to 20 Gy [3].

The acute adverse effects of radiotherapy are mild to moderate nausea and diarrhea, often combined with fatigue during the treatment period and for a few weeks thereafter, however with a complete recovery after 3 months [4]. Follow up of these irradiated patients is relatively easy with no need of regular CTs after dog-leg irradiation. After radiotherapy restricted to the paraaortic region, regular pelvic CT examinations during the first 5 years are mandatory to diagnose an eventual pelvic relapse. The recurrence rate after such radiotherapy is 1–2 %, the majority of the relapsing patients being cured by salvage treatment.

Due to the aforementioned risk of overtreatment in patients with stage I seminoma most clinicians agree that radiotherapy no longer has a place in treatment of stage I seminoma and that these patients should be followed with a surveillance strategy, with salvage treatment in relapsing patients [5, 6]. This view finds its strongest support by the increased development of radiation-related second cancers in testicular cancer survivors. Several studies have shown that abdominal radiotherapy in testicular cancer survivors is followed by a significantly elevated risk of second cancer incidence, the relative risk varying between 1.6 and 2.0 [7, 8]. The second cancers are typically diagnosed within or adjacent to the target field (pancreas, ventricle, bladder and colon). There is also evidence for increased risk of cardiac morbidity, even after infra-diaphragmatic radiotherapy alone [9] and reports on occasional renal dysfunction probably related to radiation induced stenosis of the renal arteries.

In the US adjuvant radiotherapy is still considered an option in 50–60 % of patients with stage I seminoma, as compliance to follow-up routines during surveillance has proven difficult [10]. However, the life-long risk of a radiotherapy-related second malignancy is increasingly acknowledged [11]. This awareness should gradually reduce the application of adjuvant radiotherapy of stage 1 seminoma patients. In selected patients radiotherapy may exceptionally be considered, for example if regular follow-up is extremely difficult due to geography, very high age or severe co-morbidity, and if adjuvant chemotherapy with Carboplatin is no option [12]. In this case, radiotherapy should be restricted to the para-aortic region, the total dose not exceeding 20 Gy.

Metastatic Seminoma

Radiotherapy is still a valid option in the primary treatment of patients with early stage II disease [5]. The target field covers the retroperitoneal and ipsilateral iliac lymph nodes, the target dose being 25–30 Gy, with 10 Gy given to the involved lymph node area.

The relapse rate approximates 10 % in the largest series with most recurrences located above the diaphragm. Initial cisplatin-based chemotherapy seems, however, to be more efficient than radiotherapy as indicated by the following relapse rates: The Swedish Norwegian Testicular Cancer Group (SWENOTECA) reported three relapses (11.3 %) after radiotherapy with 27 Gy among 29 patients with clinical stage IIA [13]. In contrast none of the 73 patients with CS IIA or B (6 and 67, respectively) did experience a relapse after median 5 years of observation. These figures are in concordance with those from the Spanish Germ Cell Cancer Group which show no relapses among 26 with CS2A patients treated with chemotherapy, whereas three of 19 CS2A/B patients (16 %) relapsed following initial radiotherapy [14]. Also Kollmannsberger et al from British Columbia observed similar figures in their study; 3 of 19 (16 %) irradiated patients with small volume stage II seminoma relapses compared to 1 of 65 (2 %) of patients with stage II/A/B treated with chemotherapy [15]. The combination of one to two cycles of Carboplatin prior to radiotherapy has been shown to lower the risk of relapse in seminoma stage II with limited extent [16].

Patients with stage II seminoma and initial retroperitoneal lymph node size >3 cm and those with stage III/IV should have primary chemotherapy [5, 6]. A post-chemotherapy residual mass <3 cm in diameter most often contains fibrotic tissue only and can safely be observed. Larger residual tumors should be assessed by Positron Emission Tomography (PET). PET positive lesions should be removed by surgery [17], whereas PET negative lesions are to be followed the gradual size reduction often requiring several months. PET may thus be helpful to decide whether any post-chemotherapy therapy is indicated, though the final place for PET in this setting has not been defined [18]. Routine post-chemotherapy radiotherapy is no longer recommended.

Radiotherapy is an important part of the multimodality treatment of patients with brain metastases in both seminoma and non-seminoma. Irradiation of cerebral metastases contributes to the cure of selected patients, preferably those who initially presented with intra-cerebral ≤2 lesions. If ever possible, high target doses should only be given to small fields, as whole brain radiotherapy at doses of >40 Gy may lead to leuco-encophalopathy [19]. Fractionated stereotactic radiosurgery should be applied whenever possible [20]. Seminoma may recur as skeletal metastases after many years and irradiation should be part of required multimodality treatment.

Finally, radiotherapy has a principal role in the treatment of histologically verified carcinoma in situ in the contralateral testis, observed in 5 % of biopsies obtained from the contralateral testicle in men with a newly diagnosed testicular germ cell cancer [21, 22]. The standard dose is 20 Gy (5 fractions à 2 Gy per week) [21]. However, lower doses (14 Gy; 16 Gy; 18 Gy) have also been successful, though post-radiotherapy single relapses have been recorded. Decreasing Leydig cell function (3.6 % per year) during the first 5 years warrants regular monitoring of serum testosterone followed by androgen substitution in hypogonadal men.

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Chapter 31
Superficial Bladder Cancer

Benjamin L. Jackson, T.R. Leyshon Griffiths, and J. Kilian Mellon

Definition

Superficial bladder cancer refers to a carcinoma of the bladder that is confined to the urothelium and/or sub-urothelial connective tissue, without invasion of the muscularis propria. The term "non-muscle invasive bladder cancer" (NMIBC)may be used synonymously. In practice, these terms are principally used to refer to transitional cell carcinoma (TCC), and around 75–85 % of TCCs are superficial at presentation.

Epidemiology

World-wide, there were around 382,000 new bladder tumours diagnosed in 2008, making bladder cancer the 9th commonest cancer [1]. The incidence is around three-fold higher in men than women. Women, however, tend to present with more advanced disease and have poorer outcomes [2]. Incidence increases in both sexes from age 50, and the median age at presentation is 70 years.

Trends in incidence of bladder cancer are difficult to quantify accurately due to variations in the reporting of low-grade lesions. However, there is clear evidence that bladder cancer mortality is falling in the United States [3], Europe [4], and world-wide [5]. This is likely to reflect reduced exposure to tobacco and occupational carcinogens.

B.L. Jackson, MB, ChB (Hons), FRCS (Urol) • T.R.L. Griffiths, BSc, MD, FRCS (Urol)
J.K. Mellon, MD, FRCS (Urol) (✉)
Department of Urology, University Hospitals Leicester, Leicester, UK
e-mail: jkm7@le.ac.uk; jkm7@leicester.ac.uk

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Risk Factors

Chemical exposure from tobacco use and occupational exposure present significant risk factors for the development of TCC. Various genetic polymorphisms confer additional susceptibility. Pelvic radiotherapy for cervical cancer in women confers a two- to four-fold increased risk of bladder cancer [6, 7]. An increased risk is seen in men following external beam radiotherapy for prostate cancer, with an estimated risk of 1 in 390, rising to 1 in 70 in long-term survivors [8]. Cyclophosphamide treatment increases the risk of bladder cancer nine-fold [9]. Chronic abusers of the analgesic phenacetin are at increased risk, estimated at four-fold [10]. Use of *Aristolochia fangchi* (a Chinese herb found in some diet pills) is also associated with an increased risk [11], as is arsenic ingestion [12].

A further possible risk factor identified recently is pioglitazone usage. Pioglitazone is a thiazolidinedione PPARγ(gamma) ligand used in the management of diabetes mellitus. A non-significant excess of bladder cancers was seen in the pioglitazone arm of the PROactive study evaluating this drug [13]. This has been further evaluated by a longitudinal cohort study, which has shown a small increase in risk in patients taking pioglitazone for greater than 2 years [14].

Smoking

Smoking is implicated in approximately two-thirds of all bladder cancers. Cigarette smoke contains at least 40 candidate carcinogens including nitrosamines, β-napthylamine, and 4-aminobiphenyl. A meta-analysis of 43 studies published in 2000 demonstrated a threefold increased incidence in current smokers, and established that bladder cancer risk correlates with number of cigarettes smoked, duration of smoking, and age of smoking initiation [15]. Recently, data from a large US study has suggested that the risk in current smokers may in fact be as much as fourfold higher [16]. This study also suggests that the impact of smoking on bladder cancer incidence is now roughly equal in male and female populations, in contrast to previous data showing that male incidence was more heavily affected by smoking. Smoking cessation reduces bladder cancer risk by 30–60 % within 4 years [17], however former smokers retain a twofold higher incidence of the disease. Low-nicotine cigarettes appear to be unhelpful in terms of reducing risk, and may in fact increase risk by stimulating smokers to inhale more deeply [18].

Occupation

Occupational exposure to carcinogens remains an important cause of bladder cancer. Data from a combined analysis of several studies from Western Europe suggests that at present around 5–10 % of bladder cancers in men are attributable to a known

Table 31.1 Occupations associated with bladder cancer

Dye industry
Textiles
Printing
Rubber industry/Tyre manufacture
Steel industry
Cable manufacture
Leather industry
Petroleum
Shoemakers
Lorry drivers
Drill press workers
Rodent exterminators
Sewage workers
Hairdressers

occupational carcinogen [19]. Occupations associated with bladder cancer are listed in Table 31.1.

In 1938, Hueper et al. [20] first demonstrated that the aromatic amine β(beta)-napthylamine could induce bladder cancer in dogs. Later, an epidemiological study by Case and Hosker [21] showed that exposure to α(alpha)-napthylamine, β(beta)-napthylamine, and benzidine were the main occupational factors in the development of bladder cancer. Some polycyclic aromatic hydrocarbons can also act as urinary tract carcinogens. Most carcinogens have a latent period of up to 20 years between exposure and the development of cancer.

Genetic Polymorphisms

Drug and carcinogen-metabolising enzymes are in part controlled by genetic polymorphism. Slow acetylation of N-acetyltransferase-2 (NAT2) [22, 23], rapid CYP1A2 activity [24], and glutathione S-transferase (GST) M1 null genotype [23] are associated with an increased risk of TCC. Approximately 20 % of Europeans are homozygous for a non-coding single nucleotide polymorphism (8q24.21) located close to the c-Myc oncogene [25].

Pathology

In Europe and North America, the majority of bladder cancer is of transitional cell origin. Transitional cell epithelium lines the renal pelvis, ureter, urinary bladder, and proximal urethra. Pure squamous cell carcinoma and adenocarcinoma account for less than 10 % of all bladder tumours, and small cell carcinoma, sarcoma, and malignant melanoma are rare. The term “superficial bladder cancer” is typically

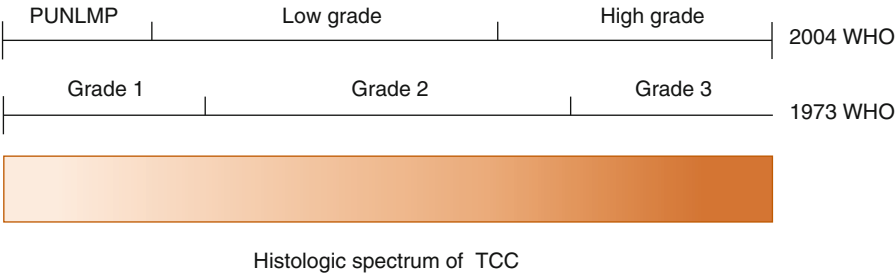

Fig. 31.1 WHO 1973 and 2004 grading systems (Reprinted from MacLennan et al. [81]. With permission from Elsevier)

confined to TCC, as the other tumour types are usually invasive, and require radical or systemic therapy depending on type and stage.

The pathological classification and grading system for urothelial tumours was updated by the World Health Organisation (WHO) in 2004 [26], replacing the 1973 classification [27]. The previous three histological grades (grade 1, 2 and 3) were replaced by two ("low" and "high" grade). An overview of the two grading systems is shown in Fig. 31.1. At the time of writing, the 2004 system has not yet been universally adopted, and much of the evidence underpinning management of superficial tumours is based on trials in which patients were classified according to the old system.

The nomenclature relating to superficial bladder cancer can be confusing. The WHO 2004 system divides urothelial malignancies into Papillary Urothelial Neoplasms of Low Malignant Potential (PUNLMPs), Non-Invasive Papillary Urothelial Carcinoma (Low-grade), Non-invasive Papillary Urothelial Carcinoma (High-grade), and Invasive Urothelial Carcinoma. However, "invasive" in this usage refers to any tumour that invades the basement membrane, and as such includes tumours that invade the lamina propria but do not invade the detrusor muscle (stage T1, see section "Staging"). These tumours are, however, still considered "superficial" as they may be treated via endoscopic and intravesical means, without necessarily resorting to radical treatment. The presence of muscle invasion (stage T2 or greater) defines a tumour that is no longer "superficial". It is this lack of clarity that has led to the proposal of the term "Non-Muscle Invasive Bladder Cancer" as opposed to "Superficial Bladder Cancer".

Non-malignant Urothelial Tumours

The 2004 WHO classification system identifies several forms of non-malignant and pre-malignant urothelial tumour [26].

Urothelial hyperplasia is defined as markedly thickened mucosa without cytological atypia. It is seen in the mucosa adjacent to low-grade papillary tumours. There is no direct evidence of any premalignant potential, although it may be clonally related to nearby tumours.

Urothelial dysplasia by contrast does involve cytological atypia, but falls short of the changes seen in carcinoma-in-situ. It is challenging to diagnose and must be distinguished from reactive atypia, which is an inflammatory finding that may be seen in association with stones, infection or instrumentation. Urothelial dysplasia is a potentially premalignant finding. Clinical information on the outcome of *de novo* primary dysplasia is limited. In one study, 7 of 36 (19 %) patients with primary dysplasia developed carcinoma [28]. A later study showed that after a mean follow-up of 3.9 years, 4 (15 %) developed biopsy-proven cancer [29]. Another retrospective study of 15 patients found that 15 % with primary urothelial dysplasia and a mean follow-up of 4.8 years developed carcinoma in situ (CIS) [30]. The presence of urothelial dysplasia in association with papillary tumours increases the risk of tumour progression [31].

Non-malignant papillary tumours include urothelial papillomas and inverted papillomas. They are not pre-malignant and have a very low risk of local recurrence [26].

Malignant Urothelial Tumours

Papillary Urothelial Neoplasms of Low Malignant Potential (PUNLMPs)

This category of urothelial tumour in the 2004 WHO classification includes lesions that are similar in appearance to urothelial papillomas but show increased cellular proliferation exceeding the thickness of normal urothelium [26]. They would previously have represented the lower end of the spectrum of Grade 1 tumours using the 1973 WHO classification (Fig. 31.2).

They are low-risk tumours in terms of recurrence and progression, with rates of 39 and 2.7 % respectively in a review of published series [32].

Non-invasive Papillary Urothelial Carcinoma – Low-Grade

This category includes the more aggressive grade 1 tumours and the less aggressive grade 2 tumours under the previous grading system. These tumours are unlikely to progress to invasive or metastatic disease, but recurrence is common, occurring in 48–71 % of patients [26].

Non-invasive Papillary Urothelial Carcinoma – High-grade

This category includes the more aggressive grade 2 tumours and all grade 3 tumours under the previous system, but is limited to those tumours that do not invade the lamina propria (stage Ta, see section "Staging"). These tumours have an increased risk of both progression to invasive disease and local recurrence.

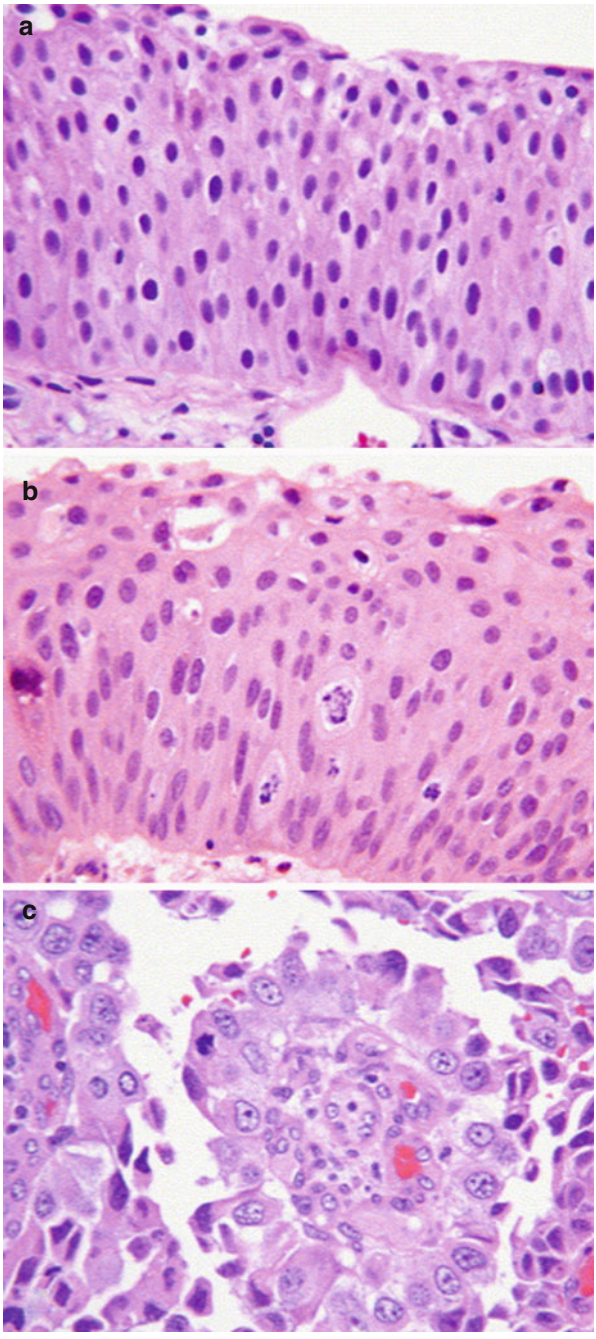

Fig. 31.2 Histological grades of urothelial tumour – PUNLMP, low-grade and high-grade. (**a**) Papillary urothelial neoplasm of low malignant potential (PUNLMP), formerly 1973 World Health Organization (WHO) grade 1 urothelial carcinoma. (**b**) Low-grade urothelial carcinoma, formerly 1973 WHO grade 2 urothelial carcinoma. (**c**) High-grade urothelial carcinoma, formerly 1973 WHO grade 3 urothelial carcinoma (Reprinted from MacLennan et al. [81]. With permission from Elsevier)

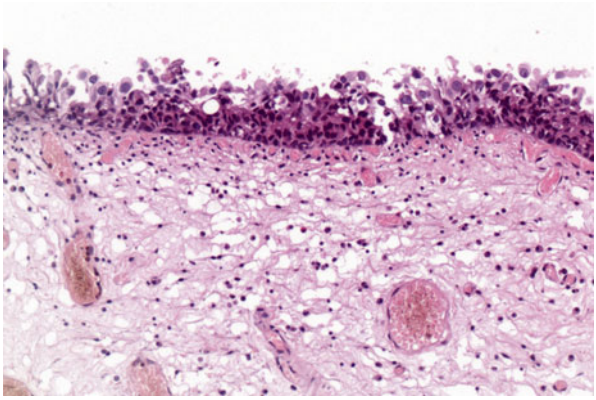

Fig. 31.3 Urothelial carcinoma in situ (Courtesy of Dr. John Dormer)

Urothelial Carcinoma In-Situ (CIS)

Carcinoma in-situ is characterised macroscopically by a flat, velvety, erythematous patch within the bladder. It may occur as a solitary finding or in association with papillary or solid tumours. Microscopically, it consists of poorly differentiated malignant cells confined to the mucosa, without invasion of the basement membrane (Fig. 31.3).

CIS represents high-grade disease by definition. Around 45 % of patients with primary CIS will progress to superficially invasive disease (stage T1, see section "Staging") [33], with around 20–30 % going on to develop muscle invasion (stage T2).

When CIS is present in association with a non-muscle invasive papillary tumour, it acts as a significant risk factor for progression to muscle invasive disease. In patients with high-grade papillary disease invading the lamina propria (G3 T1), the presence of concomitant CIS increases the risk of progression to muscle invasion from 29 to 74 % at 5 years [34].

Invasive Urothelial Carcinoma

The WHO 2004 classification regards all tumours demonstrating lamina propria invasion (stage T1, see section "Staging") as invasive urothelial carcinomas. These tumours are usually high-grade, and would have been considered grade 2 or grade 3 under the previous system. Only those tumours confined to the lamina propria without muscle invasion are regarded as superficial bladder cancers. Muscle invasive bladder cancer mandates radical and/or systemic treatment and is considered in a separate chapter.

High-grade T1 tumours are at considerable risk of both local recurrence and progression to muscle invasive disease. Around one-third of patients with this type

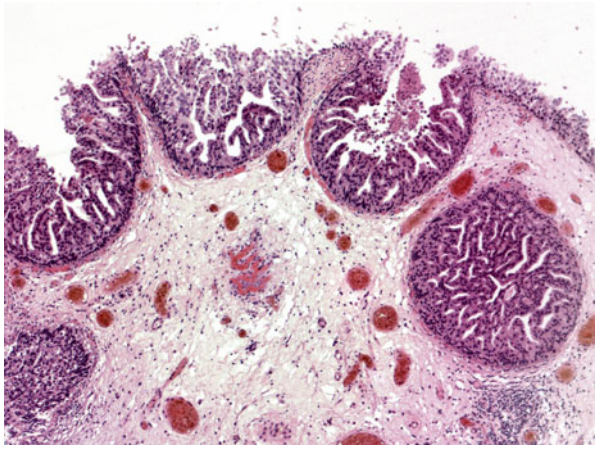

Fig. 31.4 Micropapillary variant (Courtesy of Dr. John Dormer)

of tumour will go on to die from bladder cancer, and a further third will require radical treatment due to the development of muscle invasion [35].

Micropapillary Variant

Micropapillary variant is an uncommon subtype of urothelial carcinoma that resembles papillary serous carcinoma of the ovary histologically [26] (Fig. 31.4). Its recognition is important as it may portend a poor prognosis in terms of the development of muscle invasion and lymph node and visceral metastases [36]. The amount of micropapillary change within the tumour specimen appears to be important, with higher percentages correlating with a poor response to intravesical treatment [36], and adverse outcomes [37]. Where tumours with extensive micropapillary change are encountered early radical cystectomy should be considered [36].

Staging

The 2009 tumour, node, metastasis (TNM) classification is currently recommended for bladder cancer staging (Table 31.2) [38].

Histological categories Ta, T1, and Tis are regarded as superficial bladder cancers.

Sub-staging of T1 bladder tumours according to the depth of lamina propria invasion, using the muscularis mucosae as a reference point, has been proposed. T1a describes disease into the lamina propria but not invading the muscularis mucosae, T1b disease invades to the muscularis mucosae, and T1c beyond it. This sub-classification does not form part of the current TNM classification system, but has been shown to correlate with likelihood of progression to muscle invasion by

Table 31.2 TNM (2009) staging system for bladder cancer [82]

T	**Primary tumour**
Tx	Primary tumour cannot be assessed
T0	No primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in-situ
T1	Tumour invades sub-epithelial connective tissue
T2	Tumour invades muscle
T2a	(Inner half)
T2b	(Outer half)
T3	Tumour invades perivesical fat
T3a	(Microscopically)
T3b	(Macroscopically)
T4	Tumour invades adjacent structures
T4a	(Prostate or cervix/vagina)
T4b	(Abdominal or pelvic wall)
N	**Regional lymph nodes**
Nx	Nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Single involved lymph node in true pelvis
N2	Multiple involved lymph nodes in true pelvis
N3	Common iliac nodes involved
M	**Distant metastasis**
Mx	Distant metastasis cannot be assessed
M0	No distant metastases
M1	Distant metastases

Adapted from Compton et al. [82]. With permission from Springer Science+Business Media

Orsola and colleagues [39]. There was no difference in recurrence rates between the different sub-categories. Accurate T1 sub-staging represents a challenge for the pathologist, and was only possible in 87 % of cases in the study quoted above.

Pathogenesis

Molecular Pathogenesis of Low and High-Grade Tumours

Some molecular alterations are found in all grades and stages of TCC, such as chromosome 9 deletions, which appear to be an early genetic event. However, there are well-defined differences in the molecular changes seen in low-grade non-invasive tumours and high-grade tumours including those with lamina propria or muscle invasion, and carcinoma in-situ (CIS) [40].

Mutations of the fibroblast growth factor receptor gene (FGFR3) on chromosome 4p and the TP53 gene on chromosome 17p are almost mutually exclusive [41].

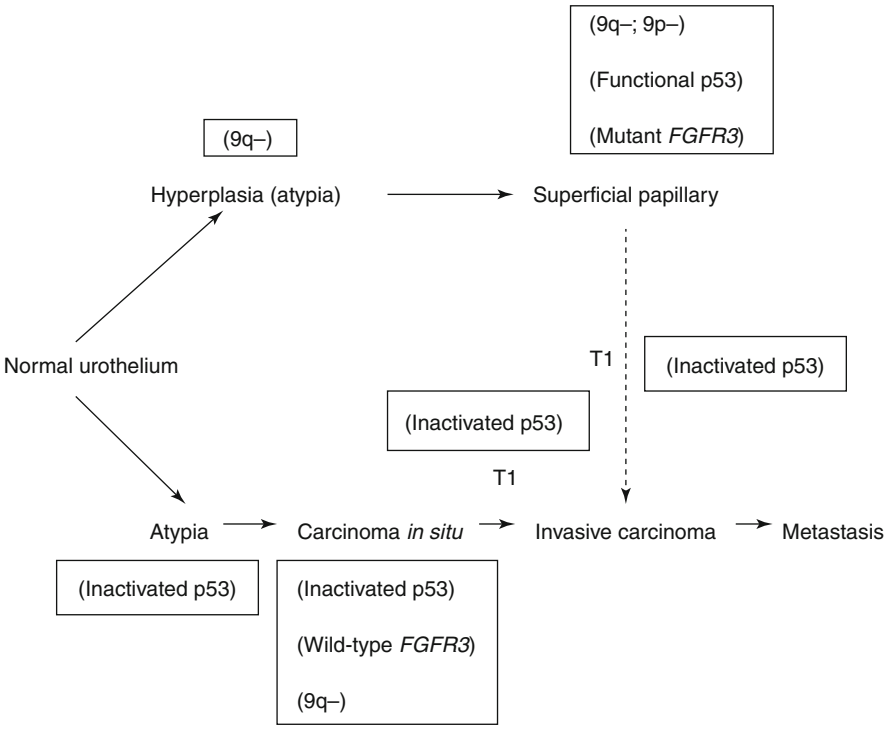

Fig. 31.5 Molecular pathogenesis of low- and high-grade tumours

FGFR3 mutations are seen in PUNLMPs and low-grade non-invasive urothelial carcinoma, whereas TP53 mutations are seen in high-grade and/or invasive tumours. These differences at the molecular level underline the quite different behaviour of high-grade tumours in terms of their potential for invasion, metastasis and consequent mortality. These molecular alterations are outlined in Fig. 31.5.

By contrast, mutations of the FGFR3 and Ras genes in low-grade tumours are absolutely mutually exclusive, but Ras mutations appear to have no prognostic significance [41].

It is likely that in the future, molecular profiling using high throughput assessment of gene and protein expression will play an increasingly important role in stratifying superficial bladder tumours according to their likelihood of progression, and may be used to determine treatment or follow-up pathways.

Theories of Multifocality

Two principal theories have been proposed to explain the frequent multifocality of bladder tumours. The field-change, or oligoclonal, theory suggests that multifocal tumours arise due to individual transformation of areas of unstable or dysplastic

urothelium into clonally unique tumours [42]. This theory is supported by the observation that tumours may recur months or years after treatment of the primary lesion.

There is some molecular evidence however, to suggest that in at least some cases recurrent or concurrent tumours may arise due to implantation or transepithelial spread of tumour cells, which are of a common clonal origin to the primary tumour [43].

The success of single instillations of intravesical chemotherapy after transurethral resection of superficial bladder tumours in preventing tumour recurrence has been attributed to prevention of implantation of tumour cells, which would lend further support to the theory of monoclonal implantation.

Clinical Presentation

The commonest presenting symptom of bladder cancer is painless visible haematuria, and approximately 85 % of patients present in this fashion. Some tumours, especially where CIS is present, may present with persistent irritative urinary symptoms, usually with concurrent haematuria (either visible or non-visible). Alternatively, tumours may be detected following investigation for asymptomatic non-visible haematuria detected during routine urine testing in primary care, or rarely with renal failure due to bilateral ureteric obstruction or symptoms of metastatic disease.

Of patients presenting with visible haematuria, approximately 20 % will have a urinary tract malignancy detected. The detection rate is much lower for patients with non-visible haematuria, with only 5 % harbouring a malignancy [44, 45].

Investigations

Flexible Cystoscopy

Cystoscopy remains the gold standard for the detection of both new and recurrent bladder cancer. Despite this, its sensitivity is limited to around 93 % for the detection of tumours during follow-up [46], and may be as low as 60 % for the detection of CIS [47].

Urine Cytology

Urine cytology was first described by Papanicolau and Marshall in 1945 [48]. When malignant cells are detected, it carries a high specificity for underlying urothelial malignancy (>95 %). However, its sensitivity is limited to 30–50 % mainly due to

the fact that low-grade tumours are often not associated with malignant cytology. The accuracy of urine cytology is operator-dependent, with more accurate results from laboratories processing larger numbers of samples [49].

Urinary Biomarkers

There are a variety of urinary biomarkers available or being investigated for use in the detection and/or monitoring of urothelial cancer. In general, they possess greater sensitivity compared to cytology, at the expense of lower specificity. None, however, have sufficient sensitivity to obviate the need to perform cystoscopy [50].

Currently available point-of-care biomarker tests include Nuclear Matrix Protein 22 (NMP22) and Bladder Tumour Antigen (BTA Stat). Laboratory-based tests include BTA TRAK, ImmunoCyt and UroVysion.

Despite the demonstrably higher sensitivity of these tests compared to urinary cytology, their usefulness is limited by their reduced specificity. The concern regarding their use as a diagnostic adjunct in patients presenting with haematuria instead of cytology is that the increased false positive rate would lead to unnecessary anxiety and further investigations in patients with a positive biomarker assay but negative imaging and cystoscopy.

Other potential uses for these tests include for population-based screening, for which there is currently no evidence base, and as part of surveillance protocols for follow-up of patients after treatment for low- or intermediate-risk superficial bladder cancer (see section "Risk stratification"). It is proposed that the use of biomarker assays may reduce the frequency with which these patients require follow-up cystoscopy. It is this last application that looks most promising, but currently large prospective trials validating such protocols are lacking.

Imaging

Ultrasonography

Ultrasonography is often performed as part of the initial assessment of haematuria. It may demonstrate tumour within the bladder, although it will not detect small or flat lesions, including CIS, and it is dependent on the patient having a full bladder at the time of the test. It will also provide information about upper urinary tract obstruction, i.e. hydronephrosis, and may detect upper tract tumours, although its sensitivity for upper tract TCC is lower than IVU or CT urography.

CT Urography/Intravenous Urography

Computed tomography urography (CTU) has now largely replaced conventional intravenous urography (IVU) as the standard non-invasive imaging modality for

detection of upper urinary tract tumours. Approximately 5 % of patients with bladder cancer will have synchronous or metachronous upper tract TCC. The incidence of synchronous upper urinary tract TCC is low (1.8 %), but higher in patients with trigonal disease (7.5 %) [51]. Patients with high-grade or multifocal tumours are at considerably higher risk of developing upper urinary tract TCC during follow-up [52], especially where CIS is present [53].

Cross-Sectional Imaging

Cross-sectional imaging with CT and/or Magnetic Resonance Imaging (MRI) for staging purposes is not required as part of the assessment of superficial bladder cancer, but is performed when muscle invasion is suspected or confirmed histologically after resection. MRI offers higher resolution for local staging, but, like CT, is unable to distinguish between post-resection inflammatory artefact and perivesical extension of tumour [54]. The two modalities are equivalent for assessing nodal involvement in the pelvis. For assessment of distant nodal disease and visceral or pulmonary metastases, CT is preferred.

Risk Stratification for Recurrence/Progression

TaT1 Tumours

The European Organisation for Research and Treatment of Cancer (EORTC) genitourinary (GU) group has devised a scoring system to predict the risk of recurrence and progression in the short and long term based on six clinicopathological variables (Table 31.3). These predictive variables were identified via a multivariate analysis of data from 2,596 patients with Ta or T1 bladder tumours, enrolled in 7 EORTC-GU trials [34]. The variables are weighted differently according to their influence on recurrence and progression to produce recurrence and progression scores (Table 31.4). These scores can then be used to stratify patients into low-, intermediate-, and high-risk categories for both recurrence and progression (Table 31.5). Criticisms of the EORTC tables include the possible bias inherent in using patients enrolled in trials, who may have more intensive follow-up than non-trial patients, and the fact that the cohort includes few patients with CIS, and few patients treated with BCG. Those patients that did receive BCG did not receive a maintenance regime and repeat transurethral resection (TUR) was not standard practice for high-grade T1 tumours. The Club Urológico Español de Tratamiento Oncológico (CUETO) group from Spain evaluated the EORTC tables in a cohort of 1,062 patients with superficial bladder cancer treated with BCG and found that they overestimated the risk of recurrence and progression in that group [55]. Despite these caveats, the EORTC tables have been validated in an external patient cohort with long-term follow-up [56], and are the risk stratification tool recommended by the European Association of Urology (EAU) [57].

Table 31.3 EORTC variables for assessing recurrence and progression

Number of tumours
Tumour size
Prior recurrence rate
T stage
Associated CIS
Tumour grade

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Table 31.4 Weighting used to calculate recurrence and progression scores

Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2–7	3	3
>8	6	3
Tumour Size		
<3 cm	0	0
≥3 cm	3	3
Prior recurrence rate		
Primary	0	0
≤1 recurrence/year	2	2
>1 recurrence/year	4	2
T stage		
Ta	0	0
T1	1	4
Associated CIS		
No	0	0
Yes	1	6
Grade (WHO 1973)		
G1	0	0
G2	1	0
G3	2	5
Total score	0–17	0–23

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Table 31.5 Risk groups for recurrence and progression

Recurrence score	Recurrence risk group
0	Low risk
1–9	Intermediate risk
10–17	High risk

Progression score	Progression risk group
0	Low risk
2–13	Intermediate risk
14–23	High risk

Reprinted from Sylvester et al. [34]. With permission from Elsevier

CIS

CIS, if untreated, carries a high risk of tumour progression, with approximately 54 % of patients developing muscle invasive disease. When assessing the risk of progression in TaT1 tumours, concurrent CIS confers a significantly increased risk [34]. Likewise, it has been shown that where CIS is seen in conjunction with T1 disease the risk of progression is higher than where it co-exists with Ta disease, which is in turn higher than where CIS present in isolation [58]. Lack of response to BCG is a significant risk factor for progression, with 10–20 % of complete responders developing muscle invasive disease, compared with 66 % of non-responders [59].

Initial Management of Superficial Bladder Cancer

Transurethral Resection

Following the initial diagnosis of a bladder tumour, usually at flexible cystoscopy, a transurethral resection of the tumour (TURT) is performed. This has therapeutic value, and also facilitates grading and staging by providing tissue for histological analysis.

The procedure begins with a bimanual examination of the bladder (and prostate in men) via the rectum in males or the vagina in females. The mobility of the bladder and any palpable mass or thickening is noted. A rigid cystoscope is then passed, with attention being paid to any urethral disease during its insertion. Once the bladder is entered it should be visualized in its entirety without over-distension with irrigating fluid. The site, size, and nature of all tumours are noted. The cystoscope is then replaced with a resectoscope, and resection of the tumour is usually conducted in two stages. Firstly the tumour is resected flush with the normal bladder wall, and secondly the base of the tumour is resected separately with care taken to include the underlying detrusor muscle to allow accurate staging. The two specimens should be sent separately to aid the histopathologist. Where the tumour is less than 1 cm in size, en bloc resection in a single piece is preferred [57]. Any abnormal areas of urothelium should be biopsied, however random biopsies of normal looking urothelium are not routinely required, owing to a low detection rate especially when the tumour is of low grade [60]. Random biopsies are recommended however, where there is positive voided cytology in the absence of visible tumour in the bladder.

Following resection, haemostasis is secured and the procedure is terminated with the placement of an irrigating catheter.

A thorough and complete TURT is a vital step in the management of superficial bladder cancer. A meta-analysis of seven EORTC trials demonstrated significant variability in recurrence rates for similar tumours between different centres, emphasising that resection quality is important regardless of the type of intravesical treatment subsequently used [61].

Adjuncts to Transurethral Resection

Photodynamic Diagnosis (PDD)

PDD involves the intravesical instillation of a photosensitising agent, usually 5-aminolevulinic acid or its hexyl ester (hexaminolevulinate [HAL]), at least 1 h prior to cystoscopy. This compound, a protoporphyrin-IX derivative, is preferentially taken up by tumour cells and produces red fluorescence when blue light of 400 nm wavelength is applied.

A recent systematic review and meta-analysis has assessed the performance of PDD in comparison to conventional white-light cystoscopy (WLC) [62]. Data from 27 component studies enrolling 2,949 patients was analysed. The authors concluded, that PDD has an increased sensitivity for papillary (TaT1) bladder tumours in general, and also demonstrates greater sensitivity for high-grade tumours, and CIS when considered in isolation. This increased sensitivity comes at a cost of reduced specificity, which may lead to additional unnecessary biopsies and therefore patient anxiety.

The ability of PDD to reduce tumour recurrence is difficult to assess, as the use of adjuvant single-instillation chemotherapy has varied between different trials, which confounds the analysis. Whilst two recent randomised controlled trials have failed to show benefit for PDD in terms of reduced recurrence rates [63, 64], a large multi-centre study conducted across North America and Europe has shown a reduced recurrence rate at 9-month follow-up [65]. The aforementioned meta-analysis combining these and other studies demonstrated improved recurrence-free survival at 2 years and an increased time to recurrence with the use of PDD [62]. To date, there is no evidence that use of PDD affects tumour progression.

PDD may be used at the time of primary TURT, during follow-up, or in preference to random biopsies to investigate positive urinary cytology when white-light cystoscopy and upper tract imaging studies are negative.

Narrow-Band Imaging

Narrow-band imaging (NBI) enhances the contrast between the bladder mucosa and vascular structures by filtering white light into two narrow bands (415 and 540 nm). These wavebands are absorbed by haemoglobin, causing vascular structures to appear dark brown or green and the mucosa pink. It has a potential advantage over PDD in that no pre-operative instillation is required. It has demonstrated the potential to improve the detection of primary and recurrent tumours in small non-randomised studies [66], and may reduce recurrence rates when used for follow-up surveillance instead of conventional WLC [67]. The role of NBI cystoscopy as an aid to TURT and in surveillance needs further evaluation in randomised studies.

Immediate Single-Instillation Intravesical Chemotherapy

A single post-operative instillation of chemotherapy, e.g. mitomycin C, following transurethral resection of superficial bladder cancer has been shown to reduce subsequent tumour recurrence rates by 39 % [68]. This instillation can be performed by the surgeon immediately after catheter placement following TURT, or can be administered in the recovery room or in the ward setting post-operatively.

Single-instillation intravesical chemotherapy is discussed in more detail in the Chap. 32.

Further Management of Superficial Bladder Cancer

After an initial TURT, usually accompanied by a single post-operative instillation of intravesical chemotherapy, the clinical and pathological characteristics of the tumour are reviewed and a treatment plan devised. This may involve a repeat TURT procedure (re-resection), further instillations of intravesical chemo- or immunotherapy, and in some cases radical surgery.

Re-resection

Repeat transurethral resection is recommended when the initial resection is judged to be incomplete, either due to the absence of detrusor muscle in the specimen or due to macroscopic residual disease at the end of the procedure. It is also recommended in all high-grade or T1 tumours [57]. Contemporary series have demonstrated residual tumour rates of 33–53 % at repeat TUR [69–71], and a second TURT has shown the potential to reduce tumour recurrence and progression even when adjuvant intravesical treatment is used [72, 73].

Re-resection is also important to prevent understaging. Herr demonstrated that up to 29 % of patients with T1 disease may be upstaged to T2 at re-resection [74], although other series have demonstrated a lower risk (2–10 %) [75, 76]. The risk is higher in patients with muscle absent from their primary resection specimen.

The presence of persistent high-grade T1 disease at re-resection has also been shown to have prognostic importance in patients subsequently treated with induction BCG, with 82 % of patients with persistent T1 disease progressing to muscle invasion within 5 years, compared to 19 % of patients who had a negative re-resection [77]. It has been suggested that early radical cystectomy should be considered for this group.

Intravesical Treatment

Further intravesical instillations of either chemotherapy or immunotherapy using Bacille-Calmette-Guerin (BCG) may be considered based on the risk of recurrence and progression determined by the clinical and pathological factors outlined earlier.

Intravesical treatment for bladder cancer is reviewed in detail in a separate chapter.

Cystoscopic Surveillance

At present, there is no satisfactory alternative to regular cystoscopic surveillance for superficial bladder cancer. Typically, the majority of cystoscopic surveillance is conducted under local anaesthesia using flexible cystoscopy. This is supplemented with cytology and regular upper tract imaging, usually with CT urography, in high-risk cases.

The EAU have issued guidance regarding follow-up strategies for different risk categories, which, whilst based on relatively low-level evidence, acts as a useful template [57].

Low-risk disease is followed up with a cystoscopy at 3 months, and again at 1 year. Annual cystoscopies are then carried out for 5 years at which time follow-up is terminated.

High-risk disease is followed up with a cystoscopy and voided urine cytology every 3 months for 2 years, then 6-monthly until 5 years, and then annually for life. This is accompanied by annual upper tract imaging.

For intermediate-risk disease an in-between strategy is suggested based on tumour characteristics.

Radical Cystectomy for Superficial Bladder Cancer

Radical cystectomy may be utilised as a primary treatment for high-risk superficial bladder cancer where risk of tumour progression is considered to be especially high, or where the patient requests it in preference to intravesical BCG. Several factors have been identified that confer an especially high risk of progression in high-grade T1 disease, including associated CIS, multifocality, tumour size >3 cm and persistent T1 disease at re-resection [78]. If more than one of these risk factors is present, then radical cystectomy should be strongly considered. Residual T1 disease at re-resection is especially associated with early progression in patients treated with induction BCG [77]. There is some evidence that outcomes may be better in patients treated with immediate cystectomy compared to those that undergo cystectomy

after failed intravesical treatment, although the benefit is heterogeneous and likely to include selection bias [79, 80]. Radical cystectomy for superficial disease may also be indicated when aggressive variants of TCC are present, such as when diffuse areas of micropapillary variant are detected.

Where a bladder-preserving strategy with intravesical BCG is adopted, radical cystectomy should be considered when treatment failure occurs. The definition of BCG failure is controversial, but the persistence of T1 disease at the 3-month check cystoscopy, or high-grade Ta disease/CIS at 6-months should prompt consideration of radical cystectomy.

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Chapter 32
Intravesical Therapy for Bladder Cancer

Benjamin L. Jackson, T.R. Leyshon Griffiths, and J. Kilian Mellon

Introduction

Transurethral resection (TUR) of bladder tumours was first described by Gibson in 1935, but by the 1960's there was a growing realisation that TUR alone for superficial bladder cancer was associated with an unacceptable rate of recurrence of approximately 50 % [1]. Following the introduction of intravesical thiotepa in 1961 by Jones and Swinney [2], a number of different agents have been investigated both as an ablative treatment (chemoresection) and as an adjuvant treatment where the primary intention is to prevent recurrence. Intravesical immunotherapy became an alternative treatment option following the introduction by Morales et al. [3] of intravesical Bacille Calmette-Guerin (BCG) in 1976. Over the last 50 years, there has been an extensive body of research devoted to establishing which tumours should be treated with which type of intravesical therapy (if any), and how that therapy should be administered. Despite this, there remains significant controversy in certain areas of the field, and our knowledge continues to evolve with the publication of new data.

B.L. Jackson, MB, ChB (Hons), FRCS (Urol) • T.R.L. Griffiths, BSc, MD, FRCS (Urol)
J.K. Mellon, MD, FRCS (Urol) (✉)
Department of Urology, University Hospitals Leicester, Leicester, UK
e-mail: jkm7@le.ac.uk; jkm7@leicester.ac.uk

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Intravesical Chemotherapy

Thiotepa (**Triethylenethiophosphoramide**) was the first intravesical agent used for bladder cancer, and remains the only agent specifically approved for that purpose by the United States Food and Drug Administration (US FDA). It is an alkylating agent that acts throughout the cell cycle. To date, 6 of 11 randomised controlled trials of thiotepa have demonstrated a reduction in tumour recurrence in comparison with TUR alone, with a mean absolute risk reduction of 17 % [4]. Its use has been limited however, as its low molecular weight leads to significant absorption, which may result in myelosuppression.

Doxorubicin (**Adriamycin**) is an anthracycline antibiotic that acts by binding DNA base pairs, inhibiting topoisomerase II, and interfering with protein synthesis. Its higher molecular weight compared to thiotepa results in a reduction in systemic absorption. Importantly, this allows it, along with epirubicin and mitomycin C, to be used safely immediately after TUR as a single instillation. A combined analysis of randomised trials using doxorubicin demonstrated a mean reduction in recurrence rate of 16 % in comparison to TUR alone [4].

Epirubicin is a derivative of doxorubicin and demonstrates a mean reduction in recurrence rate of 12 % compared to TUR alone [4]. It can be used either as a course of instillations or as a single post-operative instillation.

Mitomycin C (**MMC**) is an anti-tumour antibiotic derived from the *Streptococcus caespitosus* bacterium. It has been successfully used both as a course of weekly instillations (usually for 6–8 weeks) and as a single post-operative instillation. Complete response rates in stage Ta and T1 TCC average 36 % and a mean reduction in recurrence rate of 12 % has been demonstrated in randomised trials [4].

Which Chemotherapeutic Agent Is Most Effective?

A combined analysis of the early randomised trials evaluating the various chemotherapeutic agents above, suggested fairly modest reductions in recurrence rate with all, and no significant differences between the various agents [4]. However, a subsequent meta-analysis of 8 randomised trials of intravesical chemotherapy, using more stringent inclusion criteria, suggested that in fact the benefit of intravesical chemotherapy might be greater than initially appreciated, with a 38 % reduction in recurrence over the first year of follow-up and up to 70 % reduction in recurrence over 3 years [5]. This study suggested that doxorubicin may be inferior to the other agents. A subsequent meta-analysis by the same author pooled eight randomised trials comparing intravesical chemotherapy to BCG treatment, and suggested that MMC may be more effective than the other chemotherapeutic agents studied [6]. Furthermore, when intravesical chemotherapy is compared to intravesical BCG for the treatment of primary carcinoma in-situ, whilst BCG is clearly superior in this setting, the additional benefit is less notable when compared to MMC than to other

chemotherapy agents [7]. As a result of these data, MMC is emerging as the preferred chemotherapeutic agent.

Optimising Administration

Intravesical chemotherapy is usually administered via a urethral catheter. In the case of immediate post-operative instillation, an irrigating catheter is typically placed at the end of the TUR procedure, and the irrigation channel spigotted. This allows continuous bladder irrigation to be commenced if required after drainage of the chemotherapy agent if bleeding is present. After catheter placement the drug is instilled after appropriate dilution, and the catheter occluded by means of a flip-flow valve. Ideally, the instillation should be performed by the surgeon immediately after completing the operation. However, instillation can be performed up to 6 h later when the patient is in the ward or recovery room. After a dwell time of 1 h the valve is opened to release the agent into a catheter bag, which is disposed off as cytotoxic waste.

For patients undergoing regular instillations of chemotherapy, the instillation may be performed using a temporary Nelaton catheter, which can then be withdrawn and the patient allowed to void the solution into the toilet after 1 h. Men should void sitting down to minimise the risk of splashing.

Mechanistic studies in cultured tumour cells, animal models and human bladder tissue have suggested several approaches to enhance MMC concentration in tumour cells which may translate into improved clinical outcomes. Only one small randomised trial has compared "optimised" MMC with standard MMC administration [8]. In the "optimised" arm, the urine was alkalinised by use of sodium bicarbonate, the dose volume was reduced from the conventional 40 to 20 ml, patients were voluntarily dehydrated by fluid restriction, the volume of residual urine at the time of treatment was minimised and the MMC dose was 40 mg (i.e. standard dose). In the control arm, these optimisation measures were not performed and the dose administered was only 20 mg, a dose now considered by most to be suboptimal. With this caveat, "optimised" MMC was superior to standard MMC with respect to disease-free survival at 5 years (41 % vs 25 %). Drug concentration appears to be more important than dwell time [9]. Some have advocated asking patients to turn prone during dwell time to assist delivery to the anterior bladder wall/dome but there is no evidence to support this.

Single Instillation Chemotherapy

A single instillation of post-operative chemotherapy has been demonstrated to reduce the likelihood of tumour recurrence following TUR. This was first demonstrated in a randomised trial by Oosterlinck et al. comparing a single instillation of

epirubicin to water following TUR of solitary bladder tumours [10]. The benefit was subsequently confirmed for multiple tumours in a further randomised trial using MMC [11]. The effect can be explained by the destruction of detached tumour cells immediately after TUR, or as an ablative (chemoresection) effect of residual tumour cells at the resection site.

Sylvester et al. conducted a meta-analysis of randomised trials of single instillation chemotherapy and concluded that over a median follow-up of 3.4 years there was a reduction in tumour recurrence from 48.4 to 36.7 %. The benefit was greater in those with multiple tumours and in those at higher risk of recurrence as defined by the EORTC risk tables [12] (see Chap. 31). As a result of this the European Association of Urology (EAU) now recommends single instillation chemotherapy following TUR of all new bladder tumours [13]. An exception to this is when there is confirmed or suspected bladder perforation, where there is a risk of local complications due to extravasation of the drug, or when post-operative bleeding necessitates that continuous bladder irrigation be maintained. There is also little point in administering chemotherapy where the tumour is clearly determined to be muscle invasive based on cystoscopic or bimanual examination findings.

The timing of the instillation appears to be important. Kaasinen and co-workers found in a retrospective analysis that the recurrence rate doubled if the instillation was given more than 24 h following TUR [14]. The EAU recommends that the instillation be performed within 6 h [13]. There are a number of potential advantages to administering the drug in theatre immediately, in that the surgeon can take responsibility for administration, there is a controlled environment, the bladder can be fully emptied prior to administration, the patient will be drowsy for most of the dwell time, and there will be close monitoring following administration as the patient will be in the recovery room.

Single instillation chemotherapy has not, despite the above evidence, become uniform practice amongst urologists. Objections include doubt about whether there is benefit in those with intermediate- or high-risk tumours in whom further intravesical treatment may be required anyway. Gudjonsson et al. found no evidence of benefit to early single instillation chemotherapy for intermediate and high risk tumours [15]. However, this conclusion from this study has been criticised, as the trial was underpowered for reliable sub-group analysis [16]. Cai and coworkers also found no benefit to single instillation chemotherapy in patients who subsequently underwent BCG treatment for high risk disease, although again this study was underpowered [17]. A further objection is that in solitary, low-grade tumours the risk of recurrence is small, consequently the number needed to treat to prevent a recurrence is high (8.5) and single instillation chemotherapy may only prevent small recurrences that can be fulgurated in the office setting via flexible cystoscopy [18]. However, 50 % of patients in that study who recurred required an inpatient TUR procedure, and many would argue that the number needed-to-treat is acceptable for a treatment with good tolerability. It should be noted that whilst there is ample evidence of a reduction in recurrence rate with single-instillation chemotherapy it does not reduce the risk of progression to muscle invasive disease.

Recent publication of the results of a Phase III trial has led to the establishment of a new indication for single instillation chemotherapy, following nephroureterectomy for upper tract urothelial cancer. Up to 40 % of patients treated for upper tract tumours will subsequently develop a bladder tumour during follow-up. The ODMIT-C trial in the UK demonstrated that a single instillation of MMC at the time of catheter removal following nephroureterectomy can reduce the likelihood of developing a bladder tumour by 11 % in absolute terms; the number needed-to-treat was 9 [19].

Courses of Intravesical Chemotherapy

It has been estimated from the combined data of several randomised trials that the effect of a single instillation of intravesical chemotherapy lasts for approximately 500 days [20]. For low risk tumours a single instillation alone is considered to be sufficient adjuvant treatment. For intermediate and high-risk tumours however the risk of recurrence despite single instillation chemotherapy remains significant, and further instillations of chemotherapy are a treatment option, although for high-risk tumours intravesical BCG is preferred.

Huncharek et al. in a meta-analysis of eleven randomised trials including 3,703 patients demonstrated a 44 % reduction in the 1-year recurrence rate for patients with solitary tumours treated with adjuvant intravesical chemotherapy in comparison with TUR alone [21]. This study demonstrated significant heterogeneity in treatment effect, with greater benefit in those undergoing longer courses of chemotherapy up to 3 years in duration. A subsequent meta-analysis confirmed the efficacy of adjuvant chemotherapy in prevention of recurrence in patients with multiple tumours [1]. Intravesical chemotherapy has not been shown to reduce the risk of tumour progression [22].

The ideal duration and schedule of intravesical therapy remains uncertain [23]. At present the EAU does not recommend maintenance schedules lasting longer than 1 year [13], although individual studies have shown benefit with regimes lasting as long as 3 years [24]. A 6-week course of weekly instillations is typical in UK practice.

Toxicity

In general, intravesical chemotherapy is well tolerated [25]. Transient lower urinary tract symptoms due to chemical cystitis occur in up to 30 % of patients. Allergic skin rashes may occur in up to 12 %. Systemic complications such as myelosuppression are rare. Extravasation and consequent local tissue reaction have been reported following post-operative instillation, but these represent isolated case reports only [26–28]. The incidence of adverse events following immediate instillation has, in general, been reported to be low.

Intravesical Immunotherapy (BCG)

Mechanism of Action

The precise mechanism of BCG anti-tumour activity is unknown. The mycobacteria are thought to bind to the bladder wall via the interaction between the bacterial antigen 85 complex and fibronectin. The subsequent reaction is certainly immunologically mediated, as athymic mice are unable to mount an anti-tumour response [29], and T-cell deplete mice respond poorly [30]. BCG behaves as a non-specific immune stimulant and activates a variety of immune cells. It is likely that exposure to BCG acts as a danger signal, leading to local dendritic cell activation and enhanced antigen presentation [31]. The activated dendritic cells may then migrate to local lymph nodes where peptides of BCG and TCC origin are presented to T lymphocytes. Activated T lymphocytes then migrate to the urothelium and lyse TCC cells, either directly through the CD8-positive population or indirectly by activating natural killer cells or macrophages.

The precise underlying immune mechanisms behind BCG response are not fully elucidated, but an array of cytokines are demonstrable in the urine of patients treated with BCG, as well as in immunocompetent cell cultures [32]. High expression of Th1 cytokines (Il-2, Il-12 and IFN-γ(gamma)) has been noted in BCG-responsive patients, and hence proper induction of the Th1 pathway may be an important factor in determining efficacy. It has been demonstrated that activation of the Th1 pathway facilitates induction of BCG-induced macrophage cytotoxicity [32]. Upregulation of the Th1 pathway at the expense of the Th2 pathway occurs in patients who are co-administered interferon-α(alpha), which may explain the potential of this agent to induce tumour response in those unresponsive to induction BCG [33] (see later).

Administration and Dosing

Induction BCG

The use of intravesical BCG as a treatment for superficial bladder cancer began in 1976 with the work of Morales et al. [3, 5]. Their initial protocol of six instillations given on a weekly basis over 6 weeks has persisted to the present day, and now represents the standard induction course. Morales initially combined intravesical BCG with percutaneous injection of the same, but intravesical instillation alone has proven to be sufficient [34]. Commonly used strains include Tice, RIVM, and Connaught. The live attenuated vaccine is combined with 50 ml of normal saline and instilled via a temporary urethral catheter. If catheterisation is traumatic or haematuria is encountered then the dose should be withheld. The dose is retained in the bladder for 1 h, following which the patient voids sitting down.

Following an induction course of six instillations, initial response is assessed via a cystoscopy with or without bladder biopsies, usually undertaken a further 6 weeks after the final instillation. If residual or recurrent disease is present then various options may be considered including radical cystectomy, further BCG treatment, or newer intravesical treatments (see BCG Failure). If there is no persistent or recurrent tumour present, then a maintenance schedule of treatment may be instituted, or further cystoscopic follow-up scheduled.

The effectiveness of intravesical BCG was initially demonstrated in a randomised trial by Lamm et al. [24, 35] who demonstrated a reduction in recurrence rate from 42 % in those receiving TURBT alone to 22 % with TUR followed by BCG treatment. The ability of BCG treatment following TUR to reduce recurrence in comparison with TUR alone was confirmed in a meta-analysis by Shelley and co-workers who analysed six randomised trials of BCG treatment for Ta/T1 bladder cancer and demonstrated a 56 % hazard reduction for recurrence in the BCG treated group [36].

Maintenance BCG

The concept of giving further instillations of BCG at intervals after the initial induction course, in order to sustain an immune response within the urothelium, is known as maintenance treatment. Lamm and co-workers [37] in a Southwest Oncology Group (SWOG) trial compared a maintenance BCG regime with induction BCG alone in a randomised trial of patients with carcinoma *in situ* (CIS) or those at high risk of recurrence (defined as two tumour episodes in the last year, or three within 6 months). They demonstrated an improvement in median recurrence-free survival with maintenance BCG (76.8 months *vs.* 35.7 months in the induction-only group). There was also an improvement in worsening–free survival (defined as development of muscle invasive disease, or need for cystectomy, radiotherapy, or systemic chemotherapy). Since that landmark study, there have been a number of meta-analyses that have confirmed the importance of maintenance therapy, particularly in terms of reduction in tumour progression. Sylvester et al. reviewed data from 24 randomised trials, 20 of which included some form of maintenance therapy, and concluded that BCG treatment reduced the overall risk of progression to muscle invasive disease from 13.8 to 9.8 % over a median follow-up of 2.5 years, but only where maintenance therapy of at least 12 months duration was used [38].

Whilst it remains likely that maintenance therapy is required to achieve optimal outcomes with BCG treatment, this conclusion has been thrown into doubt by a recent study by Herr et al. [39] who reviewed the outcomes of 1,021 patients with high-risk non-muscle invasive bladder cancer treated with induction BCG only following initial TUR and re-resection. They demonstrated similar progression and recurrence rates to those seen in other studies where maintenance BCG was used. However, these results need to be interpreted with caution. The study in question was non-randomised and a further caveat is the lack of patients with CIS.

The ideal maintenance schedule is not known. The SWOG regimen used by Lamm involves three instillations given over a 3 week period at 3, 6, 12, 18, 24, 30, and 36 months following induction. Various other regimens have been proposed, but none has proven superiority over the SWOG protocol. A minimum of 12 months treatment appears to be required for superiority over MMC in terms of recurrence and progression [40, 41].

The principal drawback of maintenance therapy is toxicity. Only 16 % of patients enrolled in the aforementioned SWOG study [37] completed the full maintenance course due to the side-effects of treatment. However, the majority of patients in the SWOG trial were able to tolerate at least one instillation every 6 months. Furthermore, Van der Meijden found in a large cohort of patients receiving the SWOG regime, that whilst cessation of treatment increased from induction to 6 months it remained stable or decreased thereafter. They concluded that local and systemic side-effects tended to remain stable or even decrease after the first 6 months on maintenance BCG [42].

Reduced Dose BCG

The toxicity of BCG maintenance regimes have led to attempts to reduce the administered dose in order to minimise side effects. The Club Urológico Español de Tratamiento Oncológico (CUETO) group from Spain compared one-third dose to standard dose BCG and found no difference in recurrence or progression rates overall, however there were higher recurrence and progression rates in multifocal tumours [43]. The same group compared one-sixth dose to one-third dose BCG in intermediate risk tumours and found a significant reduction in efficacy with the lower dose, indicating that one-third dose may be the maximum feasible dose reduction [44]. The European Organisation for Research and Treatment of Cancer (EORTC) 30962 study is soon to be reported comparing one-third to full dose BCG in 1 and 3 year maintenance regimes, and may give further information as to the ideal treatment dose and duration. The study protocol does not include multifocal high-grade T1 tumours or those with CIS however, so its conclusions will not be applicable to most patients with high-risk disease.

Sequential or Alternating Intravesical Chemotherapy and BCG

Several investigators have tested the hypothesis that alternating or sequential chemotherapy and immunotherapy is more effective and less toxic than chemotherapy or BCG alone. A phase III trial compared the efficacy of sequential MMC and BCG (MMC weekly for 4 weeks followed by BCG weekly for 10 weeks) with MMC monotherapy (weekly instillation for 10 weeks) in patients with intermediate and

high-risk superficial bladder cancer including CIS [45]. The sequential schedule was comparable with MMC alone in terms of recurrence, progression and toxicity. Another randomised trial compared alternating MMC and BCG instillations (MMC weekly for 6 weeks followed by alternating monthly instillations of BCG and MMC for 1 year) with BCG monotherapy (weekly for 6 weeks followed by monthly for 1 year) in the treatment of CIS [46]. Alternating therapy was shown to be less effective for reducing recurrence but better tolerated than BCG monotherapy. Sequential BCG and epirubicin (alternating weekly BCG and epirubicin for 6 weeks followed by alternating monthly instillations for 1 year) has been compared with BCG monotherapy following the same schedule, and shown to be similar with regard to efficacy and superior in terms of toxicity [47].

Choice of Intravesical Therapy According to Risk Stratification

The EORTC risk tables [12] may be used to quantify the risk of recurrence and progression in patients with superficial bladder cancer, and thus may be used to stratify them into low-, intermediate-, and high-risk groups (see Chap. 31). This is useful as a basis for determining which adjuvant intravesical treatment is required. It should be noted however that various approaches have been taken in different trials in order to stratify risk of recurrence and progression, and hence the definitions of low, intermediate and high-risk are somewhat heterogeneous amongst the available evidence.

Low-Risk Disease

Patients with solitary, low-grade, non-invasive tumours have a low risk of recurrence (24–37 % at 5 years) and a very low risk of progression (0–1.7 % at 5 years) [12]. Consequently, the EAU recommend that a single post-operative instillation of chemotherapy is adequate treatment [13], and no further intravesical therapy should be considered unless there is recurrence.

Intermediate-Risk Disease

Intermediate-risk bladder cancer represents a broad spectrum, and within this risk group there will be a variable risk of recurrence and progression depending on tumour characteristics. It is difficult, therefore, to recommend a single intravesical treatment option. The EAU recommend that either a course of intravesical

chemotherapy (the duration and intensity of which is not specified) be given or intravesical BCG depending on whether prevention of simply recurrence, or recurrence and progression is required.

A recent meta-analysis by Malmstrom et al. [48] has helped to clarify the relative efficacy of intravesical BCG and intravesical chemotherapy with regard to prevention of recurrence in intermediate-risk patients. Some [41, 49], but not all [25], of the previous meta-analyses had demonstrated a lower recurrence rate for BCG-treated intermediate-risk patients in comparison to those treated with intravesical chemotherapy. However, it had been suggested that this might partly be due to pre-treatment with chemotherapy biasing the results of these studies in favour of BCG [50]. Malmstrom et al. conducted a meta-analysis using the individual data from 2,820 patients in nine randomised controlled trials comparing MMC with BCG. Three quarters of the patients had intermediate-risk disease. They demonstrated a 32 % lower recurrence rate in the group receiving maintenance BCG. The additional benefit was seen regardless of whether previous chemotherapy had been given.

It seems likely, therefore, that maintenance BCG offers greater prophylaxis against recurrence than intravesical chemotherapy in intermediate-risk patients. However, as discussed previously, this comes at the cost of more side-effects [25]. For patients at the low end of the intermediate risk spectrum, therefore, it seems difficult to justify. Furthermore, it must be remembered that the EORTC risk tables may overestimate the risk of recurrence in some patients [51], as the data they are compiled from is from an era when single-instillation chemotherapy was not in routine use.

In practice, the management of this group of patients varies according to individual tumour characteristics, patient choice, and local protocol, with some receiving singe-instillation chemotherapy only, others a course of chemotherapy, others a BCG schedule, and still others a single post-operative instillation of chemotherapy following TUR or biopsy of a recurrence. Whether an induction course of chemotherapy should be followed by maintenance therapy is uncertain, but as mentioned previously, it is thought that maintenance should not be given for longer than 1 year [23]. The role of single-dose postoperative intravesical chemotherapy following TUR/biopsy for recurrence has not been specifically evaluated in a randomised trial.

High-Risk Disease

Patients with high-risk disease have an increased risk of both recurrence and progression and consequently BCG treatment is recommended by the EAU in all such patients, other than where early radical cystectomy is undertaken [13]. The EAU guidelines recommend the use of a maintenance schedule, although as mentioned previously this has recently been challenged in a non-randomised study [39].

A number of studies have demonstrated the superiority of BCG over MMC and other forms of intravesical chemotherapy in terms of recurrence in patients with high-risk disease. Bohle et al. in a meta-analysis including 11 trials and 2,749 patients with superficial bladder cancer demonstrated a significant reduction in recurrence rate with BCG treatment compared with MMC (38.6 % vs 46.4 %) [41]. In this study, benefit was seen in both high and intermediate risk patients, but mainly limited to those undergoing BCG maintenance therapy as opposed to induction alone. Shelley and co-workers performed a further meta-analysis comparing BCG with MMC, which demonstrated a reduction in recurrence of 31 % but only in high-risk patients. Again, the benefit was limited to those undergoing maintenance therapy [25]. Since the publication of these meta-analyses, there have been several further randomised trials including high-risk patients demonstrating the superiority of BCG in terms of recurrence compared with MMC [52], epirubicin and interferon in combination [53], and epirubicin alone [54].

The question of whether BCG treatment is capable of reducing the risk of progression of high-risk superficial bladder cancer to muscle invasive disease is more controversial. The majority of individual studies comparing BCG with chemotherapy are insufficiently powered to detect a difference in progression, as few patients progress within the follow-up period. The EORTC 30911 trial comparing BCG, BCG and isoniazid, and epirubicin, whilst not demonstrating a difference in progression to muscle invasion, did demonstrate a reduction in metastases and improvements in disease-specific and overall survival in the BCG groups (isoniazid offered no additional value) [54]. However, this may be a reflection of the lack of efficacy of epirubicin. To date, two meta-analyses have demonstrated a reduction in tumour progression in high-risk patients. The analysis by Sylvester et al. for the EORTC mentioned earlier demonstrated a reduction in tumour progression in comparison with patients receiving varying types of intravesical chemotherapy, but only with maintenance BCG [38]. Bohle and colleagues confirmed similar findings in an analysis of BCG compared with MMC specifically, with maintenance treatment again being required for benefit [40].

The ability of BCG treatment to reduce tumour progression is, however, not beyond question. The EORTC meta-analysis [38] has some weaknesses in that the control group received varying types of chemotherapy, some of which may be less effective than MMC [6], and that a heterogeneous definition of progression was used in the component trials. The meta-analysis by Bohle and colleagues [40] has also been criticised for including non-randomised studies. Furthermore, the recent individual patient data meta-analysis by Malmstrom et al. demonstrated no difference in progression between patients receiving BCG and MMC over 4.4 years follow-up [48].

Regardless of the debate about tumour progression, BCG treatment has demonstrated clear superiority over chemotherapy in terms of recurrence prevention in the setting of high-risk disease, and the balance of evidence suggests that maintenance BCG is the optimum treatment in high-risk patients, excepting those that opt for early radical cystectomy (Chap. 31).

CIS

CIS may either be primary (present in isolation), or seen in association with papillary (stage Ta or T1) or muscle invasive tumours. When present with papillary disease it confers an increased risk of progression and these tumours are in the high-risk group by definition. CIS is unlikely to be eradicated by endoscopic treatment alone so either adjuvant intravesical treatment or cystectomy is required.

Sylvester et al. [7] looked specifically at a subgroup of 700 patients from the aforementioned EORTC meta-analysis of BCG *vs.* intravesical chemotherapy that had CIS, either in isolation or in association with papillary disease. They demonstrated a higher complete response rate with BCG treatment in comparison with chemotherapy (68.1 % *vs.* 51.5 %) and a greater disease-free rate at a median follow-up of 3.6 years (46.7 % *vs.* 26.2 %). MMC performed better than other forms of chemotherapy, with a disease-free rate of 32.9 %. Superiority of BCG over MMC was only confirmed when maintenance BCG was used. As a consequence of these data, there is a consensus that maintenance BCG is the optimum treatment for patients with CIS, with or without papillary disease where radical cystectomy is not performed.

BCG Toxicity and Management of Adverse Events

Whilst BCG treatment possesses advantages in terms of efficacy over intravesical chemotherapy, this comes at the cost of increased side effects. A meta-analysis comparing BCG treatment (both maintenance and non-maintenance) to MMC demonstrated a greater incidence of local and systemic side-effects with BCG (44 % *vs.* 30 % and 19 % *vs.* 12 % respectively) [25].

Preventive measures to minimise adverse events include allowing at least 2 weeks after TUR before initiating treatment and deferring an instillation if haematuria is present or catheterisation is traumatic. A randomised trial has shown a reduction in BCG adverse events with prophylactic ofloxacin administration with each dose, although whether this affects the efficacy of BCG in an adequately powered study is unknown [55]. Isoniazid did not reduce BCG toxicity in a randomised study [54].

Common local side effects of BCG treatment include irritative urinary symptoms and haematuria due to cystitis. If these occur then urinary tract infection should be sought and treated if present. Further treatment options include anticholinergic medication or non-steroidal anti-inflammatory drugs. If symptoms persist then dose reduction or cessation of treatment may be required.

Granulomatous prostatitis is common histologically in patients undergoing BCG treatment but gives rise to symptoms in less than 5 % of cases [56]. Initial treatment is usually with a 6-week course of a fluoroquinolone antibiotic, often combined with prednisolone. If this fails, anti-tuberculous chemotherapy may be required.

Less common local complications include bladder contracture, which may give rise to intractable urinary frequency. Cystoscopic hydrodistention may be tried, but if this fails then a cystectomy may ultimately be required if symptoms are severe. Ureteric obstruction occurs occasionally and may require nephrostomy insertion or stenting, although it usually resolves spontaneously.

Allergic reactions including skin rashes and arthropathy may occur with BCG treatment. BCG-associated reactive arthritis is seen in patients with the HLA – B27 genotype. Allergic reactions are treated with cessation of treatment and corticosteroids. This is of particular importance in those with arthropathy as permanent joint damage may occur.

Sepsis during BCG treatment is most commonly due to uropathogens, and therefore the initial management of the febrile patient undergoing BCG treatment is urine culture and treatment with intravenous antibiotics. If a fever of greater than 38.5 °C persists for more than 48 h, then systemic BCG infection ("BCGosis") must be suspected and triple therapy with isoniazid, rifampicin and ethambutol for 6 months is required. Pyrazinamide, whilst commonly used to treat tuberculosis, is ineffective against *Mycobacterium bovis* and is therefore not used. Cessation of BCG treatment is mandatory.

Failure of Intravesical BCG

BCG failure can be subdivided into BCG refractory, resistant, and relapsing cases. BCG refractory disease refers to cases in which there is inadequate initial response to an induction course of BCG. If muscle invasive disease is present at the initial check cystoscopy at 3 months, then BCG-refractory disease is confirmed and radical treatment is required. If high-risk superficial disease is present at the initial check cystoscopy (either high-grade Ta/T1 tumour or CIS), then a second course of six instillations of BCG may be given, with complete response achieved in up to 50 % [57]. In the SWOG 8507 study, one-third of patients with persistent CIS after six instillations of BCG achieved a complete response after a further three BCG instillations [37]. However, failure to achieve an initial complete response to BCG, particularly if T1 TCC persists, is associated with an increased risk of subsequent progression, and hence consideration should be given to opting for radical cystectomy at this stage [58]. If high-risk superficial disease remains at the second check cystoscopy at 6 months then BCG-refractory disease is confirmed and radical cystectomy is suggested as the preferred treatment modality. Patients with persistent high-risk superficial disease who are not fit for radical cystectomy, or who decline the procedure, may be eligible for the alternative intravesical therapies described in the following section.

BCG-resistant disease refers to a situation where there is persistent superficial tumour at the 3 and 6 months check cystoscopies, but where the disease is low- or intermediate-risk by the time of the second check cystoscopy. The management of this group of patients is more controversial. Radical cystectomy may represent

overtreatment for low-grade superficial recurrent disease. These patients may be managed with endoscopic resection of recurrences alone, a trial of intravesical chemotherapy (if not given previously), or one of the alternative treatment modalities in the following section.

BCG-relapsing disease refers to patients who achieve an initial complete response (disease-free state), but who subsequently develop further disease. If the recurrent disease is muscle invasive then neoadjuvant systemic chemotherapy and radical cystectomy or radical radiotherapy is required. In those with recurrent superficial disease, especially if low- or intermediate-risk, management is more controversial. There is evidence that a longer disease-free interval prior to recurrence portends a better prognosis [59], and it has been suggested that more conservative strategies might be adopted in these patients.

In summary, radical cystectomy remains the mainstay of treatment for failure of intravesical BCG, however there are a number of further intravesical options for patients in whom this is not feasible or is declined. These are summarised in the following section.

Intravesical Therapy After BCG Failure

Post-BCG Immunotherapy

BCG Combined with Interferon

One-third dose intravesical BCG combined with interferon-α(alpha) at a dose of 50–100 million units has been utilised in patients with BCG-refractory disease. The principle is that the immunomodulatory activity of interferon-α(alpha) in terms of stimulation of natural killer cells and enhancing antibody responsiveness will enhance the activity of BCG. A randomised phase II trial enrolled 1,007 patients, some of whom were BCG-naïve and received interferon-α(alpha) in combination with full dose BCG, whilst the group who had failed BCG therapy received one-third dose BCG in combination with interferon [60]. The disease-free rate in the BCG-refractory group at 24-month follow-up was 45 %, with an improved response rate in those who failed BCG treatment more than 12 months after their induction course [59].

Keyhole-Limpet Hemocyanin (KLH)

KLH was first used clinically for intravesical treatment of bladder cancer by Olsson et al. in 1974 [61]. It is a non-specific immune response modifier, isolated from the sea mollusc *Megathura crenulata*. In BCG-refractory patients, the overall complete response rate is only 26 %, however those with BCG-refractory CIS without papillary disease fared better with a complete-response rate of 50 % [62].

Other Novel Immunotherapeutic Agents

The immunotoxin VB4-845 has demonstrated safety in a Phase I study, and the potential for efficacy with a complete-response rate of 39 % in 64 patients evaluated [63]. Urocidin[tm] (Bioniche Life Sciences) is a mycobacterial cell wall–DNA complex currently undergoing phase III trials in BCG refractory patients.

Post-BCG Chemotherapy

Mitomycin-C (MMC)

There are few reliable data analysing the use of MMC in BCG-refractory patients. In one study comparing BCG and MMC, patients were allowed to cross-over after treatment failure. Of 21 patients who underwent MMC treatment after BCG, only 4 remained disease free after 64 months of follow-up [64].

Gemcitabine (Intravesical)

Gemcitabine, a nucleoside analogue that inhibits DNA replication, is used as part of standard chemotherapy regimes for invasive urothelial cancer in the neo-adjuvant and palliative settings, and hence it was hypothesised that it may be effective as intravesical treatment. Phase II studies have shown its potential to achieve recurrence-free survival in BCG refractory patients, with one group reporting a 1-year recurrence-free survival rate of 21 % [65]. Another group reported a lower recurrence rate after 1-year in those with BCG-refractory intermediate-risk disease (25 %) in comparison with BCG-refractory high-risk disease (56 %) [66]. A further phase II study randomised 80 patients with persistent high-risk superficial bladder cancer after induction BCG to receive either intravesical gemcitabine twice-weekly for 6 weeks followed by a maintenance schedule, or further BCG treatment. The group treated with gemcitabine demonstrated an improvement in 2-year recurrence-free survival (19 % *vs.* 3 %) [67].

The apparently promising results of these small studies are tempered somewhat by data demonstrating that gemcitabine is significantly less efficacious than BCG in the primary treatment of high-risk superficial disease [68], and that it is no better than placebo when given as single-instillation treatment following TUR [69]. Its current role in BCG-refractory cases is therefore unclear.

Docetaxel

Docetaxel, a member of the taxane group of chemotherapy agents, is a microtubule inhibitor. Laudano and coworkers reported their experience of 33 BCG-refractory patients treated with intravesical docetaxel with a median follow-up of 29 months

[70]. 61 % of patients achieved a complete response, with 32 % remaining disease free at 2 years. These are promising early results, but further large scale studies are needed.

Device-Assisted Therapies

Chemohyperthermia (c-HT) describes the combination of intravesical chemotherapy and hyperthermia (HT). Although the term thermochemotherapy has been used, there is a need to distinguish treatments, which not only heat the chemotherapy but also the bladder wall to supraphysiological temperatures of between 44 and 45 °C. The most common form of c-HT uses the Synergo HT system in which local HT is administered via direct microwave irradiation of the urothelium by means of a 915 MHz intravescial microwave applicator. Over the last 15 years, c-HT has been tested in a variety of clinical settings including several phase II randomised trials in the BCG-naïve setting [71]. Hyperthermia increases cell membrane permeability, alters intracellular drug trafficking, and enhances the effects of cytostatic chemotherapy on inhibition of DNA synthesis and DNA damage [72].

Data supporting the role of c-HT in BCG-refractory disease has come from several proof-of-concept studies. The Synergo working party evaluated 51 patients with CIS, 34 of whom had failed BCG treatment. They demonstrated a complete-response rate of 92 %, with 50 % remaining disease-free at 2-year follow-up [73]. In the largest series to date, Nativ and coworkers used maintenance HT-MMC in 111 patients with superficial bladder cancer in whom BCG therapy had failed, including 77 % with high-risk disease. They reported recurrence-free rates of 85 and 56 % at 1 and 2 years; 3 % of the patients progressed to muscle invasion and 5 % withdrew from treatment due to adverse events [74].

The use of c-HT is being further evaluated in BCG-refractory patients who are not candidates for cystectomy in the UK-based HYMN trial. This study includes patients with persistent grade 2/grade 3 papillary disease or CIS after induction BCG who are randomised to c-HT or a second course induction course of BCG. Patients who have relapsed on maintenance BCG may also be enrolled, and are randomised to c-HT or their institution's standard treatment.

Electromotive Drug Administration of MMC (**EMDA-MMC**) is an alternative way of enhancing MMC absorption, by using an electrical gradient generated across the bladder wall by means of electrodes placed within the catheter and on the patient's lower abdominal wall. EMDA-MMC has been demonstrated to be superior to standard MMC in the treatment of high-risk superficial bladder cancer, but did not demonstrate superiority to BCG [75]. The same group then evaluated a regimen alternating BCG doses with EMDA-MMC in a sequential fashion. This study randomised 212 BCG-naïve patients with high-risk disease to receive either the sequential regime or BCG alone. After a median follow-up of 88 months, there were significant reductions in recurrence (42 % *vs.* 58 %), progression (9.3 % *vs.* 22 %), disease-specific mortality (5.6 % *vs.* 16.2 %), and overall mortality (21.5 % *vs.*

32.4 %). These results are promising, but it is worth noting that the mortality in the BCG-treated group in this trial is unusually high (50 %).

A recent study again from Di Stasi et al. has evaluated the use of a single treatment with EMDA-MMC immediately prior to TUR (n = 124) in comparison to patients undergoing TUR alone (n = 124) or TUR followed by standard post-operative MMC (n = 126) [76]. They demonstrated a greater median disease free interval with pre-operative EMDA-MMC (52 months) compared with TUR and standard MMC (16 months) or TUR alone (12 months). It should be noted however that patients who were found to have CIS were excluded from the analysis.

To date, no studies have specifically evaluated EMDA-MMC in patients who are BCG-refractory, although the study by Di Stasi et al. allowed crossover of patients to EMDA-MMC if they did not respond to primary BCG treatment [75]. The efficacy of EMDA-MMC in the BCG-refractory setting is therefore experimental at present.

Photodynamic Therapy (**PDT**) relies on the selective uptake of photo-sensitising compounds by tumour cells, which allows their subsequent destruction via excitation with a specific light wavelength. 5-aminolevulinic acid (5-ALA) has been used as the photo-sensitiser, and can be administered intravesically. Berger and colleagues evaluated this technique in a cohort of 31 patients 10 of whom were BCG-refractory [77]. At a mean follow-up of 23.7 months, 16 patients were free of recurrence, and the remaining 15 had recurred after a mean of 8.3 months. Four of ten BCG-refractory patients were free of recurrence at the end of the study.

Summary

Newer intravesical chemotherapy agents such as gemcitabine and docetaxel, novel immunotherapies, and device-assisted treatments have all shown promise in the treatment of patients who have failed BCG treatment and are not candidates for radical cystectomy. To date, however, much of their potential benefit is based on non-randomised proof-of-concept studies or small phase II trials, and no single treatment can be recommended as the preferred choice based on the current evidence. At best, currently available bladder-sparing treatments for those with BCG-refractory TCC are associated with 2-year disease-free survival rates of approximately 50 %. Treatments with the most promising developmental data such as c-HT are now being evaluated in phase III trials.

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Chapter 33
Molecular Biology of Urothelial Cancer

Sounak Gupta and Donna E. Hansel

Introduction

Cancer of the urinary bladder is ranked as the 5th leading cause of cancer worldwide, with an estimated global incidence of about 357,000 cases, and it accounts for about 145,000 deaths per year [1]. New cases in the United States in 2010 alone were projected to be greater than 70,000 and over 14,000 deaths were attributed to the disease in 2009 [2, 3]. Urothelial carcinoma (UCa; formerly referred to as transitional cell carcinoma-TCC) is the most common histological subtype, accounting for over 90 % of all cases, while squamous cell carcinoma, adenocarcinoma and small cell carcinoma are significantly less common [2, 4, 5].

UCa is pathologically diagnosed along a morphological spectrum, which is generally segregated into papillary and non-papillary categories. Papillary urothelial neoplasms range from the essentially benign papilloma to papillary urothelial neoplasm of low malignant potential (PUNLMP), low-grade papillary urothelial carcinoma (LGPUC) and high-grade papillary urothelial carcinoma (HGPUC). Similarly, flat urothelial lesions include a range from urothelial hyperplasia and dysplasia to flat urothelial carcinoma *in situ* (CIS).

From a conceptual perspective, the most straight-forwarded segregation of lesions is into the categories of low-grade *versus* high-grade disease, with the latter including HGPUC, flat CIS and invasive high-grade UCa. The identification of molecular marker correlates of invasive high-grade urothelial cancers, in particular, has been a major focus of bladder cancer research over the years as approximately 30–50 % of patients with muscle-invasive disease develop metastatic disease and

S. Gupta, MBBS, PhD
Department of Anatomic Pathology, The Cleveland Clinic, Cleveland, OH, USA

D.E. Hansel, MD, PhD (✉)
Department of Pathology and Laboratory Medicine Institute,
Cleveland Clinic, Cleveland, OH, USA
e-mail: hanseld@ccf.org

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Table 33.1 Reported distribution of molecular alterations in low- *versus* high-grade disease

Molecular alteration	Correlated with low-grade disease (% of cases)	Correlated with high-grade disease (% of cases)	Reference #
FGFR3	40–88	0–36	[28–30, 32–38]
RAS	0–44	2–65	[32, 33, 42, 43, 45–50]
p53	0–50	42–92	[65–70, 91–93, 95]
Rb	21–48	25–64	[85–87, 89, 91–93, 95]
EGFR	24–49	45–71	[102, 118, 119, 121, 146, 147]
HER2/neu	0–74	23–72	[69, 101, 102, 108, 110, 111, 113, 115, 141, 142, 144]
PI3-Kinase	18–26	5–16	[33, 169]
PTEN	3–49	10–94	[31, 187–191]
TSC1 (LOH)	43–68	68–71	[31, 237]
mTOR	–	65	[191, 216]
Chromosome 9	21 to >50	10–48	[4, 67, 220, 221, 224, 234]

die within 2 years of diagnosis [6–9]. Additionally, almost all patients diagnosed with metastases succumb to the disease, as the incidence of complete remission is rare [10]. Although selected genetic alterations have been defined primarily in the low- *versus* high-grade population, further investigation has made it clear that several of these molecular alterations are not necessarily exclusive to one population (Table 33.1).

In this chapter we seek to present known and emerging molecular markers of UCa. We have opted to present the molecular characteristics of these lesions using a pathway approach, highlighting areas of overlap between low- and high-grade carcinomas and emerging therapies that are pathway-specific in nature.

Fibroblast Growth Factor Receptor 3 (FGFR3)

Low-grade disease is thought to arise from localized urothelial hyperplasia and commonly reported genetic changes involve alterations in the FGFR3, constitutive activation of the HRAS oncogene and loss of heterozygosity of chromosome 9 [6, 10–15]. FGFR3 is a tyrosine kinase receptor that is thought to signal through the RAS signaling pathway (Fig. 33.1) [16–18].

Fibroblast growth factor receptor 3 (FGFR3) is a tyrosine kinase receptor that is thought to signal through the RAS-MAP-Kinase and PI3-Kinase pathways, predominantly in non-invasive, low-grade disease. Initially, specific gain of function germline mutations in exon 7, 10 and 15 associated with constitutive activation of FGFR3 were linked to autosomal dominant skeletal dysplasia syndromes such as thanatophoric dysplasia [19–27]. Subsequently, similar mutations were identified in UCas [28].

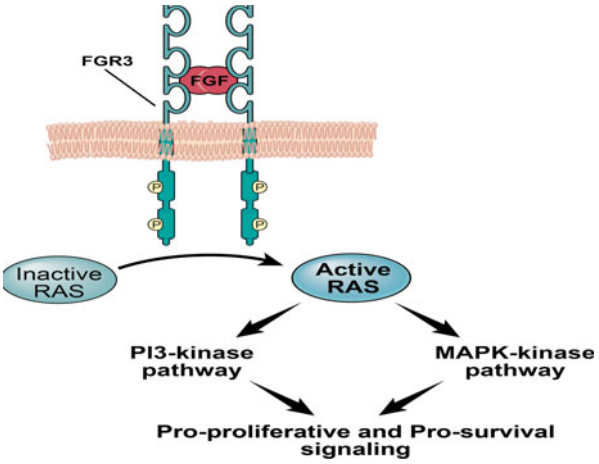

Fig. 33.1 FGFR-3

Multiple studies have reported an inverse correlation between the incidence of *FGFR3* gene mutations and UCa pathologic stage as well as grade [29, 30]. As both activating mutations in HRAS and FGFR3 are thought to signal through the RAS-mitogen activated protein kinase (MAP-Kinase) pathway, initial studies had hypothesized that both of these signaling pathways were predominantly seen in non-muscle invasive bladder cancers (NMIBC). However, while there is strong evidence for the preferential activation of FGFR3 in low-grade UCa, current studies suggest that HRAS mutations do not exhibit a strong correlation with tumor grade or stage [31–33]. In fact a recent study suggested that HRAS and FGFR3 mutations appear to be mutually exclusive events [32].

The increased incidence of FGFR3 mutations in non-invasive, low-grade disease has prompted multiple studies evaluating positive FGFR3 mutation status in these lesions as a negative predictor of disease progression, recurrence and disease-specific survival [29, 30, 34, 35]. The results suggest that low-grade lesions characterized by activating mutations of FGFR3 are unlikely to progress to aggressive muscle-invasive disease [29, 36–38].

RAS

Of the three human *RAS* oncogenes, the Harvey (*H*)-*RAS* gene is frequently mutated in bladder cancer [31–33, 39–50]. *HRAS* mutations in UCa are presumed to contribute to oncogenesis by aberrant activation of the MAP-Kinase and Phosphatidylinositol 3-Kinase (PI3-Kinase) pathways [31–33].

Constitutively active RAS signaling contributes to oncogenesis in bladder cancer by the downstream activation of MAP-Kinase and PI3-Kinase pathways. Activating mutations have been described for *HRAS* and *KRAS,* while mutations of *NRAS* are

Table 33.2 RAS mutations in bladder cancer

Year	No. of cases	RAS mutation status	Correlation with tumor grade and stage	Reference
1985	38	HRAS: 2/38; KRAS: 1/21	–	Fujita et al. [39]
1988	24	HRAS: 4/24	–	Visvanathan et al. [40]
1990	33	HRAS: 13/33	None	Czerniak et al. [42]
1992	67	HRAS: 30/67	Correlated with high-grade disease	Czerniak et al. [50]
1993	152	HRAS: 9/152	None	Knowles et al. [43]
1993	111	HRAS: 33/111	–	Levesque et al. [44]
1994	50	HRAS: 9/50	None	Burchill et al. [45]
1994	62 Ta/T1 cases; 35 recurrences	HRAS mutation frequency assessed	Increased incidence in low-stage disease	Ooi et al. [46]
1995	100 cases; 19 follow up samples	HRAS: 44/100	Increased detection of low-grade disease	Fitzgerald et al. [47]
1995	39	HRAS: 1/39; KRAS: 2/39	Correlated with high-grade, high-stage disease	Uchida et al. [48]
1998	55	KRAS: 2/55	Correlated with high-stage disease	Olderoy et al. [49]
2001	14	KRAS: 4/14	–	Ayan et al. [51]
2005	98	RAS: 13/98 cases; HRAS: 9, KRAS2: 3, NRAS: 2.	None	Jebar et al. [32]
2009	69 primary cases; 23 recurrences	RAS: 11 cases; HRAS: 5, KRAS: 6.	–	Platt et al. [31]
2010	257 primary cases; 184 recurrences from 54 patients	RAS: 28/257 cases; HRAS: 14, KRAS: 14	None	Kompier et al. [33]

rare. Initial reports identified point mutations in codon 12, 13 and 61 in a small subset of cases that led to constitutively active HRAS signaling and subsequent studies suggested that point mutations in codon 12 are the most common mutation [32, 39–41]. A single report identified concurrent codon 12 and intron D mutations in high-grade tumors associated with elevated HRAS expression, however the frequency of this event is not clear [50]. There is no clear consensus on the reported frequency of *HRAS* mutations and association to tumor stage or grade in UCC (Table 33.2).

One study involving 67 tumor samples identified *HRAS* mutations in over 44 % of cases, with a higher incidence in high-grade disease [50]. In contrast, another study based on a sample size of 152 bladder cancer specimens had a more conservative estimate of a 6 % incidence of *HRAS* mutations [43]. Moreover, the same study suggested a lack of correlation between tumor grade and/or stage [43]. Mutations

have also been described for *KRAS2* at a lower frequency than what has been reported for *HRAS,* while mutations of *NRAS* are rare [31–33, 48, 49, 51]. More recent studies have estimated the combined frequency of *RAS* mutations to be between 11 and 13 % (involving a sample size of 92–257 tumor specimens) and have corroborated a lack of correlation between tumor grade and/or stage [31–33].

TP53

Common molecular alterations that have been found to contribute to the development of invasive high-grade UCas commonly include loss of the p53, retinoblastoma (Rb) and phosphatase and tensin homolog (PTEN) tumor suppressor genes as well as loss of heterozygosity events of chromosome 9 [4, 6, 10, 12, 14, 52]. p53, encoded by the *TP53* gene on chromosome 17p13.1 behaves like a tumor suppressor by inhibiting the G_1-S cell cycle transition [53–55]. Transcriptional activation of the $p21^{WAF1/CIP1}$ gene significantly contributes to this regulation by acting as a cyclin-dependent kinase inhibitor (CDKI) (Fig. 33.2) [56, 57].

The p53 tumor suppressor inhibits the G_1-S cell cycle transition by transcriptionally activating the p21 cyclin-dependent kinase inhibitor (CDKI). MDM2, an E3 Ubiquitin Ligase, is also a transcriptional target of p53 and participates in a negative feedback loop by mediating the proteasomal degradation of p53. Most UCa exhibit loss of heterozygosity at the 17p locus and paradoxically, loss of function mutations

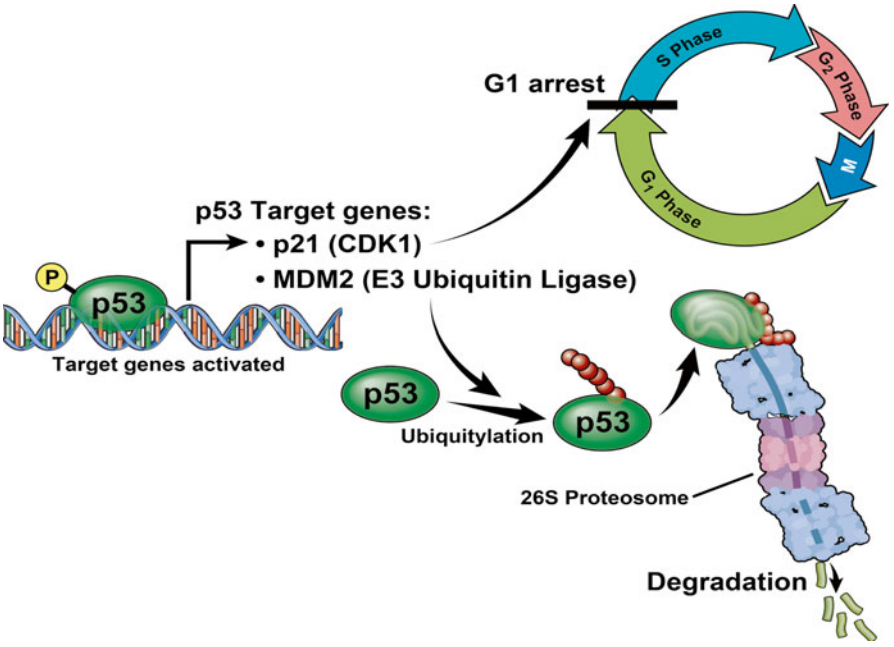

Fig. 33.2 p53

in the remaining allele leads to increased protein stability, a prolonged half-life and this facilitates its immunohistochemical detection within the nucleus compared to normal cells where p53 expression is below the threshold of detection by similar techniques [58–60]. Studies have suggested that immunohistochemical detection of p53 can detect mutations accurately in up to 90.3 % of cases, in comparison to more stringent methods such as gene sequencing [58, 61]. Immunohistochemistry based detection of p53 mutation status is limited by false positives, commonly due to the induction of non mutant p53 in response to various stresses and false negatives (due to no detectable protein expression that can be seen in rare instances of homozygous deletions and epigenetic silencing) [58, 62–64].

Clinical assessment of p53 mutations, commonly based on immunostaining results that suggest increased nuclear accumulation, has been correlated with advanced pathological stage and grade of bladder cancers and has also been implicated as a prognostic factor in determining disease progression and recurrence [52, 59, 65–71].

Cell cycle regulation by p53, as mentioned above, is primarily mediated by the transcriptional activation of the $p21^{WAF1/CIP1}$ gene, which acts as a cyclin-dependent kinase inhibitor (CDKI) [56, 57]. Loss of p21 (encoded by the $p21^{WAF1/CIP1}$ gene), in the presence of p53 mutations has also been reported to be an independent predictor of bladder cancer progression [59, 72]. Other important mediators of p53 signaling include the E3 Ubiquitin Ligase: MDM2 [73]. MDM2 is transcriptionally induced by p53 and participates in a negative feedback loop by mediating the proteasomal degradation of the p53 tumor suppressor (Fig. 33.2) [73]. MDM2, located at the 12q14.3-15 locus, has been shown to be amplified in UCas in a manner that is correlated with high-stage and high-grade disease [59, 74, 75].

Retinoblastoma (Rb)

The *retinoblastoma* (*Rb*) gene, located at chromosome 13q14, is recognized as a critical tumor suppressor gene that like p53 also regulates the G_1-S cell-cycle transition [59, 76–78]. The E2F-1 transcription factor that is critical to the G_1-S transition is sequestered by the active (dephosphorylated) form of Rb, enabling the latter to act as a negative regulator of cell proliferation (Fig. 33.3) [59, 79]. Rb is maintained in its dephosphorylated state by CDKIs such as p16, encoded by the *INK4alpha* gene at the CDKN2A locus (Fig. 33.3) [59, 80]. Rb phosphorylation, on the other hand, by cyclin dependent kinase (CDK) complexes leads to the release of the E2F transcription factor and begins a program of gene expression that initiates the transition into the S phase of the cell cycle [59, 81, 82]. Rb has been identified as an important tumor suppressor that regulates bladder cancer progression and mutations have been identified predominantly in invasive, late-stage disease [61, 77, 78, 83–86].

Mechanisms of inactivation include deletion events (low Rb expression) as well as hyper-phosphorylation due to positive regulation by CDK complexes or loss of negative regulation by CDKIs such as p16 due to epigenetic silencing (high Rb immunoreactivity, as determined by IHC) [59, 80, 87, 88]. CDK complexes that phosphorylate Rb include cyclin D1 and CDK4 [59]. However, contrary to

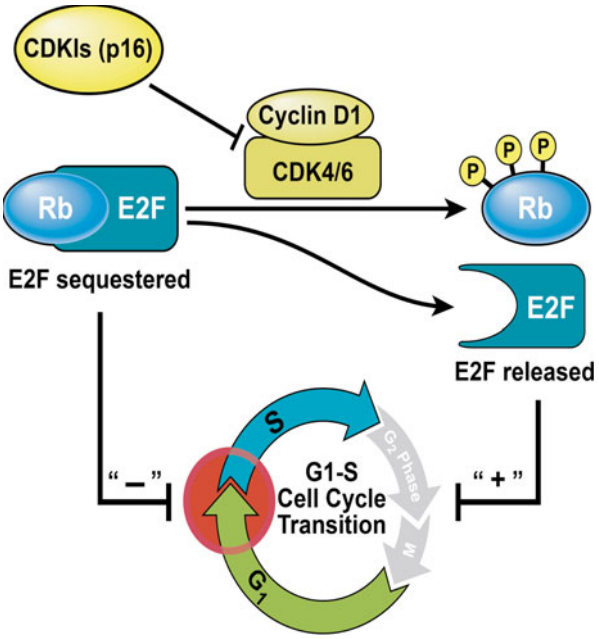

Fig. 33.3 Retinoblastoma (*Rb*): Sequestration of the E2F-1 transcription factor by the dephosphorylated form of Rb, enables the latter to act as a tumor suppressor by impeding the G_1-S transition. Cyclin-dependent kinase inhibitors (*CDKI*) such p16 also act as tumor suppressors by maintaining Rb in its active, dephosphorylated state. Rb phosphorylation by cyclin dependent kinase (*CDK*) complexes releases this inhibition, thereby allowing cells to proliferate

expectations, increased cyclin D1 expression has been reported to be correlated with positive outcomes in late-stage, muscle-invasive disease while CDK4 overexpression has been linked to high-stage and high-grade disease highlighting the complexity of the underlying regulatory processes [59, 75, 89, 90].

A combination of Rb and p53 along with other relevant markers (MDM2 and CDKIs such as p21, p27 and p16) has been used in multiple studies to successfully predict patient outcomes [59, 91–95]. Various therapeutic regimens that have been targeted towards patients harboring p53 mutations include cisplatin-based regimens that selectively target these cells by inducing apoptosis [59, 96, 97]. Other drugs that target cells with mutant p53 and Rb are in various stages of evaluation for the treatment of UCas. These include the small molecule agent: PRIMA-1, which partially promotes p53 reactivation and nonspecific CDKIs like L86-8275 and UCN-01 [59, 98–100].

The ErbB Family of Receptor Tyrosine Kinases

The ErbB family, commonly implicated in bladder cancer, includes the epidermal growth factor receptor (EGFR; also known as ErbB1and HER1) and HER2/neu (also referred to as ErbB2) (Fig. 33.4).

Recent work in this field has sought to address the broader question of the expression pattern of each of the 4 type I tyrosine kinase growth factor receptors (EGFR, ErbB2, ErbB3 and ErbB4) in urothelial carcinomas [101, 102]. Two separate studies have independently suggested that increased EGFR expression appears

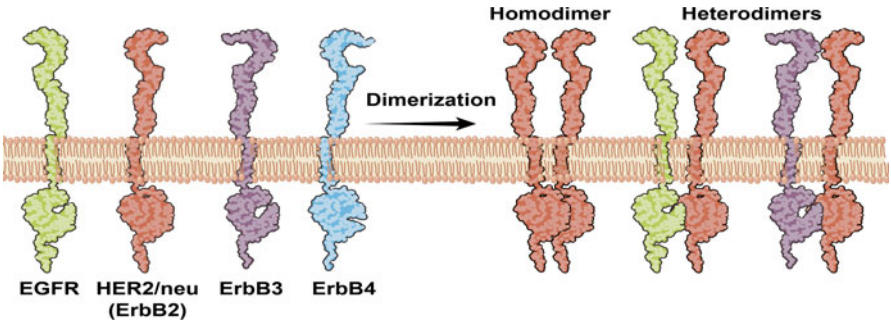

Fig. 33.4 The ErbB family of receptor tyrosine kinases. The ErbB family of receptor tyrosine kinases, commonly implicated in bladder cancer, includes the epidermal growth factor receptor (EGFR; also known as ErbB1and HER1) and HER2/neu (also referred to as ErbB2). The known ligands for EGFR include epidermal growth factor (EGF), amphiregulin (AR), transforming growth factor-**α** (TGF**α**), epiregulin (EPR), betacellulin (BTC) and the heparin-binding EGF-like growth factor (HB-EGF), while there are no known ligands for HER2. Activation of EGFR and HER2 involves heterodimerization with other ligand-bound members of the ErbB family of receptor tyrosine kinases and downstream signaling cascades that are activated include the MAP-Kinase and PI3-Kinase pathways

to be an early event in carcinogenesis and that it is not correlated with tumor grade, stage or survival [101, 102]. It must also be noted there is a considerable amount of debate regarding EGFR immunostaining patterns. There are multiple reports that suggest that EGFR expression is localized to the basal areas of the urothelium supporting the hypothesis that this naturally prevents urinary EGFR-ligands from promoting basal urothelial cell proliferation [103–105]. Contrary to this, Rotterud et al. have reported identifying EGFR expression in all layers of the urothelium suggesting that variability in expression patterns may be attributed to changes in epitope accessibility that might be mediated by lipid rafts [101, 106–108]. Like EGFR, HER2 (ErbB2) also shows increased expression in UCa with no distinct correlation with tumor grade, stage or survival [101, 102, 108–115].

Immunohistochemical detection of membrane localized ErbB3 has not shown a distinct pattern of up or down regulation in UCa and this may possibly be attributed to the presence of a secreted form [101, 116]. Future studies that account for this form will be required to address this question more effectively. On the other hand, multiple studies suggest that ErbB4 is possibly required to maintain the differentiation status of normal urothelium, where high expression levels have been noted as has been reported for multiple tissue types [101, 102, 117].

EGFR (HER1, ErbB1)

Initial studies based on competitive binding analysis and immunohistochemistry suggested that EGFR was overexpressed in bladder cancer with preferential expression in advanced, late-stage disease in studies that involved sample sizes ranging from 21 to 173 cases [118–121].

The known ligands for EGFR include epidermal growth factor (EGF), amphiregulin (AR), transforming growth factor-α (TGFα), epiregulin (EPR), betacellulin (BTC) and the heparin-binding EGF-like growth factor (HB-EGF) (Fig. 33.4) [122]. In a study aimed at determining relative EGFR-ligand expression, EGF was reported to be expressed at very low levels leading to the hypothesis that it might function in an endocrine fashion as opposed to other more abundantly expressed EGFR ligands that possibly had an autocrine or paracrine mechanism of action [123, 124]. HB-EGF, EPR and TGFα, in particular, were found to be expressed at much higher levels and this was correlated with advanced pathological stage and poor patient survival [123, 124]. However, even though EPR expression had the strongest correlation with patient survival, *in vitro* studies suggest that EPR has a much lower binding affinity for EGFR compared to EGF in bladder cancer cells, raising the possibility that it might signal in a noncanonical fashion through alternate receptors [123, 125].

EGFR mediates its actions by heterodimerization with other ligand-bound members of the ErbB family of receptor tyrosine kinases and downstream signaling cascades that are activated include the MAP-Kinase and PI3-Kinase pathways (Fig. 33.4) [114, 126, 127].

For instance, *in vitro* studies suggest that EGFR promotes invasive behavior of bladder cancer cells through both RAS-dependent (MAP-Kinase pathway) as well as in a RAS-independent, PI3-Kinase facilitated manner [127]. Similarly, urothelium-specific overexpression of either EGFR or the downstream *HRAS* oncogene (associated with increased activation of the MAP-Kinase pathway) in transgenic mice led to urothelial hyperplasia phenotype [128, 129]. Double transgenic mice overexpressing both EGFR and the downstream HRAS oncogene did not exhibit a tumor-enhancing effect, suggesting pathway redundancy [128]. This was in contrast to double transgenic mice that overexpressed EGFR and had a functional inactivation of the retinoblastoma and p53 tumor suppressor genes [due to Simian virus 40 (SV40) large T antigen expression] that led to high-grade bladder carcinomas [128]. This suggests that increased EGFR signaling coupled with non-redundant genetic events can have a synergistic effect, contributing to bladder cancer progression.

Promising EGFR-tyrosine kinase inhibitors include 4,5-Dianilinophthalimides as well as the monoclonal antibody cetuximab [130, 131]. These have been found to be effective in reducing the orthotopic tumor burden in mice, partially attributed (in the case of cetuximab) to reduced angiogenesis [130, 131]. In fact a phase II trial involving a combination of cetuximab with standard chemotherapeutic regimens is currently underway [132]. Challenges to cetuximab therapy include acquired resistance to this drug, which according to one report has been linked to increased phosphorylation of the C-terminal fragment of HER2 *in vitro* [133]. In one study, a panel of molecular markers characterized by increased expression of ErbB4 and E-cadherin, suggestive of a well-differentiated urothelial identity, predicted increased sensitivity to cetuximab [134]. From a therapeutic perspective, this calls for the comprehensive evaluation of biomarkers that would predict responsiveness to cetuximab as well as the trial of combination therapy with dual EGFR/HER2 kinase inhibitors [133].

Additional tyrosine kinase inhibitors that are being evaluated for therapeutic purposes in bladder cancer include Gefitinib ("iressa", ZD1839), which may possibly also inhibit EGFR/ErbB2 and EGFR/ErbB3 heterodimers [135, 136]. Preliminary studies suggest that responsiveness to this class of drugs does not necessarily correlate with EGFR protein levels [137]. In contrast to its *in vitro* efficacy, attributed to inhibition of MAP-Kinase and PI3-Kinase signaling, it has been shown to be effective in only certain cell types in mouse-xenograft studies for reasons that are not clearly understood [135]. In a carcinogen-induced model of urinary bladder cancers (in rats) Gefitinib was found to increase tumor latency, reduce tumor incidence as well as reduce tumor volumes in a dose dependent manner [138]. The results of this study were attributed to reduced VEGF dependent angiogenesis and a down regulation of cell-cycle genes related to the anaphase protein complex, in addition to inhibiting EGFR signaling [138]. Therefore, dual vascular endothelial growth factor receptor (VEGFR)/EGFR antagonists such as vandetanib (ZD6474) have attracted much interest due to their ability to suppress both angiogenesis and cell proliferation [139, 140]. Preliminary *in vitro* studies with vandetanib have shown promising results and this warrants further investigation [139, 140].

HER2/neu (ErbB2) been reported to show increased expression in UCa, with conflicting evidence regarding correlation with tumor grade, stage and survival [101, 102, 108–114, 141–143]. Some studies have shown a correlation with worsened pathological stage while its potential role as a prognostic variable is more controversial [101, 108, 110, 113, 115, 144]. One study (involving 73 cases) interrogated the relative abundance of ErbB receptor tyrosine kinase expression that might contribute to bladder cancer oncogenesis and progression, at the level of mRNA transcript expression [123]. The results suggested that while HER2 was markedly more abundant than EGFR, neither was correlated with patient survival and the same conclusion has been supported by multiple studies [101, 102, 121, 123, 145–147].

While *HER2* gene amplification and protein expression levels have been reported to show a high degree of correlation in the rarer and highly aggressive UCa variants: micropapillary carcinoma, this correlation is not seen in conventional UCa [148]. *HER2* gene amplification rates have been reported to be much lower (7–9 % of cases) than corresponding protein expression levels (where measured in tandem) leading to the conclusion that HER2 is significantly regulated through either transcriptional or post-transcriptional mechanisms that are yet to be elucidated in the context of bladder cancers [111, 149, 150]. A recent retrospective study that assessed over 1,000 patients estimated high HER2 protein expression in 9.2 % of cases with associated gene amplification in only 5.1 % of these [151].

Jiminez et al. [109] reported a higher HER2 expression in paired lymph nodes when compared to the corresponding primary tumors suggesting a significant role of HER2 in the metastatic process. However, these findings were not corroborated in future studies [101]. Interestingly, multiple reports have since demonstrated significantly lower HER2 expression in metastatic lesions with increasing distance from the primary tumor suggesting that alternate signaling pathways may be more relevant at these sites [112, 152].

Though there are no known ligands for HER2, it is thought to be activated by heterodimerization with other ligand-bound members of the ErbB family of receptor tyrosine kinases and downstream effectors include MAP-Kinase, PI3-Kinase signaling cascades as well as *MYC* [153, 154]. Interestingly, *MYC* and the *TOP2A* gene (the latter codes for DNA topoisomerase 2-alpha) have been reported to be co-amplified with *HER2* [114, 155, 156]. In one report, *MYC* was co-amplified with *HER2* in 57 % cases, all of which occurred only in the metastatic population associated with locally advanced high-stage (pT4) disease [114]. This is significant as *HER2* and *MYC* co-amplification has been found to influence HER2-directed therapy in other cancer types [155, 157].

Despite the inconclusive data regarding the prognostic value of HER2 as a marker of tumor progression, bladder cancer is an entity with one of the highest levels of HER2 expression [4, 158]. This has prompted an evaluation of HER2-directed therapeutic agents such as trastuzumab (a humanized monoclonal antibody directed against HER2) and lapatinib (a dual EGFR/HER2 tyrosine kinase inhibitor) [108, 159]. HER2-directed therapy has been shown to provide maximal benefit in the presence of gene amplification. Immunohistochemical detection of HER2 expression has therefore been proposed as a screening tool to identify cases of *HER2* gene amplification using fluorescent *in situ* hybridization (FISH) [114, 160].

Initial trials of trastuzumab in combination with standard chemotherapeutic agents in small trials of 6–7 patients with HER2 over-expressing metastatic or locally advanced disease suggested that the drug was well tolerated but did not offer a clear trend with regards to the therapeutic response [161, 162]. In a more extensive phase II trial, combination therapy with trastuzumab in a group of 44 patients with HER2 positive tumors had a promising overall response rate of 70 % [163]. On the other hand, a phase II trial of lapatinib monotherapy in 34 patients showed limited benefit that was found to be correlated with EGFR status and to a lesser extent HER2 expression [164]. Further studies are required to identify the molecular signatures of tumors that are likely to respond to these therapeutic interventions.

PI3-Kinase Signaling Cascade

Class I_A PI3-Kinases are composed of a regulatory subunit (p85-alpha, p85-beta and p55-gamma encoded by *PIK3R1, PIK3R2 and PIK3R3,* respectively) and a catalytic subunit (p110-alpha, p110-beta and p110-delta encoded by the *PIK3CA, PIK3CB* and *PIK3CD* genes) [165–168]. Of these, *PIK3CA* is commonly mutated in bladder cancers [31, 33, 169]. Growth factors (signaling through receptor tyrosine kinases), activated RAS as well as G-protein coupled receptors can activate the catalytic subunit of PI3-Kinase leading to the phosphorylation of phosphatidylinositol bisphosphate (PIP2) to phosphatidylinositol triphosphate (PIP3) [167, 168, 170–174]. This leads to the recruitment of AKT1 to the cell membrane where it is

activated by a series of phosphorylation events by phosphoinositide-dependent kinase 1 (PDK1) and the mammalian target of rapamycin complex 2 (mTORC2) [168, 175–184].

AKT, in particular, has been referred to as a "master" kinase that regulates numerous pro-survival signaling cascades implicated in cancer progression [185]. Downstream signaling mediators of AKT that have been shown to be significant for bladder cancer progression include the mammalian target of rapamycin complex 1 (mTORC1) [178].

PI3-Kinase

The incidence of mutations in the catalytic component of PI3-Kinases (*PIK3CA*) has been estimated to be as high as 24–25 % in studies that assessed primary tumors from up to 257 patients as well as recurrences where the sample size ranged from 23 to 54 patients [31, 33]. Common mutations in *PIK3CA* have been found to be localized to the helical and kinase domains and induce gain of function through distinct mechanisms, that vary in their dependence on either the inhibitory effect of the p85 regulatory subunit or their interaction with RAS [31, 186].

Mutations in *PIK3CA* appear to have a higher incidence in low-grade and low-stage disease but were not found to be accurate predictors of recurrence-free, progression-free or disease-specific survival [33, 169]. The above-mentioned study also reported a high co-occurrence of mutations in *FGFR3* (RAS-MAPK activation) with mutations in the *PIK3CA* gene [33]. This is particularly significant as receptor tyrosine kinase targeted therapies (EGFR targeted therapies in clinical trials: CALBG-90102, NCT00088946, NCT00380029) are likely to have limited efficacy in the presence of downstream *PIK3CA* mutations [33].

PTEN

The phosphatase and tensin homolog (PTEN), through its lipid phosphatase activity catalyzes PIP3 to PIP2, thereby preventing activation of AKT1 downstream of PI3-Kinase [182, 187]. Loss of the *PTEN* tumor suppressor gene at chromosome 10q23 was found to predispose to Cowden disease, an autosomal dominant cancer predisposition syndrome characterized by occasional cases of bladder cancer [84]. Initial studies estimated the incidence of loss of heterozygosity (LOH) events at the 10q locus at about 6.6 % in superficial (non-muscle invasive) urothelial cancers and up to 24.5 % of cases of late-stage, muscle-invasive bladder cancer [31, 84, 188, 189]. However, these and subsequent studies have shown a low incidence of biallelic inactivation of PTEN suggesting that loss of the PTEN tumor suppressor by itself is unlikely to be the primary regulator of bladder cancer progression [84, 188, 190].

Nevertheless, loss of PTEN has been found to be correlated with disease stage and grade [187, 188, 191]. In one study, PTEN expression was found to be significantly reduced in 94 % of cases representing late-stage disease in contrast to only 42 and 8 % of superficial papillary urothelial carcinomas and carcinomas *in situ*, respectively [187]. A developing focus of ongoing research has been directed at noncanonical functions of PTEN in promoting cancer progression that involve its subcellular localization. Nuclear localization of wild-type PTEN has been found to be critical for maintaining centromere stability and the downregulation of various cell cycle factors such as cyclin D1 that eventually induce a G_0-G_1 arrest [178, 192–194]. In fact, a new study of 63 primary bladder cancer patients reported a significant reduction in the nuclear expression of PTEN in advanced, late-stage disease [187]. A subsequent study involving 69 primary and 23 recurrent bladder cancer samples corroborated the finding of reduced expression of PTEN (49 % of cases), with a predominance of reduced nuclear expression [31].

A combination of reduced *PTEN* mRNA expression along with specific mutations of *PIK3CA*, with or without amplification of the *HER2* gene has been proposed to be a good predictive tool for determining PI3-Kinase pathway activation [195]. Indeed, in an analysis of 80 bladder cancer samples, this PI3-Kinase pathway activation signature was strongly correlated with patient outcomes based on overall survival [190, 195].

Furthermore, increased activation of the PI3-Kinase pathway in the urothelium of transgenic mouse models has been shown to contribute to urothelial hyperplasia [128, 129] [187]. Specifically, overexpression of either EGFR or the downstream HRAS oncogene, that was spatially restricted to the urothelium, led to an urothelial hyperplasia phenotype while a deletion of PTEN within the urothelium led to the spontaneous development of papillary urothelial carcinomas in at least 10 % of the mice studied [128, 129, 187]. Additionally, in the latter case, the frequency of papillary urothelial carcinomas was found to be significantly increased following exposure to a chemical carcinogen and the resultant lesions showed a strong correlation with increased AKT activation, a hallmark of PI3-Kinase signaling [187].

Mechanistic studies have also shown that decreased signaling through the PI3-Kinase pathway, as a consequence of PTEN overexpression, is correlated with decreased cancer-cell invasiveness in both *in vivo* orthotopic assays as well as *in vitro* organotypic assays [196]. The same study showed that PTEN can inhibit tumor invasion even in the absence of its lipid phosphatase activity and suggested a role for its protein phosphatase activity, which is poorly understood [196].

p53 and PTEN

Recent studies by Puzio-Kuter et al. evaluated the effect of monoallelic and biallelic, urothelium-specific deletions of the p53, Rb and PTEN tumor suppressor genes alone, or in combination on bladder cancer progression [197]. The simultaneous inactivation of both p53 and PTEN led to the spontaneous development of a

wide spectrum of invasive lesions, characterized by increased downstream signaling through mTORC1 [197]. Consistent with these results, this study also reported that a high percentage of late-stage, muscle-invasive patient samples that had altered p53 also had deregulated PTEN expression [197]. Future studies involving larger datasets will be required to determine the relative frequency of combined PTEN inactivation and p53 alterations and to identify effective therapeutic targets that counter these molecular changes.

Wnt Signaling and PTEN

Unlike colorectal cancers, where deregulated Wnt signaling due to somatic mutations in the *adenomatous polyposis coli* (*APC*) gene has been commonly described, its role in bladder cancer is controversial [198–201]. A number of studies have suggested increased activation of Wnt signaling in bladder cancer, based on epigenetic silencing of secreted receptor protein antagonists (such as the Wnt-inhibitory factor-1), loss of function mutations and deletions of the *APC* tumor suppressor gene and immunohistochemical detection of the key signaling intermediate: β-catenin [201–210]. Recent studies in mouse models have suggested an important interaction between the Wnt signaling pathway and the PTEN tumor suppressor [201]. In these studies, urothelium-restricted over activation of Wnt signaling led to hyper-proliferative lesions that did not undergo malignant transformations and were characterized by increased PTEN expression [201]. However, increased Wnt signaling in a PTEN null background promoted a transition to papillary UCas in these mice [201]. This study also reported a correlation between increased Wnt signaling and robust PI3-Kinase pathway activity (due to a loss of PTEN) in a limited number of human bladder cancer cases and therefore calls for further investigation into the incidence of combined dysfunctions in the Wnt and PI3-Kinase signaling pathways in bladder cancer [201].

mTOR

The complex mTORC1 consists of mTOR, mLST8 and regulatory associated protein of mTOR (RAPTOR) [178, 180]. Activation of AKT, as part of PI3-Kinase signaling, leads to a disruption of the tuberous sclerosis complex (TSC) and this releases the inhibition of RAS homolog enriched in brain (Rheb), an activator of mTORC1. Known targets of activated mTORC1 kinase include p70 S6 kinase 1 (S6K1) (which phosphorylates ribosomal protein S6) and eukaryotic initiation factor 4E binding protein 1 (4EBP1) which play key roles in the translation of 5′ terminal oligopyrimidine tract mRNAs and in cap dependent translation initiation, both processes that are critical to the translation of cell cycle regulators such as cyclin D1 [178, 180, 181, 184, 211–214].

In an exhaustive study, involving 803 cases of bladder cancer and 803 controls that were matched for gender and age, single-nucleotide polymorphisms (SNPs) in 19 genes belonging to the PI3Kinase-AKT-mTOR signaling cascade were evaluated as predictors for bladder cancer susceptibility [215]. Germ-line genetic variations in the gene coding for *RAPTOR*, an mTORC1 component, were found to be correlated with increased risk of bladder cancer along with a significant gene-dosage effect implying that deregulated mTORC1 signaling significantly contributes to bladder cancer risk [215]. Furthermore, Hansel et al. reported a significant correlation between increased mTOR signaling (55–74 % of cases), increased pathological stage and reduced disease-specific survival in an analysis of 121 cases of late-stage, muscle-invasive UCas [216]. This has been corroborated by a subsequent study which looked at multiple parameters corresponding to the PI3-Kinase signaling cascade, including mTORC1 targets, in a broader subset of 887 cases and reported an association between deregulated PI3-Kinase signaling and high-grade, high-stage cases of bladder cancer [191].

There is considerable interest in the mTOR signaling pathway, due to the availability of numerous small molecule inhibitors such as rapamycin and its structural derivatives (temsirolimus, Wyeth pharmaceuticals; everolimus or RAD 001, Novartis pharmaceuticals; deforolimus or AP-23573, Ariad pharmaceuticals) [178, 179]. Rapamycin and its derivatives complex with the immunophilin: FKBP12 so as to primarily inhibit the kinase activity of mTORC1 [178, 179]. While these drugs are being investigated in phase I and II clinical trials for cancers such as metastatic renal cell carcinoma, they have not been evaluated as potential therapeutic agents in the management of UCa, as yet [178, 179, 217]. However, a number of *in vitro* studies have shown that this class of drugs significantly inhibits mTOR signaling in a dose dependent manner and consequently leads to a G_0-G_1 cell-cycle arrest, as well as a reduction in VEGF-dependent angiogenesis [216, 218, 219]. The antiproliferative efficacy of these drugs has also been demonstrated *in vivo* in mouse xenograft studies [197, 201, 216, 219].

Given the published data on the safety and efficacy of rapamycin derivatives in various cancers, and the increased volume of literature regarding its efficacy *in vitro* and in multiple mouse models, it is likely that these drugs will soon be evaluated for their therapeutic efficacy in cisplatin-refractory UCa [179].

Chromosomal Abnormalities

In low-grade disease, alterations of chromosome 9 such as loss of heterozygosity are a frequent event and are seen at a similar frequency in late-stage, muscle-invasive disease [4]. This suggested the presence of a common tumor suppressor gene, critical to bladder cancer initiation on chromosome 9 and led to the identification of common areas of loss of heterozygosity (LOH) on both 9p and 9q (Fig. 33.5) [4, 220–225].

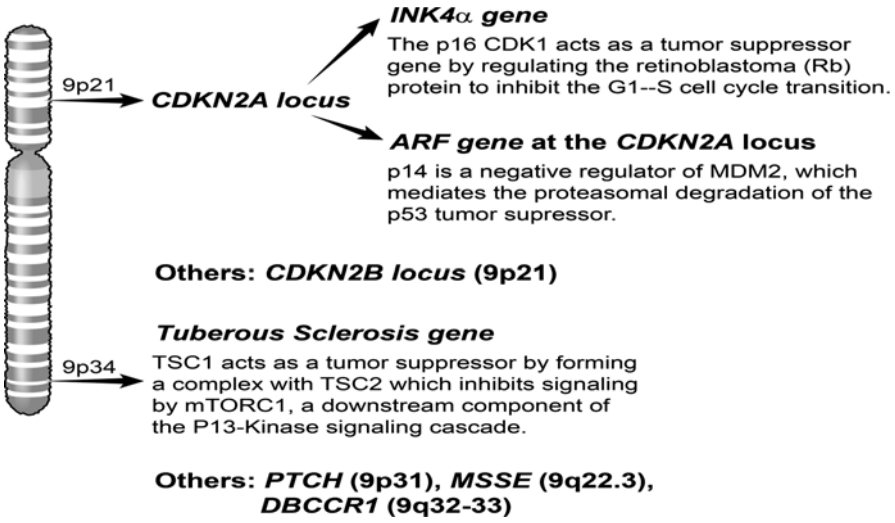

Fig. 33.5 Chromosome 9 alterations. Common areas of loss of heterozygosity have been identified on both chromosome 9p and 9q and this is thought to be an important event in bladder cancer initiation. The *CDKN2A* locus on 9p encodes for the tumor suppressors *p16* and *p14*, which act by regulating p53 and Rb function. Important tumor suppressors that have been mapped to mapped to 9q3 include *deleted in bladder cancer chromosome region 1* (*DBCCR1*) and *Tuberous Sclerosis 1* (*TSC1*)

Chromosome 9p

Mapping studies led to the identification of two regions of LOH on 9p21 [220, 222–224]. As deletion and methylation events were more common at the *CDKN2A* locus than the *CDKN2B* locus at this site, the former has been hypothesized to be the primary target of loss of 9p21 [222, 226]. The *INK4alpha* gene at the *CDKN2A* locus encodes for the tumor suppressor p16, which regulates Rb so as to inhibit the G_1-S transition [59]. Additionally, the *alternate reading frame* (*ARF)* gene at the *CDKN2A* locus encodes for p14, which indirectly regulates expression of the p53 tumor suppressor by interacting with the MDM2 E3 ubiquitin ligase [59]. In one report, homozygous deletions of p16 and p14 leading to deregulated expression of both the Rb and p53 tumor suppressors, respectively, was correlated with poor patient outcomes [227]. p53 and Rb regulation, in the context of bladder cancer development, has been discussed in greater detail earlier in this chapter.

In a direct clinical application, fluorescence *in situ* hybridization based diagnostics tests (UroVysion™, Vysis Inc.) are used to detect homozygous deletions at the 9p21 locus [228]. These tests have been used to predict the risk of tumor recurrence for superficial non-invasive lesions, post-therapy [59, 228].

Chromosome 9q

Putative tumor suppressors have been mapped to mapped to 9q31 (*patched* gene, *PTCH*), 9q22.3 [*multiple self healing squamous epithelioma*, gene (*MSSE*)], 9q32-33 (*deleted in bladder cancer chromosome region 1* gene, *DBCCR1*) and the *Tuberous Sclerosis 1* gene (*TSC1*) at 9q34 [229]. The relevance of the frequent deletions of *MSSE* and *PTCH* genes, which have been linked to the Transforming growth factor beta-receptor I (TGFBR1) and Hedgehog signaling, respectively, to bladder cancer progression is unclear [224, 229–233]. On the other hand, biallelic loss and hypermethylation appear to be the main mechanisms contributing to *DBCCR1* silencing, a potential tumor suppressor which has been found to be lost in up to 50–73 % of bladder cancer samples in two independent studies [230, 234].

Tuberous Sclerosis 1 (TSC1, also known as hamartin) and Tuberous sclerosis 2 (TSC2, also known as tuberin) form a complex which inhibits signaling downstream of AKT (also known as protein kinase B) [31, 178, 235, 236]. Loss of TSC1 leads to increased mTORC1 dependent pro-survival signaling (discussed in greater detail earlier in this chapter), which is exploited by urothelial carcinomas [31, 237–241]. TSC1 is the only gene on 9q for which mutations have been reported in bladder tumors, and may therefore be a critical regulator of bladder cancer progression [31, 241]. Finally, studies aimed at assessing LOH events on chromosome 9 suggest that it might have a high predictive value in determining the risk of tumor recurrence in low-grade, non muscle-invasive disease, particularly when associated with LOH for the TSC1 gene [239].

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Chapter 34
Invasive Bladder Cancer: Combined Modality Treatment

Derek Raghavan and Howard M. Sandler

Introduction: The Biology of Invasive Bladder Cancer

Invasive bladder cancer, including tumors that penetrate through lamina propria into muscle and beyond, constitutes around 20 % of incident cases of bladder cancer. This translates into an annual incidence of about 5 cases per 100,000 males and 1 case per 100,000 females. However, the issue is more significant demographically as superficial bladder cancers may evolve into invasive disease in up to about 20–30 % of cases. As these are not "new" cases, they are not reflected in national incidence figures.

The majority of bladder cancers (90 %) are urothelial carcinomas (UC), formerly termed "transitional cell carcinomas" (TCC) [1], whereas less common cell types include squamous cell carcinoma, adenocarcinoma, small cell carcinoma and rarely sarcoma, lymphoma, or melanoma [2, 3]. The majority of invasive bladder cancers are moderately to poorly differentiated, and it is uncommon for well differentiated tumors to invade early in the course of the disease [1]. Studies in our laboratory have suggested that there is a stem cell tumor of origin in bladder cancer, and that this allows dominant transitional cell carcinoma to coexist with (and probably give rise to) squamous and glandular differentiation [4]. We have also shown that there is clonal heterogeneity, with regard to histology, ultrastructure, growth kinetics, expression of growth factors and growth factor receptors, and parameters of response to chemotherapy within individual tumor deposits [4]. This creates a more complex target for therapeutic intervention [5].

D. Raghavan, MD, PhD, FRACP, FACP, FASCO (✉)
Levine Cancer Institute, Carolinas HealthCare System,
32861, Charlotte, NC 28232, USA
e-mail: derek.raghavan@carolinashealthcare.org

H.M. Sandler, MD, MS, FASTRO
Department of Radiation Oncology, Cedars Sinai Cancer Center,
Los Angeles, CA, USA

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Table 34.1 Limitations of studies of novel prognostic indicators

Parameter	Limitation	Examples
Laboratory methodology	New assay system	Standardization in progress
		What is "normal"?
		Optimal technology?
		e.g. I-H vs. FISH?
		e.g. RNA vs. protein?
		Inter-laboratory variation
	Lab test applied to clinical samples	Differences in fixation
		Tumor sampling error
		Tumor heterogeneity
		"Live" tissue vs. fixed tissue
		Limited range of samples tested early in history of assay
Clinical analysis	Studies not designed for marker correlation	Missing data
		Post hoc analysis
		Uninformative cases
		Case/sample selection bias
		Limited sample size
		Inadequate follow-up
		Not all initial analysis is blinded

Where possible, it is important to attempt to predict natural history and treatment response when defining management protocols, allowing a more aggressive focus to be placed on tumors with a worse anticipated outcome. Stage (extent of invasion) and grade (degree of differentiation) are the most important conventional prognostic determinants [1, 6]. In some early series, investigators did not recognize that the lamina propria is invested with a muscularis of its own, the muscularis mucosae [7], and thus some noninvasive tumors were over-staged when they were noted to have interspersed fibres of muscularis mucosae abutting the tumor tissue. The pattern of growth (solid rather than papillary), large size, aneuploidy, presence of hydronephrosis, lymphatic and vascular invasion have been shown to be adverse prognostic determinants in univariate analysis [1, 6, 8–13].

In addition to the conventional histo-pathological and clinical predictors of natural history and response to therapy, a series of adverse molecular prognosticators have been identified. An important caveat in any discussion of novel prognostic markers is that many new marker technologies have important limitations with respect to execution and interpretation in this context (Table 34.1), a construct that has unfortunately been validated in a major randomized trial assessing the utility of P53 mutation as a prognostic and predictive marker, as discussed below.

Molecular Prediction of Natural History of Bladder Cancer

Our understanding of the molecular biology of bladder cancer is still evolving [14]. The simplest molecular predictors of outcome have correlated with tumor differentiation. For example, absence of expression of ABO blood group substances on the

surface of noninvasive bladder cancer cells is associated with higher rates of relapse and progression to invasion [15]. Similarly, the presence of aneuploid populations of cells is also associated with an increased prevalence of relapse and tumor progression, although most invasive bladder cancers actually are aneuploid.

Noninvasive and invasive bladder cancers have different patterns of molecular pathogenesis. Noninvasive disease is particularly characterized by a loss of heterozygosity of chromosome 9, which is where the most important associated gene(s) may reside [16]; fibroblast growth factor (FGF)-3 and RAS are two of the genes associated with noninvasive bladder cancer. With the development of more invasive and undifferentiated disease, aberrations of chromosome 17 are detected, in association with mutations of P53 [17]. Similarly, increased expression of RAS and its variants appears to be associated with loss of differentiation and a worse prognosis [18, 19], and may correlate with P53 function [18].

The functions of P53 and P21 are linked, functioning in a complex, and thus accurate molecular characterization of bladder cancer requires the study of both genes, with outcome being linked to the combination of presence/absence of each gene. In addition, the deletion of the Rb gene confers an adverse prognosis, and its normal function is influenced by the action of the P53/P21 complex [20]. Immunohistochemical studies of a relatively small number of bladder cancer specimens obtained by radical cystectomy have shown that the most favorable prognosis appears to be associated with expression of wild-type P53 and normal expression of P21 [21]. The presence of mutant P53 with deletion of expression of P21 has been reported to predict a high relapse rate. Initial studies from the University of Southern California (USC) have shown that expression of P53 mutation confers prognostic information additional to that afforded by stage and grade [17, 21]. This became the basis of an international randomized trial (see below), which reassessed the true importance of P53 mutations in a much larger sample size (as discussed in detail below) (Table 34.1).

Another relevant gene with a locus on chromosome 9 is $p16^{INK4a}$, which functions as a tumor suppressor. It probably inhibits cyclin D function, and is particularly associated with the evolution of squamous carcinoma and bilharzial bladder cancer [22].

The expression of the epidermal growth factor receptor (EGFR) is another molecular determinant of prognosis [23]. This cell surface protein, with known cell growth regulatory functions, is correlated with expression of P53, aneuploidy, and invasive growth [24], but has been shown independently to have prognostic implications for several malignancies. As discussed below, it may also play a role in resistance to cytotoxic agents, such as cisplatin. The transferrin receptor [25], also located on the surface of bladder cancer cells, appears to be another independent prognostic determinant, although the nature of this function is unknown, as is its relationship to the expression of EGFR and other molecular determinants.

The genes that control vascular invasion and angiogenesis also seem to have important prognostic implications. It is known that microvessel density, the extent of tumor vascularity per high power field, is associated with metastasis and prognosis – the higher the microvessel density, the worse the prognosis [26]. Cote and colleagues have also studied the expression of thrombospondin-1 in bladder cancer. This is a glycoprotein component of the extracellular matrix, which inhibits

angiogenesis [27], and its expression is directly correlated with prognosis. These studies also have suggested that P53 mutation is associated with suppression of expression of thrombospondin-1.

Investigators at Memorial Sloan Kettering Cancer Center have used oligonucleotide arrays to analyze the transcript profiles bladder tumors and have carried out immunohistochemical analyses on bladder cancer tissue arrays to validate the associations between marker expression, staging and outcome. They were able to achieve a greater than 80 % accuracy in prognostication [28].

Overlapping and interacting molecular functions regulate growth, differentiation and prognosis of bladder cancer. Several of these oncogenes and suppressor genes may be suitable candidates for gene therapy, or for downstream regulation through inhibitors of transcription and translation.

Molecular Prediction of Response to Chemotherapy

Studies in the late 1980s revealed higher objective response rates from the use of combination chemotherapy regimens than were achieved with single agents, both for the treatment of metastatic bladder cancer and in the neoadjuvant setting [5, 29]. For many tumor types, there is an increasing level of focus on the molecular biology of tumor response to chemotherapy.

We have previously studied the expression of the intracellular scavenger, glutathione, which decreases the available level of cytotoxic agents, such as cisplatin, within tumor cells [30]. In a series of bladder cancer xenografts, high levels of glutathione were identified, representing higher concentrations than are found in malignant melanoma and ovarian cancer, the classical models of the role of glutathione in cytotoxic resistance. In addition, we showed that higher levels of glutathione are expressed in human tumor biopsy specimens than in biopsies from patients with a past history of bladder cancer, and in turn, these levels were higher than those found in normal bladder tissue. The measurement of this protein has not become a standard predictive test in the management of bladder cancer, although there are several sets of preliminary data that implicate glutathione and glutathione-S-transferase in the biology of responses to chemotherapy.

One particularly controversial issue has been the clinical significance of mutation of the P53 suppressor gene in the context of resistance to cytotoxic chemotherapy. Innate resistance to chemotherapy may be a function of expression of P53, although there are conflicting data on whether mutation of P53 confers increased responsiveness [31, 32] or increased resistance [33] to the impact of chemotherapy. Cote and colleagues have reported a post hoc study of immuno-histochemical staining of tumor biopsies from a randomized study of adjuvant platinum-based chemotherapy [32] and suggested that tumors exhibiting mutation of P53 benefited from adjuvant chemotherapy [31]. By contrast, those with wild-type P53 did not exhibit any difference in survival between the control population and those receiving adjuvant chemotherapy. The major problem with this study was small sample size and its post hoc nature.

Studies from Memorial Sloan Kettering Cancer Center initially suggested that P53 mutation was associated with resistance to neoadjuvant chemotherapy with the methotrexate-vinblastine-doxorubicin(Adriamycin^{R})-cisplatin (MVAC) regimen [33]. A detailed study of molecular prognosticators in patients treated with the MVAC or cisplatin-methotrexate-vinblastine (CMV) regimens for advanced bladder cancer at Princess Margaret Hospital, Toronto, did not identify any prognostic impact from expression of P53 immunohistochemically [34]. It was not clear whether this reflected a true lack of prognostic relevance or is an artifact of methodology or small sample size. That said, in this small study, another marker (metallothionein expression) did have statistically significant prognostic implications.

The data regarding the prognostic role of metallothionein expression are interesting. Metallothioneins are a family of sulfhydryl-containing cysteine residues that are involved in absorption, transport and metabolism of heavy. Previous studies have suggested that these proteins may be related to resistance to cisplatin and alkylating agents [35]. Satoh et al. demonstrated that an increase in the concentration of metallothionein in mice caused a reduction of nephrotoxicity, accompanied by cisplatin resistance in a mouse bladder cancer [36]. Siu et al. [34] showed in univariate analysis that good performance status, low percentage of metallothionein staining, and high tumor grade were significant positive predictors of response to cisplatin chemotherapy, but that the latter factor was lost in multivariate analysis.

In a detailed study of cell lines, Kielb et al. [37] showed that P53 mutation is required for paclitaxel to induce cell death in vitro in human bladder cancer cells, whereas cells with normal P53 function were not affected by this agent. By contrast, the cytotoxic impact of gemcitabine was not influenced by P53 mutations, suggesting a potentially different spectrum of responses to this agent in bladder cancer.

Multidrug or pleiotropic resistance, in which cell surface protein complexes function as efflux pumps or modulators of intracellular cytotoxic drug concentrations, appears to be relevant to bladder cancer. A family of multidrug resistance (mdr) proteins, including p-glycoprotein, correlates with resistance to the taxanes, vinca alkaloids and anthracycline antibiotics. This phenomenon has been found to be particularly relevant in ovarian cancer and multiple myeloma, but studies of expression of mdr in bladder cancer have been difficult, for reasons that are not fully clear. For example, our xenograft studies identified major clonal differences in response to doxorubicin and vinblastine, but we were unable to demonstrate clear and reproducible expression of p-glycoprotein in the tumor specimens. Others have encountered similar problems. Siu et al. [34], studying patients treated with MVAC or CMV chemotherapy, did not find any prognostic significance from expression of p-glycoprotein, although any impact for response or resistance to chemotherapy might have been overcome by the presence of cisplatin in both regimens, an agent that is not influenced by mdr expression.

However, Petrylak et al. [38] were able to demonstrate clear enhancement of expression of p-glycoprotein in pre- and post-treatment biopsies of human tumors treated with the MVAC regimen. The highest proportion of tumor cells expressing p-glycoprotein was observed in metastases from patients treated with six or more cycles of chemotherapy. These workers speculated that mdr could contribute significantly to the patterns of resistance seen in the use of the MVAC regimen.

However, this technology has not been applied routinely to the treatment of invasive bladder cancer, largely because of the difficulty of demonstrating mdr expression in bladder cancer tissues.

Adopting a more technically sophisticated approach, investigators at Memorial Sloan Kettering Cancer Center have studied the transcript profiles of more than 100 bladder specimens, representing the spectrum from normal to relatively benign to malignant disease, in an attempt to identify useful novel prognosticators [28]. In an elegant study that will require validation, they identified a hierarchy of determinants, including peptidyl propyl isomerase A, nuclear RNA export factor 1, tetratricopeptide repeat domain G, hematopoietic cell specific Lyn substrate 1, ankyrin G, baculoviral IAP repeat-containing 3, intercellular adhesion molecule 1 and TP53-activated protein 1. In each instance, Kaplan-Meier curves identified differences in survival based on expression, but further study will be required to identify the utility of such gene expression in predicting the outcome of specific chemotherapy regimens.

In this context, Takata et al. [39], studying a small number of patients treated with MVAC style chemotherapy, identified another series of potential genetic predictors of outcome using array techniques. Again the significance of their preliminary observations will require clarification, although it was interesting to note that these array studies further implicated P53 gene function and mutation in predicting the outcomes of chemotherapy.

At a more pragmatic level, the Radiation Therapy Oncology Group (RTOG) have carried out retrospective analyses of their series of cases treated with radiotherapy and cisplatin-based chemotherapy, and have demonstrated that expression of EGFR is associated with improved outcome, including response to chemoradiotherapy, whereas expression of the her-2-neu gene correlates in univariate analysis with reduced response and survival after such treatment [40].

As outlined in Table 34.1, validation of these applied technologies in much larger patient sets will be required before this approach becomes a standard of care in clinical practice.

Management of T1-T2 Bladder Cancer: Impact of Molecular Biology

As noted above, mutation of P53 has been shown to have prognostic significance independent of stage and grade for P1-2 urothelial cancer [17, 20, 21]. Consequent upon the promising early data from USC, a randomized trial, carried out by an Intergroup, studied the effect of adjuvant MVAC chemotherapy after radical cystectomy for pathological stage P1-2 tumors with negative lymph nodes and expression of mutated P53 [40]. Nearly 500 patients underwent P53 assessment, of whom 55 % showed immunohistochemical reactivity, and 114 were randomized to 3 cycles of adjuvant MVAC versus observation. Although there were several problems of trial

execution, including lack of patient compliance, the study did not confirm the prognostic significance of P53 expression [41]. The recurrence rate was unexpectedly low in both arms, with an overall 5 year probability of recurrence of 0.20, with no differences in outcome, node status or lympho-vascular invasion associated with P53 reactivity.

The Role of Surgery for Invasive Bladder Cancer

As discussed elsewhere in this volume, the least aggressive surgical treatment of bladder cancer is transurethral resection (TUR) or fulguration, in which the aim is to remove the tumor completely via a cystoscope, while attempting to spare the bladder. Depending on the care in case selection, the extent of tumor, and the population of patients being treated, TUR may lead to an overall 5 year survival of 30–69 %, the majority of patients retaining an intact bladder [42, 43], with higher long-term survival for patients with T1-2 disease.

Another option that has also allowed bladder preservation has been the use of surgical resection of the portion of the bladder that contains the tumor – partial cystectomy [44]. The general consensus is that this is a technique that should only be used in highly selected cases, provided that the following criteria are met: (a) solitary primary lesion at the dome of the bladder, well removed from the bladder neck and ureters; (b) 2 cm margin of normal bladder tissue around the tumor; (c) likelihood of good bladder capacity and function after the procedure; (d) absence of carcinoma-in-situ from random biopsies. When present, carcinoma-in-situ is associated with superficial recurrence, and lymph node involvement is associated with systemic disease [44].

However, the standard of care for most patients with invasive bladder cancer is radical cystectomy [11, 45, 46], as discussed in detail elsewhere in this volume. The cure rate depends on well-defined prognostic factors, including conventional indices, such as stage and grade, and the more recent correlates discussed above. In addition, it appears that delay in cystectomy may lead to impaired survival [46]. Cure is even possible from surgery alone in advanced stage disease, although the chance is much lower. In well-staged patients in contemporary series, the relapse rate after surgical resection of PS T3-4 tumors remains 50 % or higher, with most relapses occurring at distant sites, indicating that this is a disease with the potential for early micrometastatic spread (which forms the basis for neoadjuvant chemotherapy strategies).

As a result, and in view of the modest successes of chemotherapy for metastatic and recurrent disease (see Chap. 36), attempts have been made to combine systemic therapy with definitive local treatment. In addition, surgical templates and techniques have been modified, including the creation of continent pouches and artificial neo-bladders [11], the use of laparoscopic approaches [47] and the avoidance of prostatectomy [48] in an attempt to ameliorate toxicity for an approach with a high relapse rate.

Chemoradiation and Bladder Preservation Techniques

The use of radiotherapy as an alternative to cystectomy for invasive bladder cancer was previously favored in parts of Europe and Canada, although the pendulum has swung back somewhat towards radical cystectomy in recent years because of the perception of higher surgical cure rates. It should be noted that this perception may be influenced heavily by the fact that comparisons in the literature, between the results of surgery and radiotherapy for bladder cancer, reflect the comparison of surgical versus clinical staging. Furthermore, patients treated in radiation series are characteristically older and less robust than those subjected to cystectomy. The traditional approaches to radiotherapy included doses of external beam irradiation in the range of 50–70 Gy, with a higher level of local control achieved in series reporting higher dose schedules [9, 10, 49–52]. Ideal radiotherapy candidates have had aggressive pre-radiotherapy TUR, absence of extralesional carcinoma-in-situ, no anemia, and no hydronephrosis.

The techniques used to deliver curative irradiation to the bladder tumor volume, while sparing normal tissue, vary from one institution to another, depending on the availability of equipment an the quality of physics and computer support [10, 49, 50]. Irrespective of field size and technique, it is clear that dose is critically important, with total doses less than 60 Gy being ineffective [51]. Whether the newer techniques of intensity modulated radiation therapy (IMRT) and image guided radiotherapy will truly improve local control and/or reduce local tissue toxicity remains to be seen [49]. What is clear is that careful treatment planning is critical and requires close collaboration between radiation oncologist and urologist [52]. Of particular importance is the definition of the site and size of the tumor, and treatment planning should require a localizing cystogram or planning CT scan; the latter is preferred as extravesical disease or recent evolution of lymph node involvement can be discerned, in the treatment position. Furthermore periodic on-treatment CT scan assessment will ensure adequacy of ongoing coverage of the tumor and tumor bed within the treatment fields. It is clear that the bladder moves to some extent, despite fixity of bony landmarks, but with appropriate treatment planning, the movement of the bladder does not appear to affect treatment outcomes [53]. Various approaches have been studied in an attempt to improve local control, to shorten the duration of treatment or to ameliorate toxicity. To date, attenuated dose schedules with hyper-fractionation appear to have increased toxicity without any improvement in local control or survival [54].

Preservation of a well-functioning bladder is more likely if a portion of the bladder can safely be excluded from the high dose of radiation needed for the bladder cancer itself. Treatment of the entire bladder with high doses per fraction or a high total dose is more likely to results in scarring and contracture, especially for the bladder that has sustained multiple TUR's. Care should be taken with respect to the known tolerance of the surrounding normal tissues.

One of the key issues of debate has been the respective merits of surgery versus radiotherapy. However, after many decades of comparison, there is still no absolute

proof regarding the superiority of radical cystectomy or radical radiotherapy. A recent report from a single institution in the Netherlands suggests that, once differences in staging techniques are taken into account, there is no major difference in outcomes between these modalities of treatment [55]. However, others have claimed that, notwithstanding the problems of comparison of surgical versus clinical staging, radical cystectomy ultimately offers better local control and survival, in part because surgical resection of involved pelvic nodes will allow long-term survival in 20–30 % of cases [11]. This view remains controversial and has not been proven in randomized trials. In our clinical practice, for fit patients without major intercurrent medical disorders, we tend to refer for radical cystectomy for deeply invasive tumors, reasoning that useful information is gleaned from the surgical staging, and that local control is likely to be more robust. The optimal treatment of superficially invasive disease (clinical stage T1 and perhaps T2) is less clearly defined.

Combined Modality Strategies

Combined modality approaches, incorporating systemic chemotherapy with definitive local modalities, have been studied extensively in the past few years in the hope of sparing the bladder or to improve overall survival [13, 56]. This has been predicated on the following concepts:

- systemic chemotherapy may reduce the extent of local tumor;
- it allows clinical assessment of chemo-responsiveness of the tumor, thus allowing more rational decisions to be made regarding continuation of chemotherapy;
- it may control occult micro-metastases;
- if radiotherapy is planned, it may cause enhanced radiation responsiveness via synergistic effects between some cytotoxics (e.g. doxorubicin, cisplatin, 5-fluorouracil, mitomycin, gemcitabine) and the biological impact of radiation.

However, as around 30–60 % of tumors are absolutely or relatively chemo-resistant, some patients will sustain unnecessary toxicity for no benefit, and there is the risk that effective local treatment will be delayed while ineffective systemic chemotherapy is used.

In a randomized, prospective trial assessing the utility of concurrent chemoradiation, a protocol of single agent cisplatin administered during the period of radiotherapy resulted in 67 % sustained pelvic tumor control compared to 45 % from radiation alone; however, overall survival was not statistically different, although there was a survival trend in favor of the combined modality therapy [57]. It should be noted that this study was not powered to demonstrate a survival benefit.

James et al. [58] have recently reported the results of a randomized comparison of chemoradiation with 5-fluorouracil-mitomycin C versus radiation alone. In a series dominated by patients with clinical stage T2 disease, this trial demonstrated improved response rate, progression-free and overall survival achieved by chemoradiation [58].

We know of no other randomized trials that have tested the impact of chemo-radiation, compared to radiation alone, for invasive bladder cancer, although a range of phase II trials have demonstrated antitumor efficacy (with response rates as high as 80 %) and toxicity (varying with the doses and regimens employed). The Radiation Therapy Oncology Group (RTOG) has completed several studies that have assessed the utility of neoadjuvant or adjuvant chemotherapy in association with concurrent chemo-radiation. However, none of these trials has addressed the comparison of chemo-radiation versus radiation alone.

Neo-adjuvant Chemotherapy

The role of neoadjuvant (first-line) systemic chemotherapy, followed by definitive radiotherapy or cystectomy has been studied in detail [13, 56]. The early, randomized trials, employing single agent chemotherapy, failed to show a survival benefit from combined modality treatment. However, with the introduction of cisplatin-based multi-drug regimens, such as MVAC and CMV, modest but significant improvements in survival have been documented in randomized trials and in a meta-analysis (Table 34.2) [13, 59–62].

The MRC-EORTC-International trial of neoadjuvant CMV, which recruited 976 cases between 1989 and 1995, was designed to identify a 10 % difference in long-term survival, but failed to do so (achieving a 6–7 % difference in outcome) and was thus reported as a "negative" trial initially [59]; however, a recent long-term update showed a sustained 6 % 10 year survival benefit from neoadjuvant CMV, with a more obvious impact in surgical cases [60]. The hazard ratio of .84 (indicating a 16 % reduction in death) favored combined therapy ($p = 0.037$). By contrast, the RTOG, also testing the utility of neo-adjuvant CMV chemotherapy followed by chemo-radiation versus chemo-radiation alone, showed identical 3 year survival [63]. This may have reflected a different patient population or perhaps the impact of the cisplatin chemotherapy in the chemo-radiation components of each treatment arm.

Although the North American Intergroup trial of neo-adjuvant MVAC revealed a very dramatic difference in median survival (6 years versus 3.8 years), the absolute improvement in long-term survival and potential cure rate was only of the order of 8 % [61], a figure consistent with most other published studies [62], as summarized in Table 34.2.

These data suggest that, in 2012, deeply invasive bladder cancer should be treated by neoadjuvant MVAC or CMV chemotherapy followed by cystectomy if the patients are deemed fit for chemotherapy and surgery. However, this precept does not address the role of radical cystectomy with adjuvant systemic chemotherapy for patients chosen on the basis of histological, biochemical or other predictive factors. As a consequence, there is still considerable controversy regarding the true standard of care – many clinicians still believe that it is appropriate to perform

Table 34.2 Results of randomized clinical trials of preemptive chemotherapy for invasive bladder cancer

Series	Regimen	Median survival (month)	Actuarial long-term survival[a]
Shipley	CMV → C-RT	36	48 % 5 years
Shipley	C-RT	36	49 % 5 years
Shearer	M → RT	23	39 % 3-years
Shearer	RT only	20	37 % 3 years
Wallace	C-RT	~24	39 % 3-years
Wallace	RT only	~22	39 % 3-years
MRC-EORTC	RT/S only	37.5	30 % 10-year
MRC-EORTC	CMV-RT/S	44	36 % 10-year[b]
Intergroup	MVAC	72	42 % 10 year
Intergroup	Observation	45	35 % 10 year

Abbreviations: *RT* radiotherapy, *C* cisplatin, *M* methotrexate, *A* doxorubicin (Adriamycin™), *V* vinblastine, *S* surgery (usually radical cystectomy)

[a]Deaths from ALL causes, including death from intercurrent disease in an elderly population

[b]Hazard ratio 0.84 (p = .037)

radical cystectomy as the first step in management of invasive bladder cancer, with subsequent management decisions regarding chemotherapy being predicated on the pathologic stage of the tumor.

Adjuvant Chemotherapy

Adjuvant (postoperative) chemotherapy had shown some promise in improving survival for patients with invasive bladder cancer. Randomized trials assessing the utility of combination chemotherapy (such as the combination of methotrexate, vinblastine, and cisplatin, with or without doxorubicin or epiribicin – the CMV, MVAC or MVEC regimens), administered after radical cystectomy for patients with deeply invasive disease and/or involved lymph nodes, have shown improved disease-free survival [32, 64, 65].

However, the published trials have been weakened by poor statistical design or execution, and these studies have not demonstrated a statistically significant improvement in overall survival. For example, in one study, there was an uneven distribution of salvage chemotherapy, making the trial a test of chemotherapy at any time after cystectomy, rather than addressing the role of early chemotherapy as classical adjuvant treatment [64]. The interpretation of data in this study was confounded by the addition of non-randomized cases into the follow-up analysis [64].

The study reported from Stanford University was predicated on disease-free survival, and thus was closed early by its Data Safety and Monitoring Committee, and there were insufficient cases to provide a meaningful overall survival analysis [65]. Unfortunately the situation has been confused by a well-publicized but flawed meta-analysis [66], which ignored the various problems of individual published and

unpublished trials and grouped them together into a comparison of observed versus expected outcomes. This study erroneously concluded that there is a statistically significant survival benefit from adjuvant chemotherapy. While this may ultimately be proven to be correct, this specific study did not prove this point.

The EORTC has attempted to address this issue in a well-designed, randomized trial, in which standard local therapy has been compared to standard local therapy plus the addition of adjuvant chemotherapy. Unfortunately this important trial closed prematurely due to lack of accrual, presumably because of preconceptions of participating clinicians (or their patients) about the true role of neoadjuvant or classical adjuvant chemotherapy, and it will now be challenging to produce level 1 data to resolve the issue.

Also relevant to this issue is the P53 study noted above. While this study was not designed to address the utility of adjuvant chemotherapy per se, it is noteworthy that the patients who received three cycles of adjuvant MVAC did not appear to have improved overall survival, compared with those who were treated with surgery alone [41]. Although this may simply have reflected the population of patients with P53-mutant urothelial cancer, this study clearly did not provide any additional data to support the routine use of adjuvant chemotherapy for invasive bladder cancer. We still believe that a randomized trial testing the use of adjuvant chemotherapy is needed to resolve the issue.

Novel Agents for Neo-adjuvant and Adjuvant Therapy

Little information is available regarding the use of newer cytotoxic agents in the adjuvant context for bladder cancer, although there are extensive data revealing the anticancer efficacy of gemcitabine, the taxanes, some of the novel platinum complexes and tyrosine kinase inhibitors against recurrent and metastatic disease (as discussed elsewhere in this volume).

Perhaps of greatest interest has been the potential for using gemcitabine-cisplatin as neoadjuvant or adjuvant chemotherapy, based on its similar activity to MVAC chemotherapy for metastatic disease [67]. This doublet has been interesting because of its lower level of toxicity. However, despite a series of under-powered single arm and randomized comparisons, no definitive trial has proven that gemcitabine-cisplatin provides a survival benefit in addition to definitive treatment in either the neoadjuvant or adjuvant setting. The problems of historical, non-randomized or under-powered comparisons, with the risk of case selection bias or follow-up bias, preclude meaningful assessment of the published data.

Our approach, when patients are not deemed sufficiently robust to tolerate the MVAC or CMV regimens, is to discuss the potential utility of gemcitabine-cisplatin, explaining that this is likely to be less toxic, based on comparisons in patients with metastatic disease, but has not been validated in the neoadjuvant or adjuvant setting with any high level of certainty.

Another regimen that was recently reported in a randomized comparison against MVAC for metastatic disease is the combination of gemcitabine, cisplatin and paclitaxel (GCP) [68]. Although there was a modest increment in response rate from GCP against metastatic urothelial cancer, there was no large difference in survival. Nonetheless, a Spanish cooperative group recently reported a survival benefit from adjuvant GCP after cystectomy in a presentation at the Annual Scientific Meeting of the American Society of Clinical Oncology [69], although it should be noted that their preliminary data for GCP in the metastatic setting were not confirmed by the international randomized trial [68].

There have been recent reports at scientific meetings of the use of targeted therapies, such as erlotinib (targeting the epidermal growth factor receptor), in the neoadjuvant setting for invasive bladder cancer [70]. Although there may have been objective responses, the published information is not definitive with regard to extent of down-staging, duration of response, or survival outcomes, and we are not aware of peer-reviewed publications on this topic.

We know of no definitive studies that have proven the utility of gemcitabine, the taxanes, any novel platinum complexes or any of the targeted therapies in this context, and thus we do not deem it appropriate to make any recommendations about their use, other than in the context of clinical trials, at the present time.

Current Patterns of Practice

Despite the extensive evidence that there is a significant improvement in survival for patients who receive neoadjuvant MVAC chemotherapy and cystectomy or radiotherapy for invasive bladder cancer, compared to local modalities alone, surveys of patterns of practice consistently indicate that most patients do not receive neoadjuvant chemotherapy for invasive bladder cancer. A recent study of the SEER-Medicare data base for 1992–2002 indicated that the use of such treatment is uncommon [71]. A report from the National Cancer Data Base showed similar data for the period 1998–2003 [72]. This seems reasonable, given that our positive randomized trial data were first published in peer-reviewed form in 2003.

However, two studies from contemporary time frames show that far fewer than 50 % of patients receive such treatment [73, 74], despite the well publicized, definitive survival benefit. At present, the reasons for this are unclear.

The Future

It seems likely that molecular prognostication and prediction will dominate our approach to invasive bladder cancer in the future [28, 39]. It appears that we have reached a plateau with surgical and radiation techniques to control local disease.

Progress in cytotoxic chemotherapy has been slow in the past 15 years, since the introduction of the taxanes and gemcitabine.

Despite the lack of success of the randomized neoadjuvant trial predicated on expression of P53 mutation [41], this study may provide a useful paradigm of future trial design. The concept of designing specific clinical approaches based on established gene targets makes sense, but these studies may require additional patient-directed materials to improve participation and compliance.

The development of structured arrays that identify gene clusters associated with specific patterns of clinical behavior [28, 39, 75, 76] may also allow more precise prediction of outcome, thus allowing the identification of high risk cases that require systemic therapy. Alternatively, the identification of clusters of these specific gene arrays and their functions may facilitate the targeting of specific therapies directed against them. This will be especially important in view of the promiscuity of targeted therapies and our lack of knowledge of the specifics of their up-stream and down-stream interactions in tumors.

It also will be important to continue to educate patients and their physicians about the progress that has been made, and to ensure that the medical community capitalizes fully on those gains.

Summary

Systemic chemotherapy has been shown in randomized trials to improve outcomes of definitive local treatment when used as first-line treatment. Classical adjuvant therapy has been shown to prolong disease free survival, and appears to produce an improved non-significant trend in overall survival, but no clinical trials have been completed to prove this concept. Novel biochemical and molecular predictors of prognosis and response to treatment are being evaluated as aids to clinical management, although definitive proof of their clinical usefulness is not available. The substantial changes in diagnosis and management will ultimately improve survival from invasive bladder cancer, while reducing the toxicity of treatment. Well designed clinical trials, linked to sophisticated and thoughtfully designed molecular studies, will be our pathway to the future.

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Chapter 35
Surgical Management of Bladder Cancer

Murugesan Manoharan and Prashanth Kanagarajah

Clinical Evaluation

Approximately 70 % of bladder cancer (BC) cases present as Ta, T1 or carcinoma in situ (CIS) [1]. Like many other cancers, TNM staging has a vital role in treating BC (Chap. 30). Ta, T1 and CIS are collectively referred to as non-muscle invasive BC (NMIBC). Majority of patients with NMIBC are diagnosed following an episode of haematuria (Chap. 8).

Role of Cytology and tumour antigens: None of the currently available urinary markers and cytology can replace cystoscopy but may be helpful for follow up purposes and in patients with specific diagnostic problems. Voided urine is satisfactory for cytology. There is no significant difference in sensitivity and specificity of voided urine and barbotage washing sample [2] although some studies have shown slightly better results with barbotage. This has been already addressed in the early part of the Chap. 30.

Transurethral resection is an important step in the diagnostic and therapeutic aspects of all types of BC particularly so in NMIBC. Up to 70 % of patients may have residual bladder tumor after transurethral resection [3]. Newer techniques therefore have been in some cases utilised to improve the diagnostic yield of cystoscopy.

- **Fluorescence cystoscopy** allows visualizing malignant urothelial cells that fluoresce due to the accumulation of photoactive compound protoporphyrin IX. Protoporphyrin IX is produced by malignant urothelial cells after bladder

M. Manoharan, MD (✉) • P. Kanagarajah, MD
Department of Urology, University of Miami-Miller School of Medicine,
1150 NW 14 Street, Suite 309, Miami, FL 33136, USA
e-mail: mmanoharan@med.miami.edu

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instillation of the precursor 5-aminolevulinic acid or hexaminolevulinic acid 1 h prior to cystoscopy [4].

- **Narrow band imaging (NBI)** facilitates the differentiation of malignant and normal mucosa. Narrow band imaging does not require special reagents to be instilled in the bladder. Instead, this technique employs light filtered at 415 and 540 nm bands. The filtered light allows better visualization of vascularized lesions. The sensitivity and specificity for detecting bladder tumor using this technique has been reported to be 92.7 and 70.9 % respectively [5].
- **Optical coherence tomography** is a non-invasive imaging technique which employs near infra-red light waves for cross-sectional micro-imaging of tissues. Ninety percent sensitivity and 89 % specificity has been reported using this technique to detect BC confined to the mucosa and 100 % sensitivity to detect muscle invasive BC [6].

Surgical Management of Non Muscle Invasive Bladder Cancer (NMIBC)

Transurethral Resection of Bladder Tumor (TURBT)

Transurethral resection is the initial and critical step in the initial management of any bladder tumour. It has several purposes including establishing a detailed histological diagnosis, staging, determining important prognostic factors (grade, number, size and presence of carcinoma *in situ*) and finally achieving extirpation of all non-muscle invasive tumour. Ensuring complete resection of the tumor carries a great significance as residual disease can be found even after resection by experienced surgeons [3]. Leaving behind residual tumor can lead to local recurrence and disease progression [3].

Conventionally, transurethral resection of bladder tumor is performed in the following fashion:

- It is imperative that a full relaxation of the abdomen is mandatory and this can be achieved by general or spinal anaesthetic.
- After positioning the patient in lithotomy position it is important to carry out bimanual examination of the bladder per rectally (in men) and per vaginally in women to assess the mobility and clinical staging of the tumour prior to the resection.
- It may be useful to dilate the urethra with a dilator to about 30 F if there is evidence of submeatal or meatal stenosis. Any strictures proximally need to be dilated.
- A 24 or 27 F resectoscope is then passed transurethrally under direct vision. Cystoscopy is performed with a 30/70° telescope in a systematic fashion. It is important to make a note of size of the tumour (comparing with the diameter of the loop), anatomic location (lateral walls, fundus, neck of the bladder and ureteric orifices) of the tumour and any urothelial abnormalities suggestive of CIS. Residual urine may be measured and urine sent for exfoliative cytology. Most commonly used irrigating fluid is glycine 1.5 %w/v in water (230 mOsm/L).

Saline can be used with special plasma vaporisation electrode. Bladder perforation is a possibility with over distended bladder at any time; therefore bladder has to be filled to half its capacity with the irrigating fluid.

The lesions are resected using a 30° telescope in two parts (a) the tumour proper (b) the base of the tumour to aid the pathologists for correct staging of the tumour. Smaller tumours can be resected *en bloc* and sent for histology in one piece including the base. Larger tumours are resected in fractions excluding the base. Once the exophytic part of the tumour is resected the base is resected including detrusor muscle for accurate staging. Special attention is given to velvety areas, red erythematous patches which should be sampled separately with punch biopsies as diathermy can damage the epithelial architecture. Excessive cautery should be avoided as it leads to tissue artefacts limiting pathological diagnosis.

- Random bladder and prostatic urethral biopsies (R- biopsies) in presence of multifocal disease are controversial. However the result of these biopsies has no impact on patients' outcome [7].
- TCC in Prostatic Urethra: Prostatic involvement by bladder TCC is relatively common compared with primary prostatic urethral UCa; however, its staging interpretation is controversial. Bladder TCC on or near the neck of the bladder involving adjacent prostate and its stroma has worse prognosis than CIS or TCC confined to the prostatic ducts [8]. In presence of TCC in the prostatic urethra further information is required on stromal involvement. TURP may be required in such cases. In such cases informed consent for prostatic resection is necessary.
- Obturator nerve reflex; Obturator reflex is seen during the resection of low lateral wall tumours. The reflex can be blocked by obturator nerve block or by muscle paralysis during general anaesthesia. Uncontrolled obturator reflex can lead to bladder perforation [9]. Ensure hemostasis and collect specimen using a strainer.
- Instilling travesical chemotherapy within 24 h of the procedure.

Management After Initial TURBT

Following the pathological examination of the specimen, the report describes the histological grade of the tumor (G) and the depth of invasion (T). Below we have summarized the standard of care based on tumor histology.

Low Grade Ta

Low grade Ta tumors often fail to progress to fatal cancer. It has been reported that more than 50 % of bladder tumors diagnosed are Ta and 70 % are low grade [10]. Routine follow up upper tract imaging is not recommended for patients with low grade Ta BC. Recurrence at 3-month follow-up and tumor multiplicity are major risk factors for subsequent recurrences [11]. Patients with recurring Ta tumors can be treated with additional intravesical chemotherapy lasting for <6 months.

The AUA recommends the use of BCG as an alternative first line option to intravesical chemotherapy [12].

High Grade Ta

In patients with high grade Ta the chances to progression to muscle invasion has been reported to be 20–25 % [10]. Therefore, these patients should be started on a 6-week induction course of intravesical BCG followed by 1–3 years of maintenance therapy upon diagnosis after initial TURBT. Cytology and cystoscopy should be repeated at 3 months after initiating therapy [13]. On occasions a repeat TURBT may be required and this can be considered 2–6 weeks after initial TURBT. BCG failures are candidates for cystectomy.

Carcinoma In Situ

With CIS, the progression to muscle invasive disease is high (54 %) [14]. Patients should be started on induction therapy of BCG and subjected to cystoscopy and cytology at 3 months interval. Patients who progress should undergo TURBT. If CIS persists, another 6 week course of BCG should be offered. Responders should be started on maintenance BCG and non-responders should be counselled for cystectomy [15]. Owing to the high risk of recurrence associated with CIS, all patients should be monitored for life with cytology, cystoscopy and upper tract imaging.

High Grade T1

The risk of tumor recurrence and progression to muscle invasive disease is increased with high grade T1 BC. Prior to considering intravesical BCG and cystectomy, re-staging TURBT is highly recommended [13]. Patients with concomitant CIS should be offered cystectomy as primary treatment as these patients carry poor prognosis. With 36 and 29 % probability of concomitant tumor in the prostatic urethra and upper tracts respectively, patients with high grade T1 may require biopsies of the prostatic urethra and upper tract imaging [16, 17].

Re-staging TURBT

Re-staging TURBT should include the primary tumor site and abnormal appearing urothelium. Risk of residual tumor and under staging of high grade Ta and T1 lesions demand re-staging in select scenarios. Up staging on repeat TURBT is reported to be 30 % even when muscle was present in the initial specimen [18]. If tumor resection was performed, a single dose of intravesical chemotherapy should be administered within 24 h of the procedure.

Follow-Up After TURBT in NMIBC

The risk of disease progression and recurrence dictates the frequency and duration of follow-up. Urine cytology and cystoscopy are widely employed. All patients undergo cystoscopy at 3 months after initial TURBT. The AUA recommends follow-up cystoscopy every 3 months for the first 2 years followed by every 6 months for the next 3 years and yearly thereafter for low grade BC [13]. In patients with high grade disease urine cytology and cystoscopy is recommended once every 3 months for the first 2 years, every 4 months for year 3, every 6 months for the next 2 years and yearly thereafter [19].

Management of Muscle Invasive Bladder Cancer

Muscle-invasive disease is an aggressive form of bladder malignancy and has a greater propensity for metastatic disease [20]. In the last two decades, advances in chemotherapy and continent urinary diversion have given a new dimension to the management of muscle-invasive bladder cancer. All these patients should be managed in a multi-disciplinary set up involving urologists, clinical oncologists (radiotherapy) and medical oncologists to get a proper combination of therapies. Patients need to receive adequate information on multi-centre trials during their management.

Cystectomy

Simple cystectomy is unusual in the cancer setting, although it may be necessary for a severely scarred and contracted bladder or intractable symptoms (e.g. hematuria) as a palliative measure or in a salvage setting after bladder preservation treatments have failed. Radical cystectomy is usually a radical cystoprostatectomy with or without urethrectomy in men and anterior exenteration in women (see below). It is one of the major procedures in urological surgery and involves a risk assessment prior to consideration for surgery.

Indications for radical cystectomy are outlined in (Table 35.1).

Table 35.1 Indications for radical cystectomy

1. Muscle invasive (≥T2) bladder cancer
2. Select patients with recurrent high grade T1 or CIS
3. BCG and intravesical chemotherapy failures: high grade T1, with concomitant CIS, multifocal disease
4. Recurrent T1 disease

Table 35.2 Complications of cystectomy

Intraoperative rectal injury
Bleeding: arterial and venous
Early postoperative ileus/small bowel obstruction
Wound infection/abscess/sepsis
Anastomotic breakdown, fistula
Deep vein thrombosis, phlebitis, pulmonary embolism
Pneumonia, coronary problems
Lymphatic leak/lymphocele
Late Urinary tract infections
Stricture, ureteral obstruction
Stoma: retraction, prolapse, hernia
Incisional hernia

Preoperative Assessment

To summarize, it is important to consider the patient's biological age and cardiorespiratory and vascular status, as bladder cancer patients are elderly and have medical comorbidities. Nutritional aspects should be evaluated in preoperative assessment. Obesity may lead to wound infection, dehiscence, and stomal problems.

Peri-operative Complications

Due to advances in anesthesia, intensive care, prevention, and effective management of cardiovascular diseases, there is decreased mortality and morbidity following radical cystectomy [21]. The complication rates following cystectomy approaches 20–30 % in most series (Table 35.2).

Mortality

Mortality is usually related to the patients' comorbidities, and it has decreased substantially in the last two to three decades to approximately 1–2 % [22, 23].

Radical Cystectomy

Radical cystectomy involves the removal of the entire bladder and urethra with pelvic lymph nodes bilaterally in men, and the removal of the bladder, urethra, uterus, cervix, and cuff of the vagina in women. The procedure is carried out by either a laparoscopic or an open approach. It is an effective curative treatment for

muscle-invasive urothelial cancer of the bladder. Excellent local control of the disease can be achieved. It also provides amelioration of local symptoms due to bladder cancer such as hematuria, frequency, dysuria, and clot retention.

In men, radical cystectomy is typically performed as radical cystoprostatectomy with removal of the bladder, prostate, and seminal vesicles en bloc. It maybe performed with or without cavernous-nerve sparing for improved erectile function postoperatively. Prostate-sparing cystectomy has been described to improve the potency rate [24]. However, the chances of incidental prostate cancer is high, around 15–40 %; hence this is not widely practiced. In women, radical cystectomy is typically performed as anterior exenteration consisting of removal of the bladder, uterus, ovaries, fallopian tubes, and part of the anterior vaginal wall. Bilateral pelvic lymphadenectomy involves removal of the obturator, external and internal iliac lymph nodes bilaterally up to the common iliac artery bifurcation. It is always performed in conjunction with radical cystectomy both as a therapeutic and as a staging diagnostic procedure. Occasionally these patients may have prolonged lymphatic leak and lymphocele. Recent data suggest that an extended lymph node dissection (to the bifurcation of the aorta) may also be a therapeutic procedure for patients with minimal lymphadenopathy [25]. Patients with a greater number of removed lymph nodes may have an improved disease-free survival. Most patients with positive lymph nodes require adjuvant chemotherapy. However despite these measures, the 5-year survival is poor at 20 %.

Partial Cystectomy (PC)

Partial cystectomy has not received adequate recognition it deserves amongst urologists and oncologists. It involves removal of part of the bladder wall that is involved by a discrete lesion. Patients with a solitary muscle-invasive lesion, with no evidence of carcinoma in situ (CIS) or previous history of multiple superficial tumors or metastasis, without involvement of the trigone or posterior urethra, are suitable candidates and it is desirable to have a clear margin of at least 1.5 cm around the tumor. Localised muscle-infiltrating tumours in the fundus or anterior wall are ideal for PC. Other indications include bladder tumors within a diverticulum and urachal adenocarcinoma in the urachus [26].

Before considering the bladder-preserving procedure, the following assessment should be done: (1) bladder mapping: rule out CIS and multifocal lesions by performing systematic bladder biopsies (mapping); (2) bladder capacity should be assessed preoperatively should be adequate to avoid postoperative voiding symptoms due to low bladder capacity. Patients who undergo partial cystectomy require surveillance with cystoscopy and urinary cytology due to an increased risk of recurrence secondary to multifocal nature of urothelial cancer. Bladder capacity can be increased by using a loop of ileum (ileo-cystoplasty). The mean 5-year survival after partial cystectomy for T2 to T3b tumors is 67–80 % [27, 28].

Salvage Cystectomy

Salvage cystectomy is indicated in intractable haematuria or development of fistula following chemotherapy or radiotherapy or due to severe intractable and disabling urinary symptoms. It is also considered in patients with local recurrence or progression following primary radiotherapy. The operation is usually considered palliative; however, well-selected patients may have significant long-term survival.

Risks of Salvage Cystectomy

Intraoperative blood loss tends to be high, as is the risk of injury to adjacent organs (e.g., rectum, iliac vessels, etc.). Anatomical planes are not well defined in postradiotherapy patients because of desmoplastic reaction. The surgeon should be prepared to perform only a urinary diversion if the bladder cannot be safely removed. Tissue planes are often distorted secondary to radiation. Risks of wound infection and ileus are also increased. Survival rates after salvage cystectomy are quite low [29]. Complication rates are higher with orthotopic bladder reconstruction in these cases.

Urinary Diversion in Salvage Cystectomy

The ileal conduit is the preferred method of urinary diversion in salvage cystectomy. Risk of incontinence is greater if neobladder reconstruction is attempted secondary to radiation effects on the sphincter. Assessment of the ileum must be made to ensure that there are no radiation-induced injuries, and in such cases other segments of uninvolved bowel should be used.

Sexuality Preserving Cystectomy and Neobladder

Various specialist centers in Europe and the United States have described conservative procedures involving bladder removal with pelvic lymph node dissection and preservation of the vasa deferentia, prostate, and seminal vesicles in males, and all internal genitalia in females. This is followed by an ileal neobladder reconstruction and its anastomosis to the margins of the prostate in males and urethra in females. Indications for this type of surgery are T1 to T3 BC with no tumor in the bladder neck and prostate in males and absent tumor in the trigone in females [24]. These patients need to undergo preoperative assessment and investigations for neoplasia of the prostate (prostate-specific antigen (PSA) and transrectal Ultrasound), uterus, and cervix (colposcopy and cytology), and erectile dysfunction in men. The results are encouraging, but long-term follow-up results are still awaited [30].

Intraoperative Care

Radical cystectomy and urinary diversion may be complicated by significant intraoperative blood loss. The operation can be lengthy (3–6 h), and patients would have also typically undergone complete bowel preparation for 1 or 2 days prior to the operation. Patients may also be chronically anemic secondary to gross hematuria. Therefore, intraoperative and postoperative fluid management is critical.

Intraoperative monitoring entails the following:

1. Two large-bore intravenous lines.
2. Arterial-line monitoring (if indicated).
3. Central venous line monitoring (if indicated).
4. Urine output measurement, which is often unreliable intraoperatively.

Postoperative Care

Postoperative care entails the following:

1. Initial intensive care unit monitoring in selected patients (not needed in all patients).
2. Strict fluid balance.
3. Nasogastric tube drainage removed once the bowel functions recover.
4. Slow advancement of diet (most common perioperative complication is ileus, necessitating replacement of nasogastric tube).
5. Antibiotics: no prospective randomized studies have demonstrated improved outcomes for prolonged prophylactic antibiotics; most urologists prefer 36 h of broad-spectrum antibiotics; prolonged use of antibiotics is not recommended due to the risk of *Clostridium difficile* infection (pseudomembranous colitis).
6. Deep vein thrombosis prophylaxis: sequential compression devices (SCDs) are placed on patient prior to the induction of general anesthesia.
7. Subcutaneous heparin (5,000 mL q12 h) and low molecular weight heparin prophylaxis may be utilized; early ambulation and active chest physiotherapy are warranted.

Urinary Diversion: Ileal, Jejunal and Colonic Conduits

Bowel preparation reduces the risk of infection and provides the surgeon greater visibility in performing an ureterointestinal anastomosis. Mechanical bowel preparation combined with antibiotics is the preferred option. However, there are studies that failed to show any benefit with mechanical bowel preparation.

The typical bowel preparation includes the following:

1. Mechanical bowel prep:
   (a) Liquid diet on the day prior to surgery.
   (b) Nil per oral after midnight the day prior to surgery.
   (c) Go-Lytely or magnesium citrate on the day prior to surgery.
   (d) No intravenous fluids required the day prior to surgery (i.e., patient can complete bowel prep at home).
2. Antibiotic bowel prep: neomycin and erythromycin on the day prior to surgery.

Principles of Technique of Conduit Creation

Virtually every possible type of bowel segment has been utilized in the creation of both urinary conduits and urinary diversions. Ileum is currently the preferred choice of bowel for conduits due to its low risk of metabolic abnormalities, ease of use, and length of mesentery [31]. Jejunum is rarely used because of its greater risk of metabolic complications. Transverse colon is typically second choice if ileum is not available or diseased secondary to prior pelvic radiation.

The bowel must be handled gently. The "butt" end of the conduit is usually oversewn with nonabsorbable sutures if metallic staples are used to divide the bowel. The ureterointestinal anastomosis must be widely spatulated to prevent anastomotic strictures [32]. Anastomosis performed over 7-Fr stents. Alternately a T-tube can be used as a splint with horizontal limbs of T in each ureter and vertical limb in the lumen of ileaum. Mesenteric defect should be re-approximated with nonabsorbable sutures to prevent internal herniation.

Complications of Conduit Diversions Surgical

Stomal stenosis (5–15 %) can be exacerbated by poorly fitting appliances [32, 33]. Ureterointestinal anastomotic stricture is seen in 5–15 %, and when present it is important to rule out malignancy. Chronic pyelonephritis and renal failure are seen in 15 % of cases on long-term followup. Parastomal hernia (5 %) and conduit calculi (5–20 %) are also seen.

Metabolic complications include the following:

1. Ileal conduit: hyperchloremic metabolic acidosis.
2. Jejunal conduit: hypochloremic hyperkalemic metabolic acidosis.
3. Colonic conduit: hyperchloremic hypokalemic metabolic acidosis.

Bladder Substitution

Orthotopic bladder substitutions are being increasingly offered to patients undergoing cystectomy due to documented improvement in the quality of life, our increased understanding of pelvic anatomy, and advances in the surgical techniques [34].

The pelvic anatomy should be favorable and should not compromise the functional and oncological outcomes. Meticulous preservation of the external sphincter mechanism is essential. The distal urethra should be free of malignancies and strictures. Locally advanced disease is not a strict contraindication for bladder substitution, and the decision to perform bladder substitution should be individualized. Adjuvant and neoadjuvant chemotherapy are safe in these patients, and hence orthotopic bladder substitution should not be denied unfairly to patients who may require chemotherapy [35]. Detailed preoperative discussion with the patient regarding bladder substitution is essential. Patients should always be counseled for alternate urinary diversion options, such as ileal conduit preoperatively in case the neobladder formation is not feasible. Enterostomal therapists play a pivotal role in patient-education both pre- and postoperatively.

Patient Selection and Principles

The long-term outcome is dependent on careful patient selection, meticulous postoperative care, and follow-up.

Renal Insufficiency

Renal insufficiency increases the chances of complications such as metabolic acidosis and electrolyte imbalances. In patients with serum creatinine levels >2.0 mg/L, bladder substitution should be avoided. However, if the renal insufficiency is due to ureteral obstruction that can be reversed during surgery and bladder substitution should be considered.

Bowel Disease

A history of previous bowel resection, inflammatory bowel disease, and radiation therapy increases the chances of postoperative bowel dysfunction. These patients should be fully evaluated and counseled regarding the bowel dysfunction. An attempt should be made to preserve the terminal ileum and ileocecal valve to minimize bowel dysfunction and maintain vitamin B12 and bile salt metabolism.

Hepatic Dysfunction

Patients with liver dysfunction are at a higher risk for hyperammonemia following neobladder formation, particularly if the patient develops infection with urease-splitting organisms.

Pelvic Floor

In patients with significant sphincter deficiency and stress incontinence, neobladder reconstruction should be avoided.

State of Urethra

It is imperative that the urethral margins at the anastomotic level be negative for malignancy to avoid tumor recurrences. The presence of carcinoma in situ, multifocal disease and prostatic urethral involvement increases the chances of tumor recurrence, but they are not absolute contraindications for reconstructive procedures.

Psychological

Patients should be compliant and motivated. They should demonstrate good manual dexterity and hand–eye coordination.

Types of Bladder Substitution

The continent bladder substitutions can be broadly classified as continent ileocecal reservoirs and orthotopic neobladder reconstruction.

Ileocecal Reservoirs

These catheterizable reconstruction techniques involve the use of the right colon as the urinary reservoir, and continence is achieved by a variety of techniques using the ileocecal valve, appendix, and terminal ileum. The commonly used techniques include the Koch pouch, the Indiana pouch, and the T pouch [36–38]. Common complications associated with continent reservoirs are listed in Table 35.3. Studies with long-term follow-up indicate that the need for repeat surgical procedures is high.

Orthotopic Neobladders

These diversion options are becoming more popular and increasingly replacing other methods. This method involves using the ileal segment to create a low-pressure reservoir and relies on the patient's sphincter for continence. The two common techniques used were described by Studer and Zingg [41], and Hautmann et al. [39]. Several techniques have been described for improvising and modifying above

Table 35.3 Complications of orthotopic neobladder

Early	Incidence (%)	Late	Incidence (%)
Ureteral leak	4	Ureteral stricture	2
Ureteral stenosis	2	Bladder neck stricture	5
Retained stents	1	Fistula	2
Ileus	10	Calculus	2
Acute pyelonephritis	2	Renal impairment	4
Sepsis	2	Acidosis	4
Pelvic abscess	2	Bowel dysfunction	2
Instestinal leak	1	Bowel obstruction	3
Wound infection	3	Pyelonephritis	5

Based on data from Refs. [39, 40]

techniques. A variety of early and late complications have been described. Most of the complications are transient and self-limiting without compromising the quality of life significantly (Table 35.3); different institutions report a variable incidence of complications, and average incidences are shown in the table.

Techniques of Anastomosis: Suturing and Stapling

Bowel Resection and Anastomosis

Bowel resection and anastomosis are commonly performed using metallic stapling devices with gastrointestinal anastomosis (GIA) and thoracoabdominal (TA) staplers. This decreases the operative time, fecal spillage, and anastomotic stricture rates.

Neobladder Reconstruction

Neobladder reconstruction is best performed with hand-sewn anastomosis using absorbable sutures. The absorbable staplers can be used to reduce the operative time. However, they are bulky and cause persistent rigidity and internal septations in the neobladder. This results in poor compliance and decreased functional results compared with hand-sewn anastomosis. The absorbable staplers are more favorable for ileocolic reservoirs than for the orthotopic neobladders. Use of metallic staplers in the neobladder can result in stone formation along the suture line and hence should be avoided.

Ureteral Anastomosis

Simple nonrefluxing, end-to-side ureteroileal anastomosis provides the best results in neobladder reconstruction with the least complications and lowest reoperation rates [32]. It is essential to create a well-vascularized, tension-free, and watertight

anastomosis to achieve the best results. The anastomosis can be performed with either interrupted or continuous absorbable sutures. Most urologists utilize the ureteral stents to protect the anastomosis, though stenting may not be essential in every case.

Local Recurrences Following Neobladder Reconstruction

Urethral recurrence is seen in 2–4 % of patients [42, 43], mostly close to the bladder neck region. Urethral wash cytology or flexible cystoscopy is recommended every 6 months in the first 2 years and yearly following that. If the recurrences are small and low grade, they can be treated with fulguration. There is always a risk of developing strictures due to fulguration. When lesions are of high grade or multiple, urethrectomy and conversion to ileal conduit is recommended.

Pelvic recurrences are seen in 10–15 % of patients following neobladder reconstruction [44]. In general these pelvic recurrences are not amenable to surgical resections and are usually treated with chemotherapy. Up to two thirds of these patients maintain good bladder function until the last follow-up or death. The type of diversion does not affect the local recurrence rates.

Follow-Up

Lifelong follow-up is essential, and the recommended follow-up schedule is given in (Table 35.4) [45].

Table 35.4 Recommended follow-up scheme following urinary diversion procedure

Evaluation	3 months	6 months	12 months	18 months	Year 2	Years 3 and 4	Years 5, then Q 2 years
Physical examination	×	×	×	×	×	×	×
CT/MRI abdomen and pelvis	×	×[a]	×	×[a]	×	×[a]	×[a]
CT/MRI urography	×		×		×	×	×
Chest X-ray/CT chest	×	×	×	×	×	×	×
Blood work up[b]	×	×	×	×	×	×	×
Urine cytology	×	×	×	×	×	×	×
Vitamins A, D, B12 and folate					×	×	×

[a]May be omitted in patients with > T2N0M0

[b]Electrolytes, BUN, creatinine, liver profile, lipid profile, magnesium

Quality of Life

No randomized controlled studies assessing the quality of life (QOL) in different urinary diversions are available at present. Follow-up studies have demonstrated significant improvement in patients with a neobladder, including functional, social, emotional, and cognitive aspects of life.

Rectal/Sigmoid Neobladders

This procedure utilizes the anal sphincter to provide continent urinary diversion. This may be the procedure of choice in the presence of intractable urinary incontinence or extensive small bowel disease that is not suitable for continent urinary diversion [46]. These procedures are contraindicated in patients with incompetent anal sphincter and anorectal pathology.

Ureterosigmoidostomy

Currently ureterosigmoidostomy is reserved for elderly and debilitated patients. Patient selection is very important in these situations. It is imperative to ascertain that the anal sphincter is intact. The ureters are implanted to the rectosigmoid region with an antireflux mechanism. The Mainz II pouch is a modified ureterosigmoidostomy that consists of folded rectosigmoid pouch with suitable antireflux ureterointestinal anastomosis. The procedure follows the principles of detubularization and spherical reconfiguration to create a low-pressure reservoir and stratifying ureteric implantation between submucosal and serous-lined extramural tunnel techniques. It has shown good continence rates and better long-term preservation of the upper urinary tract than with a classical ureterosigmoidostomy [47].

Complications

A variety of complications including metabolic disturbances, hepatic dysfunction, pyelonephritis, stone formation, and bone demineralization discourage urologists from performing this form of urinary diversion. The incidence of neoplasia occurring in the ureterosigmoidostomy is high, ranging from 6 to 29%. The risk increases with time. Eighty-five percent of these tumors are adenocarcinoma and 10 % are transitional cell carcinoma. Various modifications to the standard ureterosigmoidostomy have been described, but they are rarely used.

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Chapter 36
Management of Metastatic Bladder Tumours

Matthew D. Galsky

Cancer of the urothelial tract is the second most common genitourinary malignancy. Each year, over 73,000 new cases of urothelial cancer (UC) are reported in Europe and over 56,000 new cases in the United States [1]. A substantial percentage of these patients develop metastases despite initial management for presumed localized disease, while others have metastases at the time of presentation. Once metastasis occurs, the median survival for patients with UC is slightly longer than 1 year. In an attempt to improve this poor survival rate, research efforts initially focused on the development of combination cytotoxic regimens and more recently have begun the unravel the molecular pathogenesis of UC in an effort to target disease-specific genetic aberrations.

Cytotoxic Chemotherapy in Advanced UC: A Historical Perspective

Older Single Agents

Cisplatin is the most active single agent in advanced UC. During the late 1970s, trials evaluating single-agent cisplatin were initiated in patients with advanced TCC, yielding overall response rates (OR) ranging from 26 to 65 %. Although uncommon, complete responses (CR) were also observed (5–16 %). Subsequently, additional single agents demonstrated activity in UC. The most active of these drugs included methotrexate (OR ~30 %), doxorubicin (OR ~17 %), and vinblastine (OR ~22 %) [2, 3].

M.D. Galsky, MD
Department of Medicine/Oncology, Tisch Cancer Institute/Mount Sinai School of Medicine, 1 Gustave L Levy Place, New York, NY 10029, USA
e-mail: matthew.galsky@mssm.edu

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Combination Chemotherapy and the Development of MVAC

Multi-agent chemotherapeutic regimens were developed during the 1980s in an attempt to improve upon the results with single-agent therapy. A landmark trial reported in 1985 used the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). In this trial, 24 patients with advanced or unresectable UC were treated with MVAC [4]. Remarkably, responses were observed in 71 % of those treated (95 % CI, 53–89 %), with complete clinical responses in 50 % (95 % CI, 30–70 %). A follow-up report from the same investigators confirmed the activity of MVAC, albeit with a lower response rate, in a larger patient population [5]. Subsequent randomized trials showed improved survival with MVAC compared to single-agent cisplatin [6] and CISCA (cyclophosphamide, cisplatin, and doxorubicin) [7].

Limitations of MVAC

Despite the superiority of MVAC in phase III trials, the limitations of this regimen were readily apparent. Although many patients responded to MVAC, median survivals were consistently reported as less than 13 months. In addition, the durability of responses with MVAC was poor, with less than 4 % of patients alive and continuously disease-free at 6 years or more [8]. The most significant limiting factor associated with MVAC was treatment-related toxicity. Treatment-related deaths occurred in 2–4 % of patients and severe toxicities such as febrile neutropenia (20–30 %) and mucositis (10–20 %) were also common. Other toxicities associated with this regimen included renal insufficiency, hearing loss, and peripheral neuropathy.

Attempts to Improve MVAC

In an attempt to decrease the toxicity and enhance the efficacy of MVAC, several investigators evaluated the use of altered doses and schedules with granulocyte colony- stimulating factor support (GCSF). Based on the potential for improved anti-cancer activity conferred by increased dose density, the European Organization for Research and Treatment of Cancer (EORTC) conducted a randomized trial comparing MVAC administered every 2 weeks (with GCSF) with MVAC administered every 4 weeks [9]. In the initial report of this trial, the dose-dense regimen demonstrated a significantly greater CR rate (21 % compared to 9 %, $p = .009$) and progression-free survival ($p = .037$; hazard ratio 0.75; 95 % CI, 0.58–0.98) compared with conventional MVAC dosing, though there was no significant difference in the overall survival distributions. However, at 5 years, the survival rate was 21.8 % in the dose-dense arm compared with 13.5 % with conventional MVAC [10]. This is among the highest 5-year survival rates reported

in patients with advanced/metastatic UC. Given the tolerability of the dose-dense regimen, its use as a standard treatment, and in clinical investigation, has recently increased.

Newer Generation Cytotoxic Regimens in Advanced UC

During the 1990s, several newer generation cytotoxic drugs, including the taxanes and gemcitabine, were explored in UC as single-agents, doublets, and triplets. Only a few of these regimens demonstrated sufficient activity to advance to randomized phase III trials (Table 36.1).

Taxane-Based Doublets

Based on encouraging activity in phase II trials, a randomized phase III trial comparing docetaxel plus cisplatin (DC) with MVAC + GCSF was conducted by the Hellenic Cooperative Oncology Group (Table 36.1) [13]. Although DC was

Table 36.1 Randomized trials of cisplatin-based chemotherapy in advanced urothelial carcinoma

Regimens	Reference	N	OR (%)	CR (%)	Survival (months)	P
MVAC	[6]	120	36	13	12.5	<0.0002
Cisplatin		126	11	3	8.2	
MVAC	[7]	55	65	35	12.6	<0.05
CISCA		55	46	25	10	
MVAC	[11]	86	59	24	12.5	0.17
FAP		83	42	10	12.5	
MVAC	[9]	129	58	9	14.1	0.122
HD-MVAC		134	72	21	15.5	
MVAC	[12]	205	46	12	14.8	0.746
Gemcitabine + Cisplatin		203	50	12	13.8	
MVAC	[13]	109	54	23	14.2	0.025
Docetaxel + Cisplatin		111	37	13	9.3	
MVAC[a]	[14]	44	40	13	14.2	0.41
Paclitaxel + Carboplatin		41	28	3	13.8	
Gemcitabine + Cisplatin	[15]	314	44	11	12.7	0.075
Gemcitabine + Cisplatin + Paclitaxel		312	56	14	15.8	
Dose-dense MVAC	[16]	118	47	15	18.4	0.7
Dose-dense Gemcitabine + Cisplatin		57	47	10	20.7	

MVAC methotrexate, vinblastine, doxorubicin, cisplatin, *CISCA* cyclophosphamide, cisplatin, doxorubicin, *CMV* cisplatin, methotrexate, vinblastine, *MV* methotrexate, vinblastine, *FAP* 5-fluorouracil, interferon-alpha-2b, cisplatin, *HD-MVAC* high-dose MVAC, *OR* overall response, *CR* complete response

[a]Trial terminated early with only 85 patients, underpowered, preliminary results

associated with less hematologic toxicity and febrile neutropenia, response rates and survival favored the MVAC arm. Notably, a failure to stratify for baseline performance status may have resulted in an imbalance between the two arms and contributed to the outcome of this trial [17].

The Eastern Cooperative Oncology Group (ECOG) launched a phase III trial comparing MVAC with paclitaxel plus carboplatin which was terminated after 2½ years of slow accrual (Table 36.1) [14]. Only 85 of the planned 330 patients were enrolled. Patients treated with MVAC had more severe myelosuppression, mucositis, and renal toxicity. Interestingly, a quality of life instrument revealed no significant differences between the two arms. At a median follow-up of 32.5 months, there was no significant difference in response rate or median survival between the two arms. However, this trial was underpowered, and definitive conclusions cannot be made due to its early closure

Gemcitabine and Cisplatin: A new Treatment Standard

Based on the promising activity and favorable side-effect profile of single-agent gemcitabine, trials exploring the combination of gemcitabine + cisplatin in metastatic UC were initiated. Several phase II studies reported OR rates of 42–57 % and CR rates of 18–22 % [18–20]. Subsequently, a multicenter, randomized phase III trial was performed to compare gemcitabine + cisplatin (GC) with MVAC (Table 36.1) [12]. Four hundred and five chemotherapy-naïve patients were randomized to GC or standard MVAC. The CR, OR, and median survival rates were similar in both arms. While GC was associated with more grade ≥3 anemia and thrombocytopenia, MVAC was associated with a greater incidence of neutropenic fever (14 % compared to 2 %), neutropenic sepsis (12 % compared to 1 %), grade ≥3 mucositis (22 % compared to 1 %) and treatment-related deaths (3 % compared to 1 %).

Notably, this randomized trial was not designed as a non-inferiority trial. However, the data can be interpreted as showing that, in terms of survival, GC is comparable to MVAC. Given the trial results and favorable toxicity profile, GC has become widely used as a standard treatment regimen for patients with metastatic UC.

Attempts to Improve Upon Gemcitabine Plus Cisplatin with the Addition of Paclitaxel

In a phase I/II trial of 58 patients, the triplet of gemcitabine, cisplatin, plus paclitaxel (GCT) resulted in 16 complete responses (28 %) and 29 partial responses (50 %) for an overall response proportion of 77.6 % (95 % CI: 60, 98 %) [21]. This led to a randomized phase III trial comparing GCT with GC as first-line therapy in

patients with advanced UC (Table 36.1) [15]. This trial enrolled 626 patients and demonstrated a significantly higher response rate with GCT compared with GC (55.5 % versus 43.6 %, P=0.0031). After a median follow-up of 4.6 years, the numerical improvement in with GCT compared with GC (15.8 months versus 12.7 months) did not achieve statistical significance.

Attempts to Improve Upon Gemcitabine Plus Cisplatin with Dose-Dense Administration

The Norton-Simon hypothesis posits that due to Gompertzian growth kinetics exhibited by solid tumors, more frequent administration of chemotherapy may reduce tumor re-growth between cycles and lead to higher log cell kill [22]. Based on promising results with dose-dense administration of MVAC, Bamias and colleagues performed a randomized phase III trial of dose-dense MVAC (n=118) compared with dose-dense GC (gemcitabine 2,500 mg/m^2 plus cisplatin 70 mg/m^2 administered every 2 weeks, n=57) [16]. Due to poor accrual, the MVAC arm was supplemented with additional patients with advanced UC who were treated off-study with the same regimen, but did not undergo randomization, leading to difficulty interpreting the overall study results. Nonetheless, the dose-dense GC arm demonstrated similar outcomes compared with the dose-dense MVAC arm (overall response rate: 47.4 % versus 47.4 %, p=0.9; median survival: 18.4 months versus 20.7 months, p=0.7). However, dose-dense GC was better tolerated. As a result of the methodological issues, the ultimate position of this regimen in the armamentarium of therapy for advanced UC remains to be defined.

The Impact of Prognostic Factors

Pretreatment prognostic factors play a key role in predicting the outcome of patients with advanced UC. In a retrospective analysis of 203 patients with advanced UC treated with MVAC, two pre-treatment variables retained independent prognostic significance on multivariate analysis: Karnofsky performance status (KPS) ≤80 % and visceral (lung, liver or bone) metastases [23]. The median survival for patients with 0, 1, or 2 poor prognostic factors was 33, 13.4, and 9.3 months, respectively (p=0.0001). Clearly, the proportion of patients in these various risk categories must be considered when comparing median survivals among different phase II studies. In addition, stratifying for these baseline prognostic variables is essential in the design phase III trials. Similar prognostic models have been developed utilizing data sets from patients treated with more contemporary cytotoxic agents in both the first-line and second-line treatment settings [24, 25].

Special Considerations in Metastatic UC

Treatment of Patients Ineligible for Cisplatin-Based Chemotherapy

A meta-analysis of randomized trials comparing cisplatin-versus carboplatin-based therapy in UC revealed that cisplatin-based chemotherapy was associated with a significant improvement in the likelihood of achieving an objective response [RR = 1.33 (95 % CI: 1.04, 1.71), p = 0.025] or a complete response [RR = 3.54 (95 % CI: 1.48, 8.49), p = 0.004] [26]. However, UC is largely a disease of the elderly [27] and due to age-associated (and disease-associated) impairment in renal function and performance status, approximately 30–50 % of patients are ineligible for cisplatin-based chemotherapy [28]. As a result, a disconnect has emerged between the "efficacy" of treatment as demonstrated by randomized trials, and the "effectiveness" of treatment when applied to the general population of patients with UC. Investigators, long appreciating this disconnect, have designed trials specifically for patients "unfit" for cisplatin-based chemotherapy [29–34].

There have been two randomized phase III trials initiated in the cisplatin-ineligible population. EORTC 30986 was a randomized phase II/III trial of GC versus methotrexate, vinblastine, plus carboplatin (M-CAVI) in "unfit" patients (WHO performance status of 2 and/or creatinine clearance 30–60 ml/min) with metastatic UC [32]. Both treatment arms enrolled 119 patients and the criteria for cisplatin-ineligibility were equally distributed among the arms. There was no significant difference in the progression-free survival (GC 5.8 months, M-CAVI 4.2 months; HR 1.04, 95 % CI: 0.8, 1.35; p = 0.78) or the overall survival (GC 9.3 months, M-CAVI 8.1 months; HR 0.94, 95 % CI: 0.72, 1.22; p = 0.64) between the treatment arms. The M-CAVI arm was associated with a higher incidence of neutropenic fever, grade 3 mucositis, and treatment-related deaths. This trial solidified the role of gemcitabine plus carboplatin as a standard treatment for this patient population and provided a benchmark for clinical outcomes in "unfit" patients.

The only other phase III trial to be initiated, to date, in "unfit" patients with metastatic UC was the VINCENT (Vinflunine in Cisplatin-ineligible Patients Trial) trial, a randomized trial of vinflunine plus gemcitabine versus placebo plus gemcitabine. Eligibility for the VINCENT trial was based on either renal impairment (creatinine clearance ≤60 mL/min) or New York Heart Association Classification Stage III-IV congestive heart failure. Patients were required to have an ECOG performance status of 0-2. This trial was designed to accrue 450 patients; however, the trial was prematurely closed to accrual based on a decision by the sponsor.

Trials in the "unfit" patient population have been hampered by heterogeneous eligibility criteria resulting in confusion regarding the precise population being targeted for drug development. In an effort to develop a consensus definition of patients with metastatic UC "unfit" for cisplatin-based chemotherapy, a Working Group was assembled. Based on a survey of 120 international academic and community-based genitourinary oncologists, a proposed definition of "unfit" patients with metastatic

UC was formulated with the goal of establishing uniform eligibility criteria for future clinical trials [35]. According to this definition, patients meeting at least one of the following criteria were considered "unfit": ECOG performance status of 2, creatinine clearance less than 60 mL/min, grade ≥2 hearing loss, grade ≥2 neuropathy, and/or New York Heart Association Class III heart failure [36].

Second-Line Therapy

Multiple small phase II trials exploring a variety of agents as second-line therapy for metastatic UC have been performed. Overall, the most active of these agents have demonstrated response rates of approximately 10–30 % (Table 36.2). Many of these trials have been performed at single-institutions, have been small, and have employed heterogeneous eligibility criteria.

There has been one completed phase III trial in the second-line setting, which randomized 370 patients with progressive UC after first-line platinum-based chemotherapy to vinflunine versus best supportive care [58]. The main grade 3-4 adverse events

Table 36.2 Results of second-line regimens in patients with metastatic urothelial carcinoma

Drug	Reference	N	RR %	PFS (month)	OS (month)
Bortezomib	[37]	25	0	1.4	5.7
Docetaxel	[38]	72	11	1.6	7.0
Docetaxel-Vandetanib	[38]	70	7	2.6	5.8
Gefitinib	[39]	31	3	–	3.0
Gemcitabine	[40]	30	11	4.9	8.7
Gemcitabine	[41]	35	22.5	–	5.0
Ifosfamide	[42]	56	20	2.4	5.5
Ifosfamide-Gemcitabine	[43]	34	21	4.0	9.0
Irinotecan	[44]	40	5	2.1	5.4
Ixabepilone	[45]	42	11.9	2.7	8.0
Lapatinib	[46]	59	3	2	4.5
Oxaliplatin	[47]	18	6	1.5	7.0
Paclitaxel	[48]	31	10	2.2	7.2
Paclitaxel-Carboplatin	[49]	44	16	4.0	6.0
Paclitaxel-Gemcitabine	[50]	41	60	–	14.4
Pemetrexed	[51]	47	27.7	2.9	9.6
Pemetrexed	[52]	12	8	–	–
Sorafenib	[53]	27	0	–	6.8
Sunitinib	[54]	45	7	2.4	6.9
Topotecan	[55]	44	9.1	1.5	6.3
Vinflunine	[56]	175	15	2.8	8.2
Vinflunine	[57]	51	18	3.0	6.6

RR response rate, *PFS* progression-free survival, *OS* overall survival

on the vinflunine arm included neutropenia (50 %), febrile neutropenia (6 %), anemia (19 %), fatigue (19 %), and constipation (16 %). In the intent-to-treat population, there was a numerical improvement in median survival (6.9 months for vinflunine versus 4.6 months for best supportive care) which did not reach statistical significance (hazard ratio [HR] = 0.88; 95 % CI, 0.69–1.12; P = .287). When only the eligible population was included in the analysis (n = 357), the median overall survival was significantly longer for vinflunine than for best supportive care. Based on these results, in 2009, The Committee for Medicinal Products for Human Use of the European Medicines Agency granted marketing authorization for vinflunine for the treatment of patients with advanced UC progressing on a prior platinum-containing regimen. Vinflunine is the first drug specifically approved for the second-line setting in metastatic UC. Vinflunine has not been submitted for regulatory approval in the United States.

Treatment of Patients with Non-transitional Cell Histologies

Approximately 10 % of cancers arising from the urothelial tract are of non-transitional cell histologies including squamous cell carcinomas, adenocarcinomas, and small cell carcinomas [59]. Given the rarity of these subtypes, much of the data regarding management of these malignancies is derived from single center retrospective series. However, there have been a few prospective trials attempting to define active chemotherapeutic regimens in these rare patient subsets.

A phase II trial evaluated a combination regimen of paclitaxel, ifosfamide, and cisplatin in patients with non-transitional cell histologies [60]. A total of 20 patients were enrolled including the following histologic subtypes: adenocarcinoma (n = 11), squamous cell carcinoma (n = 8), and small cell carcinoma (n = 1). Overall, 7 (35 %) of 20 patients (95 % CI: 15, 59 %) achieved an objective response (3 partial and 4 complete). This is a small cohort, and includes a mix of different histologies, but does demonstrate that combination chemotherapy has some activity in advanced adenocarcinomas and squamous cell carcinomas of bladder origin.

Investigators at MD Anderson Cancer Center performed a phase II study of an alternating doublet chemotherapy regimen (ifosfamide/doxorubicin and etoposide/cisplatin) in patients with small cell carcinoma of the bladder [61]. Of the 12 patients with surgically unresectable disease, eight had a complete clinical response, whereas three patients experienced a partial response. Despite this impressive activity, most patients with experienced relapse, with a median OS time of 13.3 months. Notably, brain metastases occurred in 8/16 patients presenting with bulky primary tumors or advanced disease, highlighting a potential role for prophylactic cranial irradiation.

Post-chemotherapy Surgery

Several studies have highlighted the importance of post-chemotherapy surgery in the setting of minimal residual disease after achieving a “near” complete response to chemotherapy [62–64]. In a retrospective study of 203 patients treated on five

trials with MVAC, 50 patients underwent post-chemotherapy surgery for suspected or known residual disease [62]. In 17 patients, no viable tumor was found at post-chemotherapy surgery. Three patients had unresectable disease. In the remaining 30 patients, residual metastatic UC was completely resected resulting in a complete response to chemotherapy plus surgery. Of these 30 patients, 10 (33 %) remained alive at 5 years, similar to results attained by patients achieving a complete response to chemotherapy alone (41 %). Optimal candidates for post-chemotherapy surgical consolidation were those patients with pre-chemotherapy disease limited to the primary site or lymph nodes.

The Role of Radiation Therapy in Metastatic or Recurrent Disease

Although the initial treatment for most patients with metastatic UC is systemic chemotherapy, a subset of patient will develop progressive symptoms related to a specific metastatic deposit. Radiation therapy plays a prominent role in palliating metastatic UC [65]. The precise radiation dose and technique needs to be individualized to the patient and pattern of metastatic disease. Radiation should be, whenever possible, delivered in a modest or short period of time [66].

Novel Therapeutic Strategies in Metastatic UC

Defining Novel Targets and Potential Predictive Biomarkers

Because UC is a chemosensitive neoplasm, yet only a fraction of patients respond to a particular chemotherapeutic regimen, there has been much interest in developing tools to allow more rational use of existing drugs. One approach has involved evaluating the levels of DNA-repair genes, or their protein products, in tumors, based on the concept that tumors with higher levels of DNA-repair genes may be more resistant to therapy. Excision repair cross complementing 1 (ERCC-1) is a critical regulator in nucleotide excision repair and its expression has been correlated with outcomes to cisplatin-based chemotherapy in a variety of solid tumors [67–72]. RRM1, the regulatory subunit of ribonucleotide reductase, has been implicated in tumor response to gemcitabine [73]. A retrospective study analyzed levels of the DNA-repair genes ERCC1, RRM1, BRCA1, and caveolin-1, in tumor tissue from 57 patients with bladder cancer treated with cisplatin-based combination chemotherapy [74]. The median survival in this cohort was higher in patients with low ERCC1 levels (25.4 vs. 15.4 months; $p = 0.03$). However, development of ERCC1 as a widely available predictive biomarker has been hampered by difficulties with analytic validation [75].

Given the genomic complexity of solid tumors, relying on a single gene or protein as a predictive biomarker for response to cytotoxic chemotherapy is unlikely to yield substantial improvements in patient selection. Alternatively, profiling expression of

multiple genes may better capture the heterogeneity of responses to therapy. Indeed, gene "signatures" of response to platinum-based chemotherapy have been generated and correlated with clinical outcomes in patients with bladder cancer [76–78]. While this approach is promising, the predictive signature is limited to the particular treatment regimen evaluated in the study in which the signature was generated. As a result, new signatures must be developed for each new treatment regimen entering clinical use, and the gene signatures cannot be used to aid in the development of novel drugs that have not yet been explored in human studies.

In an effort to overcome many of these limitations, Theodorescu and colleagues developed a novel bioinformatics approach known as Coexpression Extrapolation or COXEN [79]. COXEN utilizes the publicly available gene-expression profiling data and drug sensitivity data from the NCI-60 cell line panel as a "Rosetta Stone" to predict chemosensitivity of gene-expression profiled bladder cancer samples using a computational algorithm. The COXEN approach can be utilized to predict responses to multi-agent regimens, by combining data regarding single agents, and has also been utilized successfully to identify novel agents with activity in UC. A study is currently being planned to prospectively evaluate the COXEN approach for selection of chemotherapy for patients with UC.

Personalized cancer care via profiling tumors for potentially "actionable" genomic mutations is perhaps best exemplified by the emerging treatment approach to advanced non-small cell lung cancer where identification of aberrations in *EGFR* and *ALK* have changed the treatment paradigm [80, 81]. Several groups have evaluated UC samples for specific somatic mutations in known oncogenes and tumor suppressor genes. However, given the distinct pathways of pathogenesis of UC, and corresponding clinical phenotypes, knowledge of the genomic profiles of non-invasive versus invasive tumors is necessary to identify targets relevant for therapeutic strategies in these particular clinical states. In the most comprehensive analysis published to date, Sjodahl et al. performed mutation analyses of 16 genes (FGFR3, PIK3CA, PIK3R1, PTEN, AKT1, KRAS, HRAS, NRAS, BRAF, ARAF, RAF1, TSC1, TSC2, APC, CTNNB1, and TP53) in 145 cases of UC [82]. This study identified that FGFR3 and PIK3CA mutations were most commonly identified in non-invasive low grade tumors. Furthermore, the potential importance of APC signaling was identified as 6 % of the investigated tumors either demonstrated inactivating APC or activating CTNNB1 mutations. The mTOR regulatory tuberous sclerosis complex genes (TSC2 and TSC2) were found to be mutated at a combined frequency of approximately 15 %. Future efforts will focus on pairing these aberrations with appropriate therapeutic agents.

Targeting Oncogenes

The epidermal growth factor family of receptors has been implicated in the pathogenesis of UC, serving as the foundation for exploring therapeutic strategies targeting this pathway in advanced disease [83–85]. A phase II trial of chemotherapy-naive

patients with metastatic UC explored the combination of gemcitabine, carboplatin, paclitaxel, plus the anti-Human epidermal growth factor receptor 2 (HER-2) monoclonal antibody trastuzumab. Eligibility for this trial required HER-2 overexpression in tumor tissue by immunohistochemistry, *HER2* gene amplification in tumor tissue and/or elevated serum HER-2. The overall response rate with this regimen was 70 %. However, given the single arm design, the contribution of trastuzumab to the activity of this combination is unclear and this regimen has not been moved forward for definitive testing.

A phase II study explored lapatinib, a dual HER-2/EGFR receptor pathway inhibitor, as second-line therapy in patients with metastatic UC. Patients were eligible provided that their tumors had 1-3+ expression of either EFGR or HER-2 by immunohistochemistry [46]. The objective response rate with lapatinib was only 1.7 % (95 % CI: 0.0, 9.1 %). However, 18 (31 %; 95 % CI: 19, 44 %) patients achieved stable disease. Clinical benefit with this treatment, defined as either an objective response or stable disease, was found to be correlated with EGFR overexpression, and, to some extent, HER-2 over-expression.

Another phase II trial exploring lapatinib utilized a novel trial design focused on the putative drug target, rather than the specific tumor type [86]. Patients eligible for this study could have a wide variety of metastatic solid tumors (including bladder cancer, endometrial cancer, ovarian cancer, and gastric cancer) provided tumor tissue tested centrally demonstrated *HER2* gene amplification by *fluorescence in situ hybridization*. Unfortunately, the trial was closed early due to poor accrual. Of the 33 patients with metastatic bladder cancer screened, 12 patients had *HER2* amplified tumors, none of whom achieved an objective response to treatment with lapatinib [87]. These trials, which all utilized inhibitors of the same pathway, but different tests and "cut-offs" for the putative predictive biomarkers, highlight many of the challenges of drug development in the era of personalized therapeutics.

While activating mutations in the fibroblast growth factor receptor 3 (FGFR3) are most common in non-invasive UC, recent studies have demonstrated the presence of FGFR3 mutations in 10–20 % of muscle-invasive UC specimens, leading to interest in exploring FGFR3 inhibition as a therapeutic strategy in advanced UC [88]. Dovitinib is a small molecule inhibitor of several tyrosine kinase receptors, including the vascular endothelial growth factor receptor (VEGFR) and FGFR, which has demonstrated inhibition of tumor growth and proliferation in UC models. A multicenter, 2-stage, open-label phase II trial is currently evaluating the safety and efficacy of dovitinib in patients with advanced UC who have progressed despite prior systemic therapy, both in cohorts with and without FGFR3 mutations [89].

Targeting Angiogenesis

Over 30 years ago, Chodak et al. first demonstrated that the urine of patients with UC contained proangiogenic substances [90]. Several mediators of angiogenesis have since been identified, of which the best characterized is vascular endothelial

growth factor (VEGF). Multiple lines of evidence support a therapeutic role for targeting the neovasculature in UC. Increased microvessel density has been associated with an increased risk of recurrence and inferior survival in UC [91–93]. Several reports have correlated increased expression of VEGF in the tissue, serum, and urine of patients with UC with advanced stage and poor prognosis [94, 95]. In addition, inhibitors of angiogenesis, alone or in combination with cytotoxic chemotherapy, have shown activity in preclinical models of UC [96–98].

Aflibercept, a recombinant fusion protein that binds and neutralizes multiple VEGF isoforms, has been studied in a phase II trial in patients with metastatic UC progressing on prior platinum-based chemotherapy [99]. One patient achieved a partial response (4.5 % RR) and the median progression-free survival was 3.5 months (95 % CI: 1.8–4.1). These results suggest that anti-VEGF monoclonal antibodies may be most beneficial when used in combination with cytotoxic agents, as has been demonstrated in many other solid tumors.

The triplet of gemcitabine, cisplatin, plus the anti-VEGF antibody, bevacizumab, has been explored in a phase II trial in chemonaive patients with metastatic UC [100]. This trial, which enrolled 43 patients, initially demonstrated a seemingly excessive rate of venous thromboembolic events. The trial was amended, with a lower dose of gemcitabine, which appeared to mitigate this side effect. The trial reported an overall response rate of 72 %. While the progression-free survival of 8.2 months did not meet the study's primary endpoint, an encouraging median overall survival of 19.1 months was reported leading to the initiation of a definitive randomized phase III trial to evaluate this regimen.

Non-clinical studies have demonstrated that platelet derived growth factor receptor (PDGFR)-expressing pericytes may contribute to resistance to VEGF pathway inhibitors, and that synergistic antitumor activity is achieved by combining VEGFR and PDGFR kinase inhibitors [101, 102]. As a result, the VEGFR and PDGFR kinase inhibitors, sorafenib, sunitinib, and pazopanib, have been evaluated in advanced UC. In a phase II trial of sorafenib as second-line therapy in patients with metastatic UC, performed by ECOG, 21 patients were enrolled and there were no objective responses to therapy [53]. Sunitinib has demonstrated somewhat more encouraging antitumor activity. Trials in patients with chemotherapy-refractory disease, and as first-line chemotherapy in cisplatin-ineligible patients, have demonstrated a small proportion of patients achieving objective tumor regressions and approximately 30–45 % demonstrating prolonged stable disease (>3 months) [31, 54]. Combining sunitinib with gemcitabine resulted in synergistic activity in bladder cancer cells lines and combining sunitinib with cisplatin resulted in at least additive antitumor activity in a bladder cancer xenograft model [103, 104]. However, a phase II trial of gemcitabine, cisplatin, and sunitinib in patients with advanced UC demonstrated that the combination regimen was not tolerable due to hematologic toxicities [105]. Pazopanib has been explored in two small studies in patients with metastatic UC that had progressed on prior cytotoxic chemotherapy; these trials reported disparate results with one reporting a clinical benefit rate of 83 % [106] and the other reporting no evidence of objective responses [107]. The discrepancy between the activity of pazopanib in these independent studies is likely a result in

the differences in definitions of response; the former studies utilized a composite definition of response which included changes on positron emission tomography scan while the latter relied on the more stringent Response Evaluation Criteria in Solid Tumors (RECIST) definition.

The only randomized trial involving antiangiogenic therapy in advanced UC reported to date has been a placebo-controlled phase II trial of docetaxel with or without vandetanib, a small molecule inhibitor of the VEGFR and EGFR tyrosine kinases, in the second-line setting [38]. The combination regimen failed to achieve a significant improvement in response rate, progression-free survival, or overall survival.

Targeting the Immune System

UC is an immunogenic malignancy. Multiple studies have shown that bladder cancer specimens harbor tumor infiltrating lymphocytes [108, 109]; immunohistochemical staining for intratumoral CD8+ T cells in tissue samples from 69 patients with bladder cancer (pT2-T4) demonstrated that patients with higher numbers of CD8+ tumor infiltrating lymphocytes within the tumor had better disease-free survival ($P<0.001$) and overall survival ($P=0.018$) [109].

Despite the immunogenicity of UC, patients with UC also exhibit tumor-associated immunologic tolerance [110–112]. Bladder cancer specimens have been shown to be infiltrated by T regulatory cells (Tregs) and to express high levels of inhibitory cytokines [111]. In addition, aberrant expression of T-cell coregulatory molecules, known to inhibit the immune response, have been demonstrated on bladder cancer cells and tumor infiltrating lymphocytes and have been correlated with poorer clinical outcomes [113].

Blocking immune regulatory checkpoints may overcome tumor-induced immune tolerance in UC. Cytotoxic T Lymphocyte Antigen-4 (CTLA-4) functions as an inhibitory receptor for B7 costimulatory molecules expressed on antigen presenting cells. Following T-cell activation, CTLA4 is upregulated and successfully competes with CD28 for binding to B7, sending an inhibitory signal that downregulates T-cell activation. Blockade of CTLA-4 has been shown to enhance T cell activation in animal models and results in an increased ratio of effector: regulatory T cells which correlates with tumor regression [114–116]. In a study of bladder cancer murine xenografts, combined antibody blockade of CTLA-4 plus local toll-like receptor stimulation with CpG resulted in a high rate of complete tumor regression and a decrease in local Tregs [117].

Ipilimumab is a human immunoglobulin G (IgG1)κ anti-CTLA-4 monoclonal antibody that has been shown to improve survival in patients with metastatic melanoma [118]. Ipilimumab was administered pre-cystectomy in a pilot trial of 12 patients with clinically localized bladder cancer [119]. Most drug-related adverse events were grade 1 or 2, all patients demonstrated an increase in $CD4^{+}$ $ICOS^{hi}$ T cells in tumor tissue and systemic circulation, and 8/12 patients demonstrated

downstaging of their primary tumor. Ongoing trials are combining chemotherapy with ipilimumab in advanced UC, as well as employing other strategies to deplete Tregs, in an effort to overcome immune tolerance.

Conclusions

UC is among the most chemosensitive neoplasms of all the solid tumors. With multi-modality therapy for advanced disease, a subset of patients will achieve durable disease control. However, for the majority of patients with advanced disease, response durations to conventional treatment are relatively short. Recurrent UC tends to be very chemoresistant as highlighted by the modest response rates and poor outcomes with second-line treatment. Trials in both the first- and second-line settings have demonstrated that a ceiling in efficacy has likely been reached with cytotoxic drugs, particularly in unselected populations. Novel approaches, such as integration of agents targeting the immune system and tumor stroma, are attractive, but have yet to be explored sufficiently in clinical trials. Similarly, efforts to individualize the selection of therapy for patients with advanced UC, through the use of predictive biomarkers, is promising though standards for analytic validation of putative biomarkers and novel trials designs are likely required to truly usher in the era of personalized medicine in advanced UC.

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Chapter 37
Surgical and Minimally Invasive Management of Upper Urinary Tract Tumours

Bhavan Prasad Rai, Clare Sweeney, and Ghulam Nabi

Upper urinary tract urothelial carcinoma (UUT-UCa) arises from lining the urinary tract (urothelium) extending from calyces to the opening of ureters into the urinary bladder. It accounts for more than 90 % of the renal pelvic malignancy with other rare cancers being squamous cell carcinoma and adenocarcinoma [1]. UUT-UCa is estimated to be 5 % of all urothelial cancers and in less than 10 % of all renal tumours [2–4]. Although UUT-UCa shares many similarities to bladder urothelial carcinoma including risk factors and histology, natural history of these lesions differ. These tumours are more aggressive with a tendency to multifocality, local recurrence and progression to an advanced stage much early as compared to bladder cancer [5]. Furthermore, patients with UUT-UCa are at risk of developing bladder tumours, with an estimated occurrence of 15–50 % [2].

Aetiology

As with bladder cancer, smoking and occupational exposure remain the most significant acquired risk factors for UUT-UCa. Smoking increases the risk of UUT-UCa by 6.2 fold [6]. The latent period of smoking-related urothelial cancer is up to 20 years and cessation of smoking for more than 10 years reduces the risk by 60–70 % [7]; however, the risk persists and is generally higher than that of the general population. Occupational exposure to aromatic amines is another known risk

B.P. Rai, MBBS, MRCSEd • C. Sweeney, MBBS, MRCSEd, FRCS (Urol)
Department of Urology, Medical Research Institute, Ninewells hospital and Medical School, Dundee, Scotland, UK

G. Nabi, MS, MD, M Ch, FRCS (Urol) (✉)
Department of Urology, Ninewells Hospital, University of Dundee, Dundee, Scotland, UK
e-mail: g.nabi@nhs.net

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factor for UUT-UCa. 'Amino tumours' as these are commonly known have a latent period of 20 years [8]. The causative carcinogens were widely in use in the industry including textiles, dyes, rubber and petrochemicals until the 1960s when they were phased out and eventually banned in most industrialised countries.

In modern times, chemotherapeutics agents used for cancer treatment are associated with the developments of urothelial cancers. The alkylating agents cyclophosphamide and ifosfamide induce carcinogenesis via the urinary metabolite acrolein with a shorter latency period of around 7 years [9]. Historically analgesic abuse with the non-steroidal anti-inflammatory phenacetin was linked to UUT-UCa, the time between stopping nephrotoxic doses of phenacetin and developing UUT-UCa averaged 14 years and the drug was banned in the 1970s [10]. Balkan endemic nephropathy (chronic tubulointerstitial nephritis) and Chinese herb nephropathy are associated with a dramatically increased incidence of UUT-UCa. The mechanism is thought to be related to exposure to aristolochic acid a derivative of which causes a mutation in p53 [11]. Urinary lithiasis, chronic UTIs and hypertension along with tumour suppressor genes p19, p16, RB1 have also been implicated in the pathogenesis of UUT-UCa [11]. They are also associated with hereditary condition such as Lynch syndrome II [12].

Epidemiology

The upper tract disease is predominantly seen in men (twice more than women) with a peak incidence around 60–70 years of age [4, 13]. UUT-UCa is rare with an incidence of 1–2 cases per 100,000 per annum [14]. The population based studies suggest that of all the patients presenting with visible haematuria only 0.1 % will be found to have an UUT-UCa [15]. The anatomical location of tumours within the urinary tract varies with renal pelvis being the most common site. Approximately two thirds of UUT-UCCs are renal pelvic in location [4, 13]. Of the remaining one third, 75 % are located in the distal (below the level of sacro-iliac joint) and 25 % in the proximal ureter (above the level of sacro-iliac joint). At the time of initial diagnosis 8–13 % are likely to have a synchronous bladder tumour but 15–50 % would develop bladder cancers during follow up [4]. Recurrence in the contra-lateral ureter is far less common (2–6 %) [16].

Clinical Presentation

A majority of tumours (80 %) present with haematuria (visible or non visible) with approximately one third complaining of associated loin pain, which is related to passage of clots (clot colic). A palpable mass is the presenting complaint in up to 10–20 % of patients [4]. Similar to urinary bladder cancer, UUT-UCa is not commonly seen as an incidental finding at autopsies. Approximately, 2 % are

asymptomatic and detected during the diagnostic work up for synchronous bladder tumours [17]. Other systemic symptoms such as weight loss, anorexia, fever, bone pain or cough should raise suspicion of distant metastatic disease. Rare sites for metastases such as eye have been reported [18].

Diagnosis

Diagnosis suspected on clinical findings is usually confirmed by cytological, endoscopic and imaging modalities.

Imaging

Multidetector Computed tomography Urogram (MDCT) has replaced traditional intravenous urogram (IVU) as the main radiological tool for the diagnosis of upper tract pathology and is considered as the gold standard for the diagnosis UUT-UCa. For tumour size of 5 mm or more, the sensitivity and specificity MDCT is approximately 96 and 99 % respectively [19]. Classically, a filling defect or mass lesion is seen during the excretory phase on MDCT (Figs. 37.1 and 37.2). A particular advantage of MDCT is its ability to detect urothelial thickening which was not seen by previous excretory urography imaging tools [20]. In patients who cannot have MDCT (contrast allergy, poor renal function) and Magnetic Resonance Urogram (MRU) should be considered bearing in mind the risk of nephrogenic systemic fibrosis in patients with severely impaired renal function. MRU has several

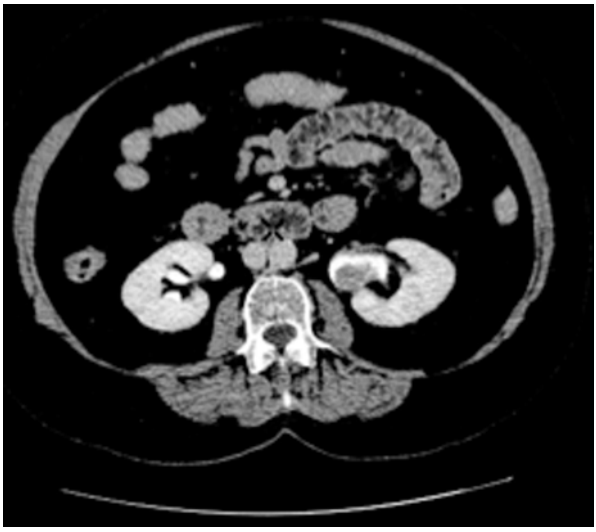

Fig. 37.1 Large filling defect on cross-sectional contrast enhanced CT urography that was proven transitional cell carcinoma

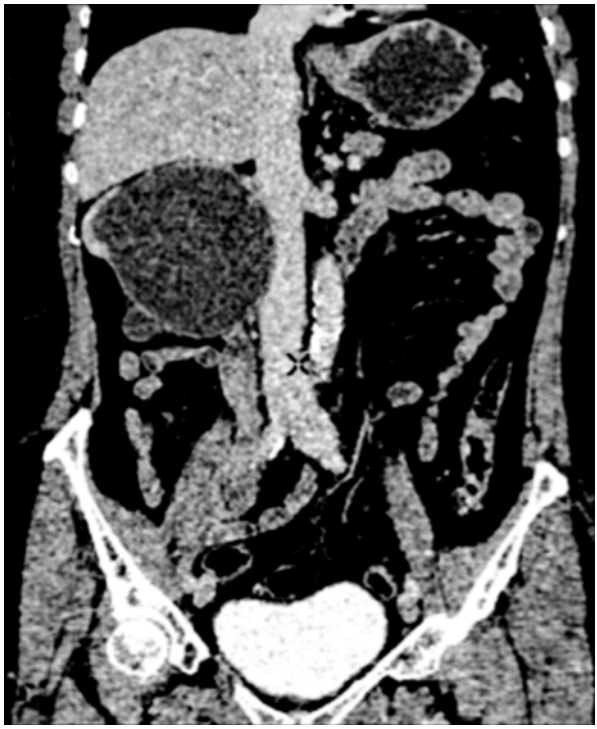

Fig. 37.2 Grossly hydronephrotic right kidney with a thin rim of cortex on contrast-enhanced CT Scan. Note a large filling defect in the upper ureter on the same side

limitations such as lower diagnostic accuracy (sensitivity of 75 % for tumours less than 2 cm) and poor correlation with pathological staging [21, 22].

Endoscopic Evaluation

Direct visualisation with ureteroscopy and biopsy were previously reserved for patients with equivocal finding on CT. However with increasing availability of fibroptic flexible urtereroscopes and endoscopic management option in selected group of patients, few centres routinely perform ureteroscopic biopsies irrespective of CT findings. The diagnostic accuracy of ureteroscopic visualisation and biopsies remains variable [23–27] (Table 37.1).

A number of challenges remain unresolved with ureteroscopic biopsies such as lack of standardisation of biopsy technique, adequacy of specimen, type of preservative and impact on clinical management. Table 37.2 shows numbers of inadequate biopsies reported in the literature [24–29].

The accuracy of ureteroscopic biopsies can be enhanced by the application of blue light with oral 5-Aminolevulinic acid or narrow band imaging particularly for

Table 37.1 Studies showing the diagnostic accuracy of ureteroscopic biopsies in the management of upper tract transitional cell carcinoma

Author	True positive	True –ve	False + ve	False –ve
Guarnizo et al. (2000) [28]	40/45 (89 %)	0	5	0
Williams et al. (2008) [23]	29/30 (97 %)	0	2	0
Keeley et al. (1997) [29]	40/42 (95 %)	0	2	0
Chitale et al. (2008) [27]	14/19 (74 %)	0	0	0
Matsumoto et al. (2006) [26]	33/35 (94 %)	35	2	6
Shiraishi et al. (2006) [25]	27/29 (93 %)	1	0	5
Skolarikos et al. (2003) [24]	62	2	0	0

Table 37.2 Problem of inadequate ureteroscopic biopsies in the management of upper tract Urothelial carcinoma

Study	Study period	Biopsy technique/instruments	Number of inadequate biopsies as observe by reporting pathologists
Chitale et al. [27]	1994–2004	Not documented	None mentioned
Keeley et al. [29]	1985–1995	Basket/cup forceps	Not mentioned
Guarnizo et al. [28]	1990–1998	3 F cold cup biopsy forceps/11.5 F resectoscope	5 (11 %)
Matsumoto et al. [26]	1998–2004	3 F cold cup biopsy forceps	4 (6 %)
Shiraishi et al. [25]	1995–2001	3 F cold cup biopsy forceps	5 (12.5 %)
Skolarikos et al. [24]	1989–2001	3 F cold cup biopsy forceps	11 (15 %)
Williams et al. [23]	1998–2006	3 F cold cup biopsy forceps	0

flat lesions such as carcinoma *in situ* [30]. Ureteroscopy enables histological confirmation with biopsies and could be taken as a further evaluation with retrograde studies. Ureteroscopic grade evaluation of biopsy correlates well with resected specimen; however the stage correlation is poor [31].

Urinary Biomarkers

There is currently increasing interest in the development of a reliable urinary biomarker in the diagnosis of UUT-UCC. They have potential role in the diagnosis as well as follow up management. Urinary cytology has poor sensitivity particularly for low grade lesion and is influenced by the experience of the examining pathologist. Its sensitivity is improved by direct ureteroscopic collection by washings or brush cytology. Despite this only a poor sensitivity of 60–70 % could be achieved at best [30]. A number of new urinary biomarkers are currently being investigated. UroVysion fluorescence *in situ* hybridization (FISH) has shown the most promising

results with sensitivity and specificity reports of 52–100 % and 80–100 % respectively in the detection of upper tract tumours (Table 37.3) [30, 32–35].

Staging

Unlike bladder cancer 60 % of upper tract tumours are invasive at the time of diagnosis. Spread is direct, lymphatic or by haematogenous route. The lymphatic spread is to paraortic, paracaval, common iliac and pelvic lymph nodes. Haematogenous metastasis can occur to liver, lungs and bone. Staging is based on the TNM classification [36] (Table 37.4).

Table 37.3 Sensitivity and specificity of FISH

Study	Number of patients	Sensitivity (%)	Specificity (%)
Mian et al. (2010) [35]	55	100	89.5
Luo et al. (2009) [34]	21	85.7	100
Chen et al. (2008) [32]	43	52	–
Johannes et al. (2010) [33]	35	56	80
Akkad et al. (2007) [30]	16	87.5	80

Table 37.4 TNM classification

Primary tumour (T)
TX-Primary tumour cannot be assessed
T0-No evidence of primary tumour
Ta- Non-invasive papillary carcinoma
Tis-Carcinoma *in situ*
T1-Tumour invades subepithelial connective tissue
T2-Tumour invades muscle
T3-(For renal pelvis only)Tumour invades beyond muscularis into peripelvic fat or the renal parenchyma
(For ureter only) Tumour invades beyond muscularis into periureteric fat
T4-Tumour invades adjacent organs, or through the kidney into perinephric fat
Regional lymph nodes (N)
NX-Regional lymph nodes cannot be assessed
N0-No regional lymph node metastasis
N1-Metastasis in a single lymph node 2 cm or less in the greatest dimension
N2-Metastasis in a single lymph node, ≤2 cm but not >5 cm in the greatest dimension or multiple lymph nodes, none >5 cm in greatest dimension
N3-Metastasis in a lymph node more than 5 cm in greatest dimension
Distant metastasis (M)
M0-No distant metastasis
M1-Distant metastasis

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Grading

Tumours are also graded often by both the 2004 and the more familiar 1973 WHO classifications [37].

1973 WHO Classification

G1 well differentiated
G2 moderately differentiated
G3 poorly differentiated

2004 WHO Classification

Papillary neoplasm of low malignant potential (PNLMP)
Low grade papillary carcinoma
High grade papillary carcinoma

Stage and grade at presentation dictate prognosis, with staging being the single most important prognostic indicator [38]. Other factors which are independent negative prognostic factors are advanced age, lymph vascular invasion, tumour necrosis, sessile tumour architecture and presence of concomitant CIS. Presence of tumor microsatellite instability (MSI) is a favourable prognostic factor [39].

Management of Localized UUT-UCa

Surgical excision or endoscopic ablations are the most common treatment modalities offered to patients with localised disease. Factors influencing treatment of localised UUT-UCa are renal function, function of contra-lateral kidney, availability of local expertise and associated co-morbidities. Broadly treatment options can be categorised into:

(i) Radical nephroureterectomy
(ii) Nephron/Ureter-sparing procedures

Radical Nephroureterectomy

Radical nephroureterectomy is the standard of care for many patients with localised disease. This procedure involves complete excision of the kidney (along with the perinephric fat and gerota's fascia) and ureter. The nephroureterectomy is combined with

an ipsilateral bladder cuff excision as the excised ureteric stump is a frequent site for recurrence. The procedure can be performed by open, laparoscopic and robotic approaches. The eventual approach employed is subject to local expertise availability, although laparoscopic approach is the favoured option in a majority of institutions.

Open Nephrourterectomy (ONU)

This is a significantly morbid procedure usually requiring two large incisions (can be performed with one long incision). Patients have considerable post operative analgesia requirement, prolonged post-operative stay and increased blood transfusion rates in comparison with minimally invasive approaches [40].

Laparoscopic Nephrourterectomy (LNU)

Laparoscopic Nephrourterectomy is increasingly becoming the gold standard procedure in a majority of institutions for localised UUT-UCC. It can be performed by transperitoneal, retroperitoneal and hand assisted approaches. LNU offers significantly better immediate functional outcomes and equivalent oncological outcomes when compared to an ONU.

Robotic Nephrourterectomy

Robotic approaches for various urological techniques have been in ascendancy in recent years. Current evidence on robotic assisted nephrourterectomy although sparse has shown promising immediate outcomes and short term oncological outcomes [41]. Cost, standardisation of technique and paucity in literature for long term oncological outcomes have limited their usage.

Open Versus Laparoscopic Nephroureterectomy

The only randomised control trial identified in a recent Cochrane review [41, 42] comparing the two approaches reported lesser blood loss (*104 ml vs. 430 ml, $P < 0.001$*) and mean time to discharge (*2.30 days vs. 3.65 days, $p < 0.001$*) in favour of LNU. At a median follow up of 44 months, the 5 year cancer-specific survival and 5 year metastasis-free survival rates were similar for the two groups. A non-systematic review reported that the laparoscopic approach was associated with a

longer operating time (*277 min vs. 200 min*), but a reduced blood loss *(241 ml vs. 463 ml*), a reduced analgesic requirement, and a shorter hospital stay compared to open surgery.

A summary of Cochrane review identified multiple case series (retrospective and prospective) reporting outcomes of laparoscopic nephroureterectomy with variations regarding the use of laparoscopic approach (transperitoneal versus retroperitoneal), and management of the distal ureter. Compared with open surgery, literature suggests that laparoscopic surgery has various benefits with respect to postoperative analgesia requirements, hospitalization duration, cosmesis, and convalescence. With intermediate follow-up, cancer-related outcomes seem similar between the open and laparoscopic surgical modalities; however design, methodology and reporting of studies were poor.

Management of the Distal End of the Ureter- Techniques and Results

Adequate excision of the ipsilateral distal ureter and adjacent bladder cuff is an essential step of nephroureterectomy procedure. Failure to achieve this can result in recurrence rates of 34 % at the ipsilateral ureteric stump [43]. Various approaches to deal with the distal end of the ureter have been described (open intra and extravesical techniques, pluck, endoscopic ureteral detachment, ureteral intussusceptions, cystoscopic unroofing and laparoscopic stapling and extravesical laparoscopic excision). There is currently no agreement on most appropriate approach and current practices are based on personal preference and expertise available [41].

Long-Term Oncological Outcomes: LNU Verus ONU

Nephroureterectomy with ipsilateral bladder cuff excision regardless of what approach is used offer the best oncological outcomes. A non-systematic review comparing laparoscopic and open approaches showed no statistically significant differences between the two groups for bladder recurrence (*24 % vs. 24.7 %),* local recurrence (*4.4 % vs. 6.3 %)* and distant metastasis (*15.5 % vs. 15.2 %).* The 2 and 5-year survival rates for the laparoscopic and open groups were 75.2 % vs. 76.2 %, and 81.2 % vs. 61 %, respectively [40].

A multicentre retrospective study of 1,249 patients compared the oncological efficacy, i.e. recurrence rate and cancer-specific mortality, between ONU and LNU. The 5-year recurrence free survival estimates were 86.8 and 76.2 % for LNU and ONU respectively. Five-year cancer-specific mortality-free survival estimates were 85.8 and 73.1 % for LNU and ONU, respectively. In a univariate

adjusted analysis to stage and also an adjusted multivariate analysis, there was no statistical difference for recurrence and cancer specific mortality between ONU and LNU [44].

Conservative Treatments

Indications

Nephron sparing techniques have traditionally been advocated for patients with solitary kidney/single functioning kidney, bilateral tumours, severe renal insufficiency and patients with significant co-morbidities. However in recent years there has been an increasing trend in their usage in small (less than 1.5 cm), solitary, low grade and stage disease in fit patients with a normal contra lateral kidney.

Nephron sparing techniques include:

(i) Endourological approaches

- *Ureteroscopy*
- *Percutaneous approaches*

(ii) Segmental resection of uereter
(iii) Partial nephrectomy

Ureteroscopy

Currently ureteroscopy and laser ablation is the most popular nephron/ureteric sparing technique in the management of UUT-UCC. The main reason for this is the development of sophisticated small rigid and flexible ureteroscopes facilitating easy accessibility to the upper ureter, renal pelvis and calyces. Commonly used energy sources for ablation are holmium: YAG; neodymium: YAG laser and rarely electrocautery. Ureteroscopic management of low-grade lesions measuring <1.5 cm has been reported in various studies to be a very favourable first line option even in the presence of a normal contra lateral kidney with oncological outcomes similar to that of a nephroureterctomy for low grade localised disease [45–47]. Ureteric stricture rates have been reported to be between 4.6 and 13.6 % while perforation rates remain less than 10 % [48]. A recent study suggested ureteroscopic management in selected patients to be more cost-effective than nephroureterectomy [49].

Long-term endoscopic follow-up of the upper urinary tract and bladder is obligatory. As is seen in other organ-preserving management strategies, surveillance remains stringent. All patients considered candidates for endoscopic management should be counseled and be motivated enough to adhere to a regular evaluation schedule. Surveillance includes cystoscopy, urine cytology, and periodic ureteroscopy as done with bladder cancer surveillance protocols.

Percutaneous Approaches

Percutaneous approach combined with resection of the tumours has been suggested to be a useful option for low-grade tumours [45, 47]. However there is theoretical risk of tumour seedling and with most tumours being able to be managed ureterscopically; this option is not usually required. Most of the case series [29, 45, 50, 51] suggest that this approach has a higher risk of recurrences despite various adjuvant treatments.

Segmental Ureteric Resection

Segmental resection and re-implantation can be performed for distal ureteric tumours that are not amenable to endoscopic treatment. The best outcomes are achieved in low grade and stage solitary tumours [49].

Open partial nephrectomy has been used in the past for large tumours in solitary kidney. This techniques is however seldom required in view of current advancements in endoscopic managements of UT-UCa.

Role of Adjuvant Treatment

Adjuvant endocavitatory therapy with BCG, mitomycin, thiopeta and eburubicin has been suggested to reduce recurrence of disease following nephron sparing approaches [2, 52–54] (Table 37.5). This can be performed via a retrograde route using a ureteric stent/retrograde catheter or via an antegrade route using a percutaneous approach Current evidence has only shown benefit in patients with carcinoma in situ with improved local disease control and progression free survival.

Adjuvant therapy does not appear to have any significant benefit in patients with pTa/pT1 disease [55].

Areas of Future Work

There has been a shift in paradigm in the treatment of small, solitary, low grade/ stage disease with increasing number of patients being treated conservatively. It will therefore be essential to develop optimal preoperative staging and surveillance modalities which will require continued advancements in imaging, endoscopic and urinary biomarker technology. Currently adjuvant therapy appears to have only a limited benefit in the treatment of UTUCC. Future research is required to establish and standardise appropriate agents, route of delivery and regime in order to achieve optimal oncological outcomes. The role of lymphadenectomy in the treatment of UTUCC and long term oncological outcomes of robotic approaches will be of continued interest.

Table 37.5 A literature review of reported results of topical adjuvant mitomycin treatment post ablation of UT-TCC

Author	Route	Agent used	Patients (tumours)	Grade/stage	Recurrence rate (%)	Nephroureterectomy (NU) or progression (P)	F/U (months)
Keeley et al. [29]	Retrograde 1–3 days after treatment	MMC (40 mg)	19 (21)	G1- 5	54	NU– 4/19 (21 %)	30
				G1/2- 2		P – 0 %	
				G2- 8			
				G3- 4			
Eastham et al. [52]	Percutaneous	MMC (40 mg)	7	G2/3 Ta– 3	28.5	1/7 – Cystectomy + distal urethrectomy	1–12
				G2/3 T1 – 3			
				CIS – 1			
Goel et al. [53]	Retrograde or Percutaneous (after a week)	MMC (40 mg)/ epirubicin (50 mg)	24	Low grade – 15	50	NU – 10 (42 %)	64
				High grade – 5		P – 2 (8 %)	
				SCC – 2			

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Chapter 38
Urachal and Urethral Cancer (Excluding Penile Cancer)

Priyadarshi Kumar and Vinod H. Nargund

Urachal Cancer

The urachus is a remnant of a channel between the upper part of the bladder and the umbilicus where urine initially drains in the fetus during the first trimester of pregnancy. This channel usually seals off and gets obliterated around the 12th week of gestation. It is left as a small fibrous cord between the bladder and umbilicus called the median umbilical ligament. The urachal remnants are likely to persist as tubular or cystic structures in nearly a third of autopsy subjects [1]. The remnants are likely to contain smooth muscle, mucosa and connective tissue elements.

Urachal cancer (UrC) is a rare entity accounting for less than 0.01 % of all malignancies and less than 0.2 % of all bladder malignancies [2, 3]. Due to its relatively long clinically silent course it has a propensity to be advanced at presentation with a poor prognosis. The first detailed description came in 1933 by Begg who suggested that all apical tumours of the bladder should be considered urachal tumours until otherwise proven [4]. These principles were built upon further by Mostofi and Sheldon to offer the foundation for the criteria used today for the diagnosis of urachal tumours.

P. Kumar, MB, BS, MRCS, MD, FRCS Urol (✉)
Department of Urology, University Hospitals Coventry and Warwickshire NHS Trust, Warwickshire, UK
e-mail: kumardoc1@yahoo.co.uk

V.H. Nargund, PhD, FRCSEd, FRCSUrol, FEBU
Department of Urology, Homerton University Hospital, London, UK
e-mail: vinodnargund@gmail.com

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Table 38.1 Criteria for diagnosing urachal cancer

1. Tumour located in the bladder dome
2. Predominant invasion of the muscularis or deeper with a sharp demarcation between the tumour and surface bladder urothelium that is free of glandular or polypoid proliferation
3. Absence of cystitis cystica and cystitis glandularis
4. Presence of urachal remnants within the neoplasm
5. Ramifications of tumour in the bladder wall with extension to the cave of Retzius, anterior abdominal wall or umbilicus

Table 38.2 Sheldon staging of urachal cancer

Stage I	**No invasion beyond mucosa**
Stage II	**Invasion confined to urachus**
III	**Local extension**
A	Bladder
B	Abdominal wall
C	Peritoneum
D	Extension into viscera other than bladder
IV	**Metastases**
A	Lymph nodes
B	Distant sites

Pathology

Urachal remnants may give rise to complications such as cysts or tumours. The usual site is the bladder dome or in the bladder in midline [5]. It is the remaining rests of enteric epithelium that can give rise to urachal adenocarcinoma which is the commonest histological type accounting for 90 % of UrC [6]. Urachal carcinoma should be considered as a distinct entity from other malignant bladder tumours. Sheldon et al. [2] proposed certain criteria for the diagnosis of UrC (Table 38.1).

Other malignant tumours of urachus include sarcomas (leiomyosarcoma, rhabdomyosarcoma and malignant fibrous histiocytoma), small cell carcinoma, urothelial carcinoma and mixed types.

Staging

Currently there is no standard staging system for UrC but the most commonly accepted system being that of Sheldon [2] (Table 38.2).

Clinical Presentation

Urachal cancer has an insidious course and when it presents with symptoms and signs it is normally of an advanced stage. It tends to be found more commonly in male patients with the largest series reporting a 2:1 ratio of men to women [1, 7–9].

Haematuria remains the most common mode of presentation in the great majority of cases being present in over 80 % of cases [1, 7]. Other symptoms and signs include suprapubic pain, lower urinary tract symptoms, mucosuria, umbilical discharge, urinary tract infection and abdominal mass.

Investigations

Because of its different behaviour compared to urothelial cancer it is important to recognise the condition as early as possible. It has also been moderately correlated with advancing pathological grade [7]. Cystoscopy will reveal a midline mass anteriorly in most cases and a biopsy should be taken. A negative cystoscopy however does not exclude an urachal tumour. Cross sectional imaging with CT or MRI will invariably reveal a mass, thickening or calcification at the bladder dome. This will also allow for accurate staging with respect to local extension, lymph nodes and distant metastasis.

Surgical Treatment

The primary surgical treatment of urachal cancer has varied in the extent of surgical resection with debate as to whether radical cystectomy or partial cystectomy were the preferred treatment options. The evidence from the literature would suggest that optimal treatment is total urachectomy. Henly et al. [10] reported their 34 cases treated with partial or radical cystectomy – 30 and 4 cases respectively. All of their cases underwent urachectomy and overall they demonstrated 43 % 5-year survival [10]. The experience from the MD Anderson noted that only 19 of 35 underwent urachal resection and it was noted that they were the majority of the long term survivors as compared with those who did not undergo urachectomy [11]. Ashley et al. [7] also analyzed the cases from the Mayo clinic and 60 cases were treated primarily with surgery but only 27 underwent urachectomy. Despite this overall survival was 48 % however they noted that that complete urachectomy and umbilectomy were significant predictors of survival on univariate analysis. In summary therefore it is recommended that complete urachectomy is undertaken which includes taking bladder dome and all the urachal remnants. There is no survival advantage of radical cystectomy over partial cystectomy as long as total urachectomy has been performed and surgical margins are clear [10, 12].

Chemotherapy

There is a limited role for chemotherapy inferred from the small amount of experience available. Logothetis et al. [13] used a combination of 5-fluorouracil, doxorubicin and mitomycin on 3 patients with urachal cancer. Two of the patients had a partial response and even then the response was short lived [13]. At MD Anderson

[11] 29 patients were treated with chemotherapy – 20 for metastatic disease, 7 received postoperative adjuvant treatment for margin or node positive disease and 2 had neoadjuvant therapy. The objective response rate was 33 % in 9 patients who had a regimen that combined 5-fluorouracil and cisplatin with either α-interferon or gemcitabine and leucovorin. The median survival in metastatic disease was 20 months and chemotherapy did not appear to make any difference to outcome apart from some objective responses. Similar findings with chemotherapy usage were reported from the Mayo Clinic with no differences in time form metastases to death [7]. Their chemotherapeutic agents were cisplatin (50 % of patients), doxorubicin (36 % of patients), cyclophosphamide (21 % of patients), 5-fluorouacil (21 % of patients), and paclitaxel (14 % of patients). A recent trial of 5-fluorouracil, leucovorin, gemcitabine and cisplatin has completed a study on metastatic urachal carcinoma with patients being followed up [14].

Radiation has had little role in urachal cancer and primarily used as adjuvant therapy in disease recurrence and loco-regional symptom control. The little use it has had as primary therapy was associated with decreased survival compared with those surgically treated although this may have been due to the patients irradiated being older and having higher stage disease [7].

Prognosis

The prognosis for urachal cancer remains poor with its insidious course and advanced disease at presentation. Factors associated with a poorer prognosis include positive surgical margins, failure to complete total urachectomy, radiation therapy as primary treatment, increasing tumour grade and stage [7, 11, 12, 15].

Urethral Cancer (UC) (Excluding Penile Cancer)

Primary neoplasm of the urethra is rare which makes its study difficult with a lack of studies in the literature – the ones reported are retrospective reviews of treatment. Therefore it has not been possible to adequately define the natural history or suggest an ideal management strategy in these tumours. At presentation it has often invaded locally contributing to its generally poor prognosis despite the treatment modality employed. This section will primarily deal with primary malignancy of urethra with specific reference to transitional cell carcinoma.

Epidemiology and Risk Factors

Primary urethral cancer is extremely rare accounting for less than 1 % of all malignancies. Female urethral cancer is four times more common than male urethral

cancer. It typically presents after the age of 60. Primary carcinoma of the urethra accounts for only 0.02 % of all malignancies in females [16]. The exact aetiology is not known. Caucasians seem to have a higher incidence [17]. There are number of differences between male and female urethral malignancy due to anatomic and histological factors.

Risk Factors

Like many other cancers chronic inflammation seems to play a role in the pathogenesis of urethral cancer. In males, an increased incidence of primary urethral cancer has been associated with sexually transmitted diseases and urethral stricture disease [18]. UC has been reported in patients with intermittent catheterization/ urethroplasty [19], external beam irradiation therapy /radioactive seed implantation [20], and chronic urethral inflammation/urethritis following sexually transmitted diseases (i.e. condylomata associated with human papilloma virus 16) [21, 22]. Clear cell adenocarcinoma may also have a congenital origin [23]. There is also evidence to suggest that human papilloma virus 16 (HPV-16) is associated with the development of squamous cell cancer of the urethra [21]. For females these associations are not so strong but chronic irritation and urinary tract infections have been implicated with urethral cancer.

Other factors quoted include pre-existing lesions such as caruncles, diverticula, papillomas, adenomas, polyps and leukoplakia of the urethra [24]. Smoking is a risk factor for bladder cancer, as well as a risk factor in the development of transitional cell urethral carcinoma.

Anatomy

The anatomy of the urethra explains the pathological types, progression and behavior of urethral carcinoma in both sexes.

Male Urethra

This has an approximate length of 20 cm. For descriptive purposes the male urethra is anatomically divided into Penile, Bulbar, Membranous and Prostatic segments (Fig. 38.1 and Table 38.3).

The male urethra may be sub-divided into ‘anterior’ and ‘posterior’ according to the lymphatic drainage in men. The **anterior urethra** comprises the urethral meatus, fossa navicularis and penile segment and their lymph drainage is to the inguinal nodes.

The **posterior urethra** comprises of bulbar, membranous and prostatic segments, which drain to the pelvic nodes.

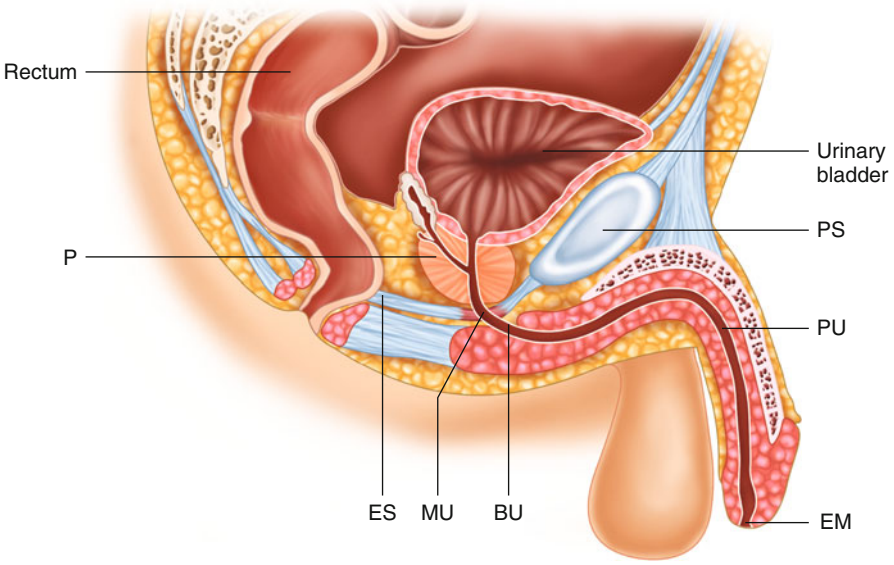

Fig. 38.1 Diagrammatic representation of urethra and bladder. *ES* external sphincter, *BU* bulbar urethra, *PU* penile urethra, *P* prostate, *EM* external urethral meatus, *MU* membranous urethra, *PS* Pubic symphisis

Table 38.3 Urethral segments and epithelial type in the male

Urethral segment	Epithelium
Urethral meatus, fossa navicularis	Stratified squamous
Penile, bulbar,	Pseudostratified and stratified columnar
Prostatic, membranous	Transitional

Female Urethra

The female urethra is shorter than its male counterpart with an approximate length of 4 cm. The distal two-thirds are lined by stratified squamous epithelium while the proximal third comprises transitional cell epithelium. The distal third or anterior urethra drains to the superficial and deep inguinal lymph nodes. The proximal two-thirds or posterior urethra drains to the pelvic nodes.

Pathology

Male

Benign Tumours

Condyloma acuminatum (*syn* genital or venereal warts) (Human papilloma virus Type 6–11); slow growing; Urethral involvement in 5 % of patients; they are commonly seen on the glans, shaft and prepuce.

Urethral polyps: fibrous (usually congenital and early presentation) or prostatic polyps (uncertain etiology and related reactive proliferations secondary to urethral injury). The lesion could be sessile or papillary.

Premaligant

Balanitis xerotica obliterans (BXO): genital variation of lichen sclerosis *et* atrophicus.

Leukoplakia are whitish plaques involving the meatus and associated with in situ squamous carcinoma and verrucous cancer.

Carcinoma in situ (Syn. Erythroplasia of Queyrat or Bowen's disease of glans) [25].

Malignant Tumours

Primary urethral malignancy accounts for less than 1 % of genito-urinary tumours in men. The common histological varieties include squamous (80 %), urothelial (15 %), adenocarcinoma (5 %) and rarer varieties including malignant melanoma, basal cell carcinoma and sarcomas. The commonest urethral tumor, squamous cell carcinoma occurs in bulbo-urethral region (60 %). Ninety percent of cancers in the prostatic urethra are transitional in origin reflecting the predominant epithelial type in this location.

Kaposi's sarcoma of the meatus has also been described although more common areas include skin, oral mucosa, lymph nodes, and visceral organs may be involved [26]. *Nearly 4–18 % of men develop urethral TCC after cystectomy* [27–29].

Female

In a series of 18 female patients Thayavihalli et al. [30] found the predominant histology to be squamous cell cancer accounting for 50 % of cases. Transitional cell cancer accounted for 28 % and adenocarcinoma 22 %.

Nearly 6 % of women undergoing cystourethrectomy have urethral TCC [31]. Mixed tumors, undifferentiated carcinomas, melanoma, cloacogenic carcinoma, and clear cell adenocarcinoma have also been reported [24, 32].

Clinical Presentation

There is no typical clinical presentation of urethral cancer. Because of the early local involvement most of the tumours are advanced at the time of presentation. The presentation is insidious and the symptoms are often ascribed to benign disorders. The most common presentation is with a palpable urethral lump or with lower urinary tract symptoms. Alternative presentations include urethral stricture disease, urethral fistulation, urethral diverticula, abscesses, recurrent urinary tract infections, dyspareunia, perineal pain and lymphadenopathy. Haemospermia may

be an additional symptom in men. It must be emphasized that a strong index of suspicion should be exercised with a low threshold for investigation so that any delay is avoided. In patients who have undergone urethra-sparing cystectomy urethral bleeding is the only sign of urethral TCC. However regular endoscopic surveillance is mandatory in these cases.

TNM Staging

It spreads locally to the corpora, periurethral muscle and adjacent organs including vagina, prostate, bladder and rectum (Table 38.4). Palpable lymph nodes are present in 20 % of patients at presentation and most of them will have tumour within these nodes. Haematogeonous spread is rare and a late event.

Prognostic Factors

The prognosis depends on its anatomical location and depth of invasion. So tumour stage clearly an important prognostic indicator with advanced tumours having poor

Table 38.4 TNM classification of urethral cancer

Primary	Tumour
Local tumour	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary, polypoid or verrucous carcinoma
Tis	Carcinoma-in-situ
T1	Tumour invading subepithelial connective tissue
T2	Tumour invading any of the following: corpus spongiosum, prostate, periurethral muscle
T3	Tumour invading any of the following: corpus cavernosum, beyond prostatic capsule, anterior vagina, bladder neck
T4	Tumour invades other adjacent organs
Regional	Lymph nodes
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node, 2 cm or less in greatest dimension
N2	Metastasis in a single lymph node, larger than 2 cm but less than 5 cm in greatest dimension; or in multiple nodes, none greater than 5 cm
N3	Metastasis in a single lymph node greater than 5 cm in greatest dimension
Distant metastasis	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

prognosis [33]. The prognosis is also poor in female urethral carcinoma involving proximal or urethral involvement [30]. Clinical course of TCC of urethra is discussed later.

Diagnostic Investigations

Apart from routine investigations like complete blood count, urea and electrolytes, liver function tests and bone profile, urine is sent for culture and sensitivity and cytological analysis for the presence of transitional cell carcinoma cells.

Flexible cystourethrosocopy allows inspection of the bladder and urethra and biopsies under local anaesthesia. In most cases however general anaesthetic is required to carry out rigid urethro-cystoscopy, biopsy followed by examination under anaesthetic (EUA) and. The EUA allows clinical assessment of local disease spread and provides useful staging information. If there is any suspicion of rectal invasion then flexible sigmoidoscopy may be warranted.

Staging Investigations

Imaging

Computed tomography (CT) is used to assess extent of local spread of urethral cancer. Magnetic resonance imaging (MRI) has also been demonstrated to be 90 % accurate in evaluating local extension of urethral cancer MRI also offers multiplanar imaging which is potential advantageous in accurately planning surgery [34]. MRI is particularly useful in evaluating the female urethra and periurethral tissues [35] and it is helpful in monitoring changes after neoadjuvant chemoradiotherapy and to aid subsequent surgical planning [36]. If the patient presents with haematuria or the histology is transitional cell cancer then evaluation of the upper tracts is required by either intravenous urography (IVU) or CT. Bone scanning and plain radiographs are required if metastasis is suspected on biochemical or clinical grounds. Barium enema may be useful in staging if rectal spread is suspected. The chest assessment is routinely done with a chest X-ray.

Treatment

It is difficult to propose the best treatment for urethral cancer in view of the small number of cases reported over a long interval. The studies in the main are comprised of retrospective reviews of treatment strategies employed. Traditionally surgery has been considered the mainstay in the treatment of urethral cancer.

Table 38.5 Surgical management of anterior urethral carcinoma

Stage	Treatment
Ta, Tis	Transurethral resection/Diathermy
T1	Transurethral resection/Partial penectomy
T2-3	Partial penectomy/Total penectomy

Male

Surgery alone has not provided very good outcomes [37] and neither has the use of radiotherapy alone [38]. Dalbagni et al. [18] have reported on three factors as predictive of survival – nodal status, histologic type and site of cancer. In their study they noted that most cases at presentation were of an advanced stage (36/43 with invasive disease). Rabbani analysed the population based Surveillance, Epidemiology and End Results (SEER) database and conlcluded that increasing age, grade, stage, nodal disease and non-surgical management were correlated with decreased survival. They also noted that surgery had a better outcome for T2 – T4 non-metastatic disease [39]. Locally advanced tumours of the anterior urethra are treated by chemoradiation and penectomy [18]. For advanced posterior urethral tumours chemoradiation and cystoprostatectomy with penectomy having been suggested. There may also be a case for conservative surgical management of superficial disease by transurethral resection, fulguration or excision provided it of low stage and low grade [40]. There is interim data suggesting penile preserving surgery for distal urethral carcinomas offers local control without comprising survival [41]. The treatment options are summarized in Table 38.5.

Nodal Management

If inguinal nodes are palpable ipsilateral dissection is carried out after frozen section confirmation [42, 43]. In absence of palpable nodes regular clinical follow up and assessment is needed.

Bulbo-Membranous Urethra

Lesions in bulbar or membraneous regions are treated with cystoprostatectomy with regional (pelvic)lymphadenectomy (≥T2 lesions) [44]. This may have to be supplemented with scrotectomy and resection of pubic rami depending on the depth of invasion and bulkiness of the tumour [37].

Radiation and Chemotherapy

Radiation is generally indicated for patients who refuse surgery and have early disease of the anterior urethra. The main advantage of radiotherapy is preservation of penis but it may result in urethral stricture and recurrence is a possibility [45]. The use of chemotherapy as a monotherapy needs further studies and so far in a

small number of patients the results are disappointing [46]. Chemoradiation in patients with locally advanced carcinoma has been encouraging [47, 48]. Gheiler et al. [49] have indicated best treatment outcome with multimodality treatment of chemoradiation (Cisplatin and 5-fluorouracil + Radiation) and surgery in their series of 21 patients. Dayyani et al. in their series of 44 patients [50] noted encouragingly a response rate to platinum based chemotherapy of 72 %. They also noted that neo-adjuvant chemotherapy offered prolonged disease free survival in a subgroup of patients with nodal disease. There remains however no consensus on the role of chemotherapy or radiotherapy in primary urethral cancer.

Female

Prognostic factors for female urethral cancer include stage, histology type, tumour site and nodal status [51]. Except for small tumours the prospects of cure are limited. Again distal tumours of low grade may be treated with conservative resection although Di Marco et al. [51] noted a high recurrence rate with this approach and recommended radical urethrectomy. Ipsilateral lymph node dissection is carried out if the initial biopsy is positive on frozen section. For locally advanced tumours involving the posterior urethra then en-bloc resection of involved adjacent viscera is required for disease control. Tumours less than 2 cms can be treated either by radiotherapy or by surgery. For tumours larger than 2 cms preoperative radiation followed by extirpative surgery may provide better outcome [52]. There are not enough studies in the literature to comment on the usefulness of adjuvant chemoradiation as yet.

Urethral Carcinoma After the Radical Management of TCC Bladder

Urethral TCC occurs in association with bladder TCC as a manifestation of multi-centric tumour. It is important to recognise those patients undergoing radical cystectomy who are likely candidates for urethral recurrence. Risk factors for urethral recurrence of TCC in the male patient are papillary tumors, multifocality, bladder neck involvement, associated carcinoma in situ (CIS), upper tract TCC, and prostatic and trigonal involvement with superficial TCC and invasion of the stroma [23, 53].

Clinical presentation may indicate advanced disease. Clark et al. [54] noted in their review of 1054 patients who underwent radical cystectomy and urinary diversion that although most patients with urethral recurrence presented with symptoms (57 %) a significant proportion (31 %) were detected by screening cytology.

The median survival of patients with recurrence was only 28 months after diagnosis with urethral stage (superficial vs. invasive) at diagnosis being the most important predictive factor [27, 54]. Patients undergoing continent urinary diversion seem to have lower incidence of urethral recurrence. The exact reason for this is not known [55–57].

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Chapter 39
Epidemiology, Screening, Pathology and Pathogenesis

Bob Djavan, Yakup Bostanci, and Amir Kazzazi

Structure of the Prostate Gland

Anatomically the prostate is described as having anterior, posterior, and lateral surfaces with a narrow **apex** inferiorly and a broad **base** superiorly in continuity with the bladder. It is composed of approximately 70 % glandular and 30 % fibromuscular stroma containing collagen and smooth muscle.

The glandular elements of the prostate are described in three distinct zones: **transition**, **central** and **peripheral** [1, 2] (Fig. 39.1). These correlate with location of their ducts in the urethra, pathology and to some extent with embryological origin. The transition zone (TZ) normally accounts for 5–10 % of prostatic glandular tissue. Its ducts arise at the angle dividing prostatic and preprostatic urethra (i.e. where the urethra angles anteriorly) and pass beneath the preprostatic sphincter to travel on its lateral and posterior sides. This zone is the location for benign hyperplasia (BPH) and 20 % of prostatic cancers. The ducts of the central zone (CZ) arise circumferentially around the openings of the ejaculatory ducts. The glands of CZ are thought to be wolffian in origin and in keeping with this they are structurally and immunohistochemically different from the rest of the prostate. Only 1–5 % of cancers arise from this zone.

The peripheral zone (PZ) (Fig. 39.1) accounts for 70 % of glandular tissue covering the posterior and lateral parts of the gland accounting for 70 % of cancers.

B. Djavan, MD, PhD (✉)
Department of Urology, VA University Hospital,
150 East 32nd Street, New York, NY 10016, USA
e-mail: bdjavan@hotmail.com

Y. Bostanci, MD • A. Kazzazi, MD
Department of Urology, New York University Hospital, NYU, New York, NY USA

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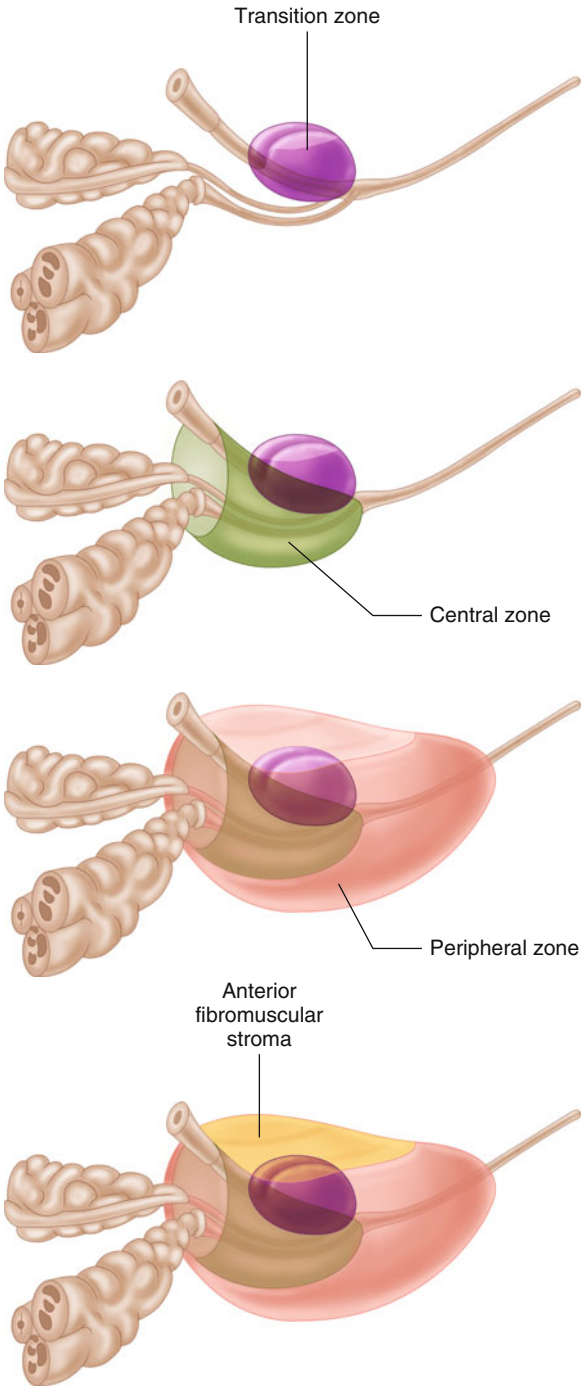

Fig. 39.1 Zonal anatomy of the prostate (Reprinted from McNeal [2]. With permission from Wolters Kluwer Health)

Its ducts drain into the prostatic sinus along the entire length of the prostatic urethra. The anterior fibromuscular stroma is the nonglandular part of the prostate and accounts for up to one-third prostate mass. It is rarely invaded by carcinoma.

Incidence and Epidemiology

Prostate cancer (PCa) is now recognised as one of the most important medical problems facing the male population [3]. For most men PCa is slow growing and does not result in clinical signs or symptoms during their lifetime [4, 5]. Despite its slow growth, in some men PCa progresses and is a leading cause of cancer morbidity and mortality. Globally, it is a less prominent cause of cancer death, contributing 5.8 % of cancer deaths in men [3]. Since 1985, there has been a slight increase in most countries in the number of deaths from PCa, even in countries or regions where PCa is not common [6]. Despite significant advances in the treatment of PCa, it remains a growing problem for men's health.

Worldwide, PCa is the second most prevalent cancer and the sixth leading cause of cancer death in males, accounting for 14 % (903,500) of the total new cancer cases and 6 % (258,400) of the total cancer deaths in males in 2008 [7]. In the United States (US), PCa is the most commonly diagnosed visceral cancer; in 2011, there were expected to be 241,000 new PCa diagnosis and about 34,000 PCa deaths. PCa is second only to nonmelanoma skin cancer and lung cancer as the leading cause of cancer and cancer death, respectively, in US men [8]. Currently, around three million European men are living with PCa and this number will grow due to population aging. There were 350,000 new cases of prostate cancer diagnosed in the EU27 (27 European countries) in 2008, which accounts for about 70 new cases per 100,000 men across the EU27 each year. However, the incidence varies considerably between various European states, ranging from 14 per 100,000 in Turkey to over 123 per 100,000 in Ireland [9].

The worldwide PCa mortality-to-incidence rate (MR/IR) ratios from the International Agency for Research on Cancer (IARC) have shown a marked decline from 2002 to 2008 [10, 11]. But new PCa cases worldwide have increased from 679,060 to 914,000 during this period. As shown in Fig. 39.2, PCa incidence rates increased from $25.3/10^5$ to $28.5/10^5$ person year (PY), while mortality rate decreased from $8.2/10^5$ to $7.5/10^5$ PY. The MR/IR ratio has decreased from 0.32 to 0.26. The PCa incidence rate in North America has decreased from $119.9/10^5$ to $85.7/10^5$ PY, and the mortality rate has decreased from $15.8/10^5$ to $9.9/10^5$ PY, accompanied with a decrease in the MR/IR ratio from 0.13 to 0.12. Of all the continents, Europe had the most remarkable change. The PCa incidence rate increased from $40.0/10^5$ PY in 2002 to $61.4/10^5$ PY in 2008. However, the mortality rate decreased from $14.2/10^5$ to $12.1/10^5$ PY and the MR/IR ratio decreased from 0.36 to 0.20. This remarkable progress could be attributed to the European Randomized Study on Screening for PCa [12]. Although Asia and Africa have shown some improvements in mortality rates and MR/IR ratios, the changes are modest compared to other continents.

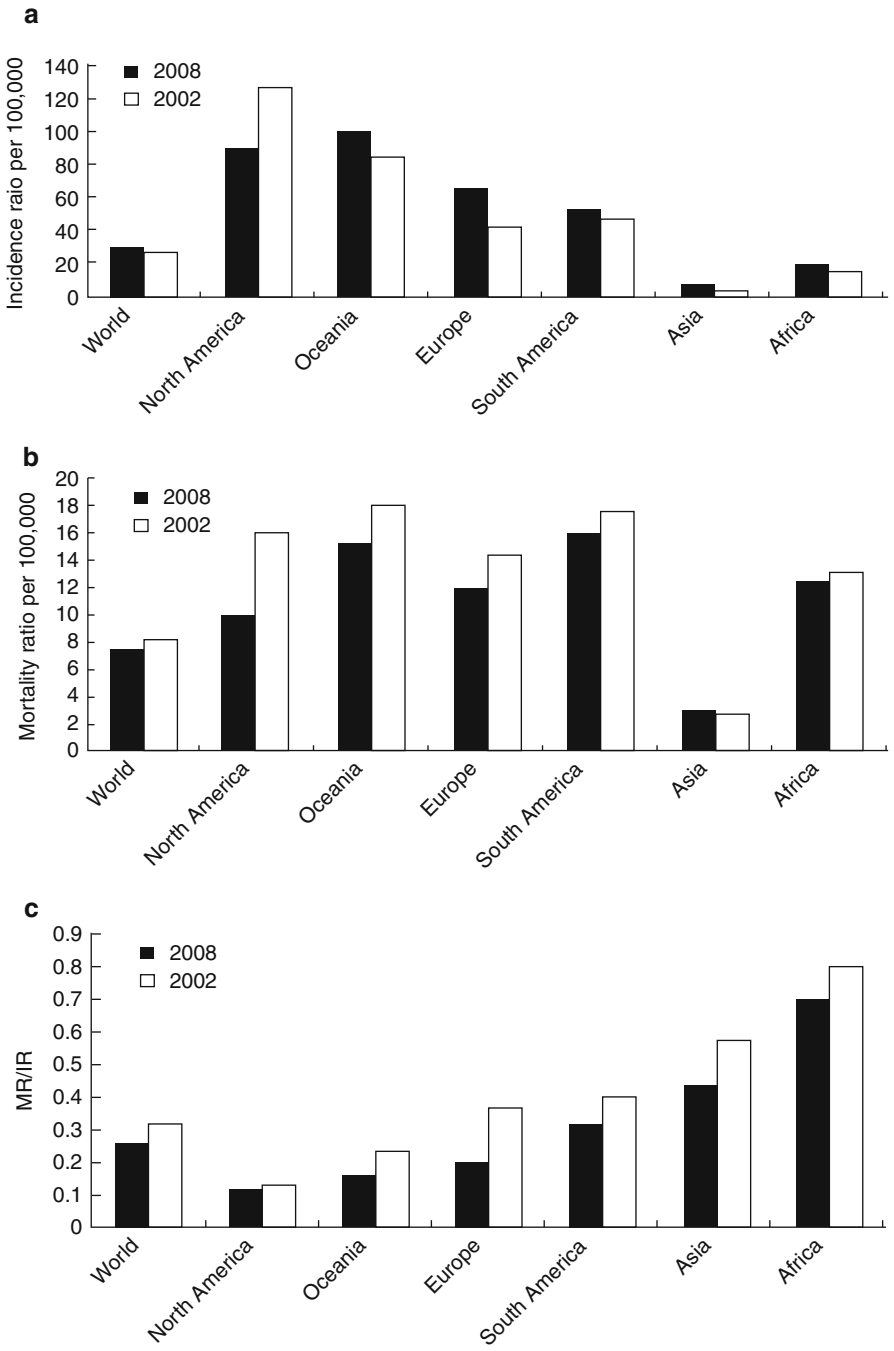

Fig. 39.2 Worldwide age-standardized incidence rates, mortality rates and mortality – incidence rate ratios [11]. MR/IR, mortality-to-incidence rate ratio (Based on data from Ref. [11])

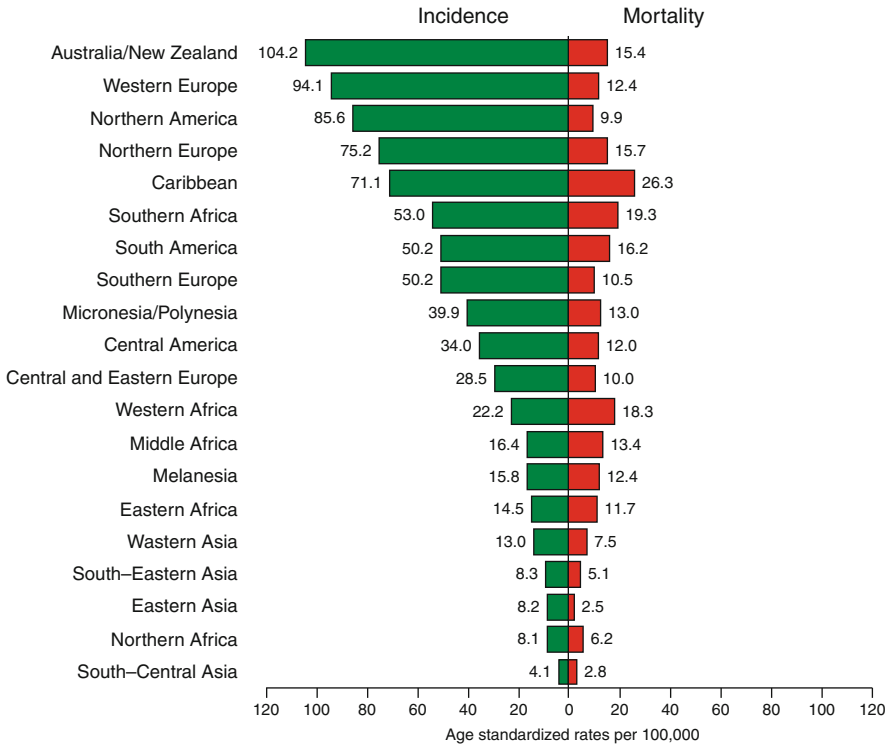

Fig. 39.3 Age-standardized prostate cancer incidence and mortality rates by world area [11] (Adapted from Ferlay et al. [11]. With permission from John Wiley & Sons, Inc.)

PCa affects elderly men more often and therefore is a bigger health concern in developed countries. There are large regional differences in incidence rates of PCa. The highest incidence rates are in the developed countries, with the lowest in Africa and Asia. About 15 % of male cancers are PCa in developed countries compared with 4 % of male cancers in developing countries [11]. Incidence rates vary by more than 25-fold worldwide, with the highest rates recorded primarily in the developed countries of Oceania (Australia and islands around it), Europe, and North America (Fig. 39.3), largely because of the wide utilization of PSA testing that detects clinically important tumors as well as other slow-growing cancers that might otherwise escape diagnosis.

In contrast, men of African descent in the Caribbean region have the highest PCa mortality rates in the world, which is thought to reflect partly a difference in genetic susceptibility [13, 14, 15].

The majority of PCa cases are slow growing and do not pose an immediate threat to the individual. The lifetime risk of a man of 50 years of age having microscopic evidence of PCa is 42 %, while his risk of dying from the disease is only 3 % [16]. Many more cases of PCa do not become clinically evident, as indicated in autopsy series, where PCa is detected in one-third of men under the age of 80 and in

two-thirds of older men [17]. These data suggest that PCa often grows so slowly that most men die of other causes before the disease becomes clinically advanced. However, there is a type of prostate cancer that can occur in younger and older men which is more aggressive and leads to a more rapid death if not detected early enough.

The most complete information available on PCa epidemiology in the US is provided by the Surveillance Epidemiology and End Results (SEER) program of the US National Cancer Institute [18]. There was a gradual rise in the pre-PSA era that could be explained by the rising rates of PCa diagnosed through the transurethral resection of prostate. As the PSA era began, an abrupt rise in PCa incidence was observed, peaking in 1992 (237 per 100,000 person-years). A subsequent decline in the incidence followed until 1995 and was attributed to the cull effect, whereby removal of detectable cases in prior years resulted in fewer available cases for repeat screening. A relatively stable incidence was observed in 1995–1999, but the rates were higher than that prior to the PSA era. Rates have since fluctuated, falling to 169 in 1995, rising again to 184 in 2001, and most recently falling again, showing rates of 171 and 153 for 2007 and 2008, respectively [19] (Fig. 39.4).

Before the PSA screening era, PCa was detected either by symptoms, or incidentally on final pathology after transurethral resection or open simple prostatectomy for presumed benign prostatic hyperplasia [20]. Thus, presentation with advanced

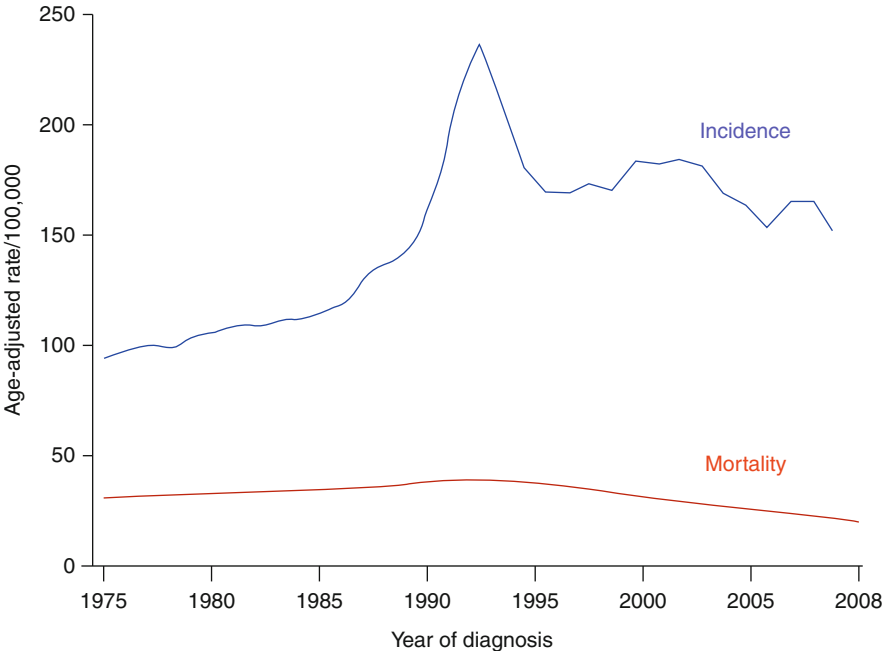

Fig. 39.4 PCa: Changes over time average annual age-adjusted incidence and mortality rates in the United States, 1975–2008 (Based on data from SEER Program)

and metastatic disease was more common in the pre-PSA era [21]. At the start of the PSA screening era, a large spike in the number of PCa diagnoses occurred in the US, with over 1.3 million additional diagnoses of PCa by 2005 compared to rates before 1986 [22]. A similar increased incidence of PCa did not occur in countries and regions where PSA-based screening was less common [23].

Related to the increased incidence of PCa detection, the proportion of men with low-stage PCa increased dramatically in the US at the start of the screening era [24]. When incidence rates are examined by grade, most of the increase in the PSA era was attributable to moderately differentiated tumors, accounting for approximately 80 % of the increase in incidence. Moderately differentiated tumors became the predominant grade of prostate cancer in 1984. A rapid increase in moderate differentiation was observed after 1988. Seventy-six percent of the increase in overall incidence is accounted for by moderately differentiated tumors and 8 % by well-differentiated tumors. Poorly differentiated tumors were more common than well-differentiated tumors after 1991.

Screening

Screening has been advocated as a means of detecting PCa in the early stages, which are amenable to local interventions with curative intent, to decrease overall and disease specific mortality [25]. The long latent period of PCa and its potential curability make this disease an excellent candidate for screening strategies that attempt to find disease in an early curative state.

The ideal screening test is minimally invasive, easily available and performed, acceptable to the general population, accurate, and significantly affects such outcomes of the disease as the mortality rates [26]. In screening, success depends on the capacity of a test to find disease that requires cure, and on its ability to improve disease-specific mortality [27]. While the intention of screening for PCa is to decrease mortality and increase health-related quality of life (HRQL), the true benefit of screening for PCa remains uncertain [28].

Screening for PCa to date has been performed with digital rectal examination (DRE) and PSA testing. Use of the DRE as a screening tool is limited due to poor reliability, sensitivity, and the inability to palpate the entire prostate gland, especially for small tumours that have not reached the prostatic capsule [29]. Most PCas develop in the peripheral zone of the prostate, making them palpable on DRE when sufficiently large. However, palpable cancers are often already advanced in both grade and stage, and are potentially no longer organ confined.

PSA elevations can arise without a palpable abnormality, the opportunity exists to use PSA to find PCa in an early, localized stage. This ability to find early PCas made PSA an interesting biomarker to use for screening for PCa [30, 31]. Despite the ability of PSA screening to find early stage PCa, controversy exists over its ability to save lives. Autopsy studies have shown that even men without a clinical diagnosis of PCa have a large reservoir of asymptomatic disease. Many men die

with, but not of, PCa. A screening test such as the PSA test that cannot differentiate between lethal and non lethal disease allows men with potentially lethal PCa to be diagnosed and treated in the early stages of their disease. However, men with non-lethal disease do not benefit from their diagnosis and subsequent treatment. Such men, in whom PCa was never destined to cause clinical symptoms, are "overdiagnosed", and if they receive treatment, they are "overtreated". Overdiagnosed patients carry the burden of a cancer diagnosis that they would not have received in the absence of screening; overtreated patients suffer the short-term and long-term adverse effects of treatment they did not need. With any screening test there is some element of both of these phenomena; for PSA testing, the low specificity of the test and its inability to distinguish latent from aggressive cancer means that a substantial number of men are overdiagnosed with and overtreated for PCa [27, 32]. Recent data has suggested that the PSA test does not attain the likelihood ratios (i.e. the likelihood of a given test result in a person with the disease compared with the likelihood that the same result would be apparent in a person without the disease) for a screening test, regardless of what threshold value for the PSA is assigned [33].

Population based recommendations for cancer screening should ideally be based on high quality evidence derived from systematic reviews of randomised controlled trials (RCTs) that document a positive impact of screening on outcomes that are the most important to patients [34]. In 2006, a systematic review published in the Cochrane Library concluded that there was insufficient evidence to either support or refute the routine use of mass, selective, or opportunistic screening compared with no screening [28]. This Cochrane systematic review was based on two randomised controlled trials that enrolled 55,512 participants overall but was limited by substantial methodological weaknesses in the design, conduct, and analysis of the included studies. The evidence drawn from this systematic review did not show that screening improved outcomes. By 2010, four additional trials [12, 35–37] enrolling 351,531 participants had been published, thereby providing strong impetus for an updated synthesis of research evidence.

To evaluate the efficacy of PCa screening, two high profile RCTs of PCa screening were published: the Prostate, Lung, Colorectal, and Ovary (PLCO) trial in the United States [36] and the European Randomised Study of Screening for Prostate Cancer (ERSPC) in Europe [12]. They have significantly contributed to our current knowledge and understanding of PCa screening, as well as the difficulties and controversies associated with their ambiguous findings. The ERSPC trial used data from seven centers in different European countries, with a total of 167,387 men undergoing randomization [12, 38]. Slightly different methods and follow-up routines were used in the different countries. PSA cut-off varied from 3 to 4 ng/ml among countries, with rates necessitating further testing ranging from 2.5 to 3.9 ng/ml. With average and median follow-up times of 8.8 and 9.0 years, respectively, there were 214 PCa related deaths in the screening group and 326 in the control group. These data result in an unadjusted rate ratio for death in the screening group of 0.80 (95 % confidence interval [CI], 0.67–0.95; $p=0.01$) and an adjusted rate ratio of 0.80 (95 % CI, 0.65–0.98; $p=0.04$). In other words, to prevent one death from PCa, 1,410 men (95 % CI, 1,132–1,721) would need to be screened and 48

would need to be treated. The ERSPC investigators concluded that PSA based screening reduced the rate of death from PCa by 20 % but was associated with a high risk of over treatment.

In the PLCO trial, 76,639 men at ten US study centers were included in the trial [36]. The incidence of death per 10,000 person-years was 2.0 (50 deaths) in the screening group and 1.7 (44 deaths) in the control group (rate ratio: 1.13; 95 % CI, 0.75–1.70). The authors concluded that after an average 7-year of follow-up, mortality did not significantly differ between the two groups, and therefore, in this study, screening was not associated with mortality (rate ratio: 1.13) [38].

The curves representing the cumulative risk of death from PCa in the ERSPC in comparison with the PLCO study is shown in Fig. 39.5. Visual comparison allows judgment of the differences seen in the two studies. Clearly, the PLCO study does not reach the goal of the original power calculation of identifying a 20 % difference in PCa mortality between screening and control. Reasons for the difference between PLCO and ERSPC are evident from the two publications. ERSPC recruited more than two times as many participants. The average follow-up is 2 years shorter in the PLCO study. A PSA cut-off of 4 was used, and compliance with biopsy indications was low as revealed in [36, 39]. Prior PSA testing occurred in 44 % of men prior to randomization into the study. This has led to a decrease in the number of cancers found in screening. In addition, 53 % of the men in the control group underwent screening. This, considering the 85 % compliance with the PSA testing in the screening arm, leaves only a window of 33 % between the two study arms. On the basis of these characteristics, it is unlikely that the PLCO study will ever contribute to determine the value of screening in lowering PCa mortality [40].

There is currently no evidence for introducing widespread population-based screening programmes for early PCa detection in all men [41]. Based on the results of these two large randomised trials, most if not all of the major urologic societies have concluded that at present widespread mass screening for PCa is not appropriate. Rather, early detection (opportunistic screening) should be offered to the well-informed man. Few organizations support routine PSA screening. The American Urological Association advocates routine PSA screening [42], and its current guidelines, updated after the publication of the PLCO and ERSPC trials, recommend a baseline PSA measurement for men when they reach 40 years of age. This measurement should be followed by tailored surveillance and biopsy based on multiple clinical factors, and no set PSA cut point applies for all patients [42]. By contrast, both the European Association of Urology [43] and the Japanese Urologic Association [44] offer no recommendation for routine PSA screening. The European Association of Urology (EAU) specifically states that its lack of recommendation is due to the large risk of overtreatment of PCa after PSA screening.

National cancer prevention organizations offer at most limited support for PSA screening. The American Cancer Society offers no recommendation for routine testing for PCa with PSA [45] (13.31). They instead advise that patients should be offered the opportunity to make an informed decision about PSA screening based on the potential risks and benefits of the test. The American College of Preventive Medicine also offers no recommendation for screening for PCa [46] (13.32). In the

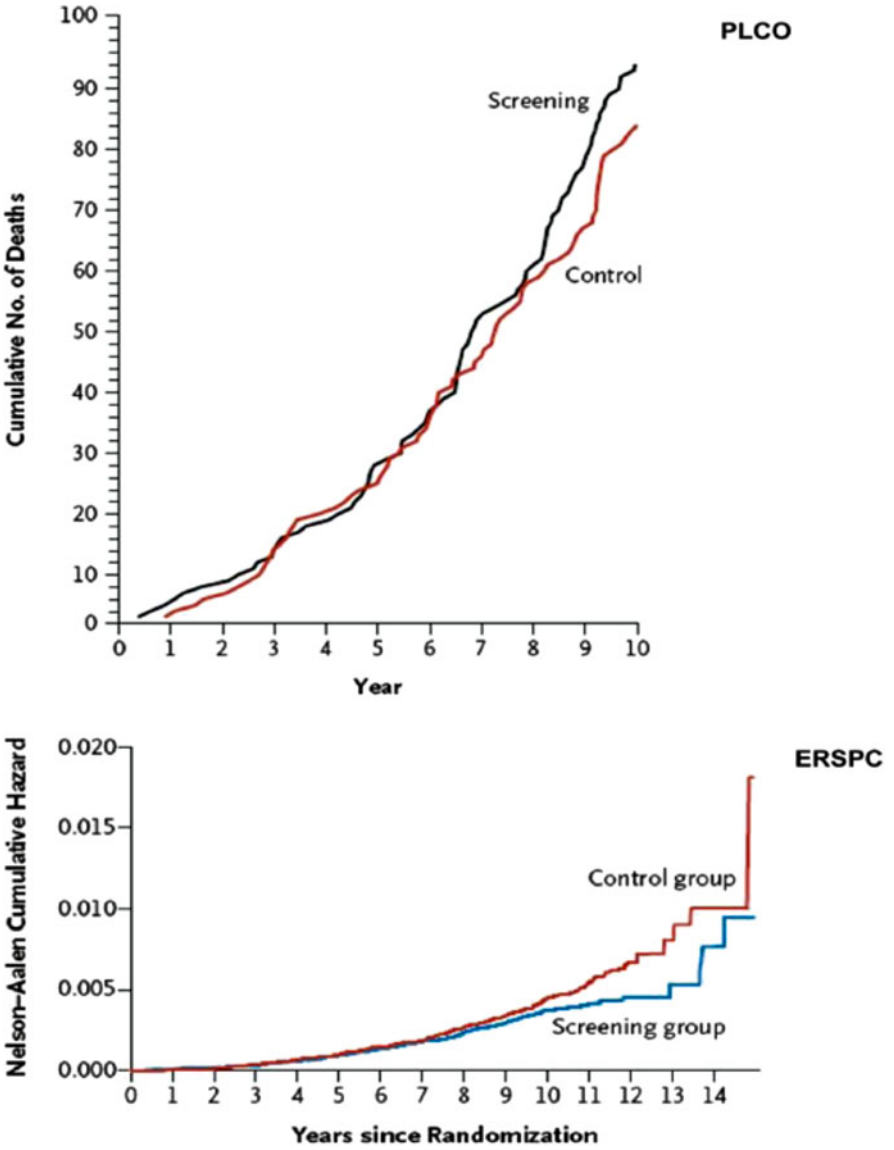

Fig. 39.5 Prostate cancer screening, prostate cancer mortality in PLCO [36], and ERSPC [12] (Based on data from Ref. [12, 36])

UK, the National Health Service (NHS) has no organized screening programme [47]. Finally, the US Preventative Services Task Force specifically recommends against PSA screening. Their guidelines state that screening should not be performed in men older than 75 years, and that the benefits of screening in younger men are uncertain [25].

Given the important tradeoffs between potential benefits and harm involved with either screening or not screening for PCa, and the lack of definitive data on screening outcomes, it is particularly important that patients make informed decisions about undergoing testing. The United States Preventive Services Task Force Guidelines [48], American College of Physicians [49], American Urologic Association [50], American Cancer Society [51], and the Canadian Task Force on the Periodic Health Examination [52] all stress the importance of informed decision making.

The American College of Physicians and the American Cancer Society have provided useful summaries of discussion points to consider when counseling patients about PCa screening [49, 51]:

- PCa is an important health problem; it is one of the most frequently diagnosed cancers in the United States and a leading cause of cancer death in men.
- Men should be involved in making the decision whether or not to be screened.
- PCa screening may reduce the chance of dying from PCa. However, the evidence is mixed and the absolute benefit is small.
- PCa screening is associated with a substantial risk of being diagnosed with PCa. Many cancers detected by screening are considered "overdiagnosed", meaning that they never would have caused problems during a man's lifetime.
- In order to determine whether a cancer is causing an abnormal test, men need to undergo a prostate biopsy. However, the PSA test and digital rectal examination (DRE) can both have false positive and false negative results and prostate biopsies may also miss finding cancers.
- The PSA blood test with or without the DRE can detect cancer at an earlier stage than when cancers are found because they are causing problems.
- Aggressive therapy is necessary to realize any benefit from finding an early-stage PCa.
- Surgery and radiation therapies are the treatments most commonly offered in an attempt to cure PCa; however, they can lead to problems with urinary, bowel, and sexual function.
- No current tests can accurately determine which men with a cancer found by screening are most likely to benefit from aggressive treatment (i.e., those whose cancers are destined to cause health problems). Most men with PCa will die from other causes, many will never experience health problems from their cancer.
- A strategy of active surveillance may be appropriate for men who are at low risk for complications from PCa. This means not immediately treating a cancer but following PSA tests, DRE, and repeating biopsies to determine whether aggressive treatment is indicated because the cancer is progressing.

Clinicians find it challenging to provide comprehensive, consistent, and balanced information about PCa screening decisions during clinic visits [53]. Consequently, efforts have focused on using decision aids to help patients understand screening issues and make informed decisions for screening [54].

Pathology

Adenocarcinoma accounts for the vast majority of malignant growths of prostate. The location they arise from corresponds to McNeal's zones [2]: peripheral (70 %), transitional (20 %), and central (1–5 %). It is multifocal in more than 85 % of cases. The Union Internationale Contre le Cancer (UICC) 2009 TNM classification is used throughout the guidelines [55] (Table 39.1). TNM Classification is also used for the diagnosis and management of prostate cancer.

Table 39.1 TNM classification of prostate cancer

T – *Primary tumour*	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically unapparent tumor not palpable or visible by imaging
T1a	Tumor incidental histological finding in 5 % or less of tissue resected
T1b	Tumor incidental histological finding in more than 5 % of tissue resected
T1c	Tumor identified by needle biopsy (e.g., because of elevated PSA level)
T2	T2 Tumor confined within the prostate
T2a	Tumor involves one half of one lobe or less
T2b	Tumor involves more than half of one lobe, but not both lobes.
T2c	Tumor involves both lobes
T3	Tumor extends through the prostatic capsule
T3a	Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
N- *Regional lymph nodes*	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M- *distant metastasis*	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

Adapted from Ref. [55]

Remarks:

1. Tumor found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c
2. Invasion into the prostatic apex, or into (but not beyond) the prostate capsule, is not classified as pT3, but as pT2
3. Metastasis no larger than 0.2 cm can be designated pN1 mi
4. When more than one site of metastasis is present, the most advanced category should be used

Most of the times PCa is multi-focal. Other histological types include transitional cell morphology, squamous differentiation and neuroendocrine variety. In relation to various parts of prostate, nearly 70 % of cancers arise in the peripheral zone, 15–20 % arise in the central zone, and 10–15 % arise in the transitional zone.

Histological grading by Gleason scoring is unique to PCa. The Gleason score is the most commonly used system for grading adenocarcinoma of the prostate [56]. In 1966, Donald Gleason and colleagues devised a PCa grading system, unique within pathology because of its sole reliance on glandular epithelial architecture.

Cytologic features including nuclear atypia play no role in the grade of the tumor. They correlated these architectural patterns with patient outcome in 270 Veterans Administration patients [57]. Both the primary (predominant) and the secondary (second most prevalent) architectural patterns are identified and assigned a grade from 1 to 5, with 1 being the most differentiated and 5 being the least differentiated. The most prevalent pattern was deemed the primary grade, the second most prevalent pattern was the secondary grade, and the sum of these grades was the Gleason score, ranging from 2 to 10. After this system was validated in 1974 by follow-up mortality data in 1,032 patients [56], Gleason grading became the universal standard for grading PCa. Recently, it was recommended to be of value to report a third most common pattern as a tertiary grade in prostatectomy specimens, and in biopsies if it is the highest grade, to promote it to secondary. According to current international convention, the (modified) Gleason score of cancers detected in a prostate biopsy consists of the Gleason grade of the dominant (most extensive) carcinoma component plus the highest grade, regardless of its extent (no 5 % rule) [56]. In radical prostatectomy (RP) specimens, both the primary and the secondary Gleason grade should be reported. The presence of the tertiary grade and its approximate proportion of the cancer volume should also be reported (Table 39.2) [58].

The Gleason score is essentially a histological finding and therefore can only be assessed using biopsy material (core biopsy or operative specimens). Cytological preparations cannot be used. The Gleason score is the sum of the two most common patterns (grades 1–5) of tumour growth found. The Gleason score ranges between 2 and 10, with 2 being the least aggressive and 10 the most aggressive. In needle

Table 39.2 Gleason grading

Gleason grade	Description
Grade 1 (Fig. 39.6a)	Grade 1 is a rare pattern of very well-differentiated growth of closely packed but separate, uniform, rounded or oval shaped medium sized acinii; often with grade 2
Grade 2 (Fig. 39.6b)	Less well defined with some glandular separation at the edge
Grade 3 (Fig. 39.6c)	Ill-defined infiltrating edges; Glands of varying sizes and shapes
Grade 4 (Fig. 39.6d)	Raggedly infiltrative; fused glands creating masses and cords; smaller or larger glands
Grade 5 (Fig. 39.6e)	Papillary, cribriform or solid masses with central necrosis; Masses and sheets of anaplastic carcinoma

Adapted from Humphrey [58]. With permission from Nature Publishing Group

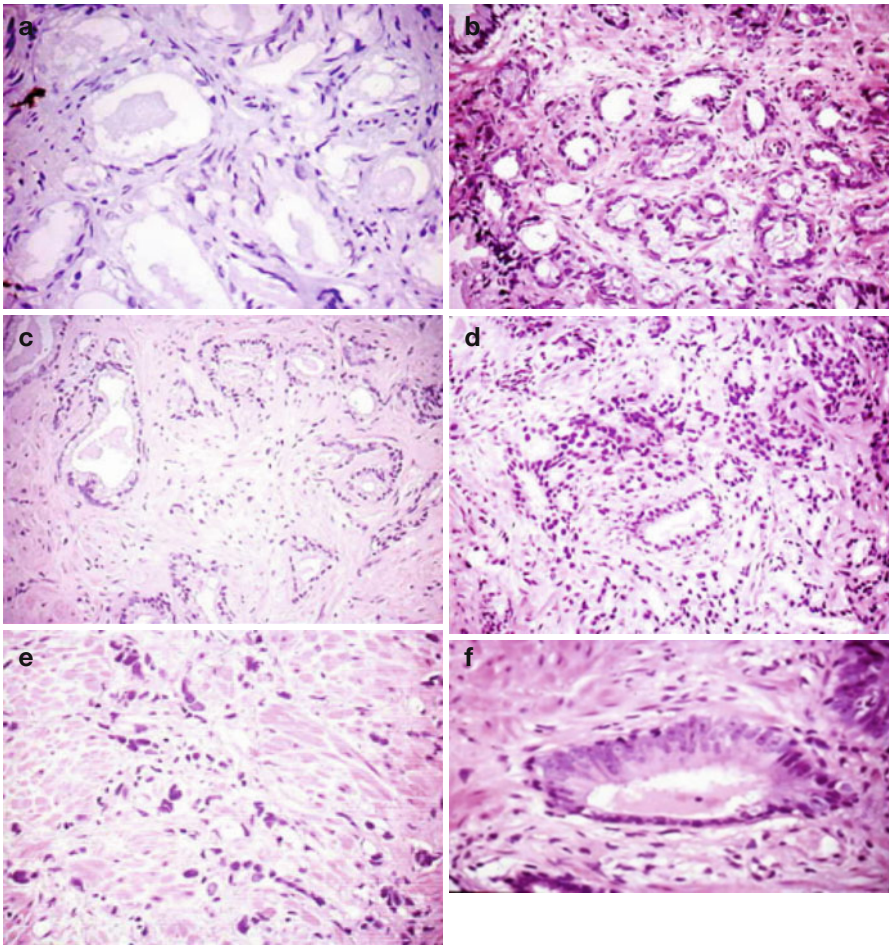

Fig. 39.6 Gleason grading system and High grade PIN [H & E] (**a**): Grade 1, (**b**): Grade 2, (**c**): Grade 3, (**d**): Grade 4, (**e**): Grade 5, (**f**): High grade PIN

biopsy, it is recommended that the worst grade always should be included, even if it is present in < 5 % of biopsy material [59]. For biopsy specimens reported to have cancer, Gleason score is one of the two major considerations for treatment decisions (the other being the volumetric assessment of tumor as described by number and percent of cores involved). Biopsy score also strongly predicts pathologic stage and margin status at prostatectomy [60–62]. Prostatectomy score is the most powerful predictor of progression after treatment.

Prostatic intraepithelial neoplasia (PIN) consists of architecturally benign prostatic acini or ducts lined by cytologically atypical cells. The reporting of so-called low-grade PIN is no longer appropriate, as it does not correlate with malignancy, and PIN should only refer to high grade. There is a significant association between

PIN and malignancy, and its presence on biopsy should prompt a repeat biopsy. The risk of cancer for a patient with PIN on subsequent biopsy is approximately 50 % [63].

More aggressive but rare forms of adenocarcinoma include mucinous adenocarcinoma and prostatic duct adenocarcinoma. They tend to present late due to difficulty in diagnosis because of normal PSA levels and DRE [64]. Other forms of prostate malignancy include transitional cell carcinoma of the prostate without bladder involvement, small cell carcinoma, lymphoma, and sarcoma.

Pathogenesis

PCa shows diverse features in clinical course ranging from an indolent disease to a lethal one. Accordingly, underlying molecular mechanisms and genetic changes involved in the development and progression of various types of PCa are very heterogeneous. Thus, investigation of pathogenesis of PCa is very challenging, and, at this point of time, only a handful of molecular and genetic factors have been identified as pathogenic factors for PCa. Plenty of data support the strong relationship between age, race and family history and the development of PCa. In addition, androgen related factors such as androgen metabolism and receptor signaling are highly correlated with tumor development and progression. There does not appear to be a unique genetic pathway for PCa to occur, and virtually the whole genome participates in the carcinogenesis, suggesting multiple pathways and mechanisms. Numerous genetic or epigenetic changes including gene mutation and methylation contribute to the development and progression of PCa.

PCa often develops very slowly compared with most other cancers and the natural history often spans several decades. However, some cancers grow fast and will give rise to early metastases and death. At diagnosis, it is still difficult to differentiate those PCas that remain indolent and those that will proliferate more quickly. There is no fixed pattern of proliferation; as mentioned earlier, it is often multifocal and usually grows locally. PCa can infiltrate and penetrate the prostatic (pseudo) capsule; often penetration is basal and lateral and continues towards the seminal vesicles or follows the neurovascular bundles [65, 66]. It may spread into regional lymph nodes to finally give rise to distant metastases [67–70]. The risk of lymph node metastasis increases with increased tumour volume and poor histological differentiation [71].

The factors that determine the risk of developing clinical PCa are not well known, although three well-established risk factors have been identified. Older age, race (black), and family history remain the only well-established risk factors and there are no established preventable risk factors for PCa [72]. In the last 20 years, evidence that PCa may be caused by multiple genes, possibly interacting with endocrine and environmental factors, has continued to grow [73–75].

An estimated 9 % of PCa are due to an inherited predisposition [76]. The risk of PCa increases with the number of relatives affected. In men with a first-degree

relative, two relatives, and three relatives affected with PCa, there is a cumulative increased risk of developing PCa of 2.5, 5, and 11-fold, respectively [77]. Hereditary PCa is defined as three or more affected relatives or at least two relatives who have developed early onset disease, i.e. before age 55 [78]. Patients with hereditary PCa usually have an onset 6–7 years prior to spontaneous cases, but do not differ in other ways [79].

The frequency of autopsy-detected cancers is roughly the same in different parts of the world [80]. This finding is in sharp contrast to the incidence of clinical PCa, which differs widely between different geographical areas, being high in the US and Northern Europe and low in Southeast Asia [6]. However, if Japanese men move from Japan to Hawaii, their risk of PCa increases; if they move to California their risk increases even more, approaching that of American men [81].

These findings indicate that exogenous factors affect the risk of progression from so-called latent PCa to clinical PCa. Factors such as food consumption, pattern of sexual behaviour, alcohol consumption, exposure to ultraviolet radiation, and occupational exposure have all been discussed as being of aetiological importance [82]. PCa is an ideal candidate for exogenous preventive measures, such as dietary and pharmacological prevention, due to some specific features: high prevalence, long latency, endocrine dependency, availability of serum markers (PSA), and histological precursor lesions (PIN) [83]. Dietary/nutritional factors that may influence disease development include total energy intake (as reflected by body mass index), dietary fat, cooked meat, micronutrients and vitamins (carotenoids, retinoids, vitamins C, D, and E), fruit and vegetable intake, minerals (calcium, selenium), and phyto-oestrogens (isoflavonoids, flavonoids, lignans). Since most studies reported to date are case–control analyses, there remain more questions than evidence-based data available to answer them. Several ongoing large randomised trials are trying to clarify the role of such risk factors and the potential for successful PCa prevention [84].

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Chapter 40
Clinical Presentation, Diagnosis and Staging

Thomas Hermanns, Cynthia Kuk, and Alexandre R. Zlotta

Introduction

Most patients with prostate cancer are diagnosed nowadays with early localized disease and are either asymptomatic or present with lower urinary tract symptoms related a concomitant benign prostatic hypertrophy (BPH). As most cancers arise in the posterior part of the peripheral zone well away from the urethra, obstructive symptoms are not common in the early stages.

Although most patients with early-stage prostate cancer are asymptomatic, locally advanced disease can lead to obstructive or irritative voiding symptoms that result from local tumor growth into the urethra or bladder neck, extension into the trigone of the bladder, or both. Very infrequently nowadays, patients present first with urinary retention or ureteral outlet obstruction leading to renal insufficiency. Also very rarely, the clinical presentation comprises tenesmus in locally advanced tumours invading the adjacent rectum. At the metastatic stage, prostate cancer most often spreads to bone, commonly leading to bone pain. A small subset of patients develop spinal cord impingement from the epidural spread of disease, resulting in pain and neurologic compromise that, depending on the location of the spinal lesion, could include the loss of bowel and bladder function and the ability to walk. Other common sites of metastatic spread include pelvic lymph nodes, with some patients presenting with progressive lymphedema or upper urinary tract compression.

T. Hermanns, MD
Division of Urology, Department of Surgical Oncology, Princess Margaret Cancer Centre, Toronto, ON Canada

C. Kuk, MSc • A.R. Zlotta, MD, PhD, FRCSC (✉)
Division of Urology, Department of Surgery, Mount Sinai Hospital, University Health Network, 60 Murray St. 6th Floor, Box 19, Toronto, ON M5T 3 L9, Canada
e-mail: azlotta@mtsinai.on.ca

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Incidental Finding of Prostate Cancer

The prevalence of microscopic prostate cancer in the population is much higher than the incidence of the clinically significant disease, which varies more than 100 fold worldwide. The lifetime risk of being diagnosed with prostate cancer for a man in North America is close to 18 %. The prevalence of the disease is much higher, over 50 % from the age of 60, as shown on autopsy studies [1]. Therefore, unsuspected and non-palpable prostate cancer may be detected in cystoprostatectomy and transurethral resection of the prostate (TURP) specimens even when no anomaly at digital rectal examination or abnormal serum Prostate Specific Antigen (PSA) levels are observed before these procedures [2].

Transition zone tumours generally have lower Gleason Scores [3] and are usually small in volume. Most such tumours that are found incidentally could be more likely to be followed by active surveillance rather than being treated nowadays. Depending on the patient age and health status, if a Gleason 6 is unexpectedly diagnosed on a TURP specimen, it may be advisable to suggest prostate biopsies in the peripheral zone to rule out more extensive and aggressive lesions. Very rarely, undifferentiated tumours may present with very low PSA levels. Some men with elevated prostate specific antigen (PSA) levels who are carefully monitored and undergo repeated negative biopsies still develop aggressive prostate cancer. These hidden tumors called PEATS (prostate evasive anterior tumour syndrome) are usually located in the anterior zone of the prostate and demonstrated by MRI as they evade traditional diagnostic procedures, including ultrasound-guided needle biopsy [4].

Hematuria/Hematospermia

Microscopic or frank hematuria may occur as a result of increased vascularity due to carcinoma or associated benign hypertrophy of the prostate. Hematospermia is another recognized manifestation of carcinoma of the prostate but most hematospermia are not caused by prostate cancer [5]. Men presenting with hematospermia in an age group at risk should be offered workup for prostate disease and therefore prostate cancer should be excluded as the cause of it.

Metastatic Prostate Cancer

Prostate cancer initially presenting as metastatic disease is a rare event nowadays in the PSA era. Less than 5 % of prostate cancer patients have distant metastases at the time of diagnosis in North America [6]. The most frequent metastatic sites in prostate cancer are bone (85 %), lymph nodes and visceral metastases (liver, central nervous system, lungs) (45 %). As prostate cancer mostly involves the axial skeleton, patients may present with severe back pain and spinal cord compression. Skeletal metastasis in weight-bearing bones may cause pathological fractures, which can adversely affect prognosis [7].

Paraneoplastic Syndromes

Metastatic prostate cancer may rarely present as a paraneoplastic syndrome. A number of conditions and neurological syndromes including peripheral neuropathy, cerebellar ataxia, and brainstem and limbic encephalopathy have been described in relation to prostate cancer [8].

Signs

Most prostate cancers are diagnosed with patients presenting with no clinical signs. A palpable prostate cancer is felt as an induration on digital rectal examination (DRE). However, with widespread PSA use, most prostate cancers are diagnosed in patients where the disease is not palpable (T1c). Suspicious findings on DRE warrant further assessment with PSA measurement and eventually transrectal ultrasound (TRUS) biopsy. DRE should be done in all men as part of clinical examination, irrespective of PSA levels. In patients with PSA >4 ng/mL with associated abnormal DRE and TRUS findings, the incidence of cancer could be as high as 75 % [9]. However, with a low sensitivity and positive predictive value, DRE performs poorly as a screening test.

Weight loss and anemia may be evident on physical examination in men who have widespread metastasis. An abnormal or rising serum PSA or DRE obtained during workup triggers further evaluation, typically with TRUS-guided biopsy but these tests should be discussed with the patient and not ordered without discussing with them.

Diagnosis of Prostate Cancer

Prostate-Specific Antigen

Serum PSA measurement is routinely proposed for men presenting with prostate-related lower urinary tract symptoms (LUTS), hematuria, or hematospermia. The risks, benefits, and the course of management in relation to various PSA levels should be explained to patients for ethical, medical, and legal reasons. Interpretation of PSA levels (normal or abnormal) and a need for biopsy depends on the urologist treating the patient and clinical findings relevant to that patient. Critics emphasize that PSA testing is an imperfect screening tool because it does not differentiate clinically significant tumors from ones that would never cause harm, and may result in overdiagnosis and overtreatment.

PSA testing is clearly controversial and the subject of heated debates. A government task force recently recommended against such screening, but other groups take a softer stance [10]. The American Cancer Society states that men should not

get a PSA test until they discuss their personal risks and benefits with their doctor [11]. Recently, some authors have argued that if the pre-PSA era rates were present in the modern US population, then the total number of men presenting with M1 prostate cancer would be approximately three times greater than the number actually observed [12].

An individualized screening algorithm using other available pre-biopsy information in addition to PSA level can result in a considerable reduction of unnecessary biopsies and PSA should be used in combination with other parameters rather than alone when deciding to biopsy or not.

Ethnicity

Black men have increased risk of developing prostate cancer and in particular, the aggressive forms. In the United Kingdom, black men have substantially greater risk of developing prostate cancer compared with Caucasian men, although this risk is lower than that of black men in the United States. This UK-based study comparing Black men with Caucasian men found no evidence of differences in disease characteristics at the time of prostate cancer diagnosis, nor of under-investigation or under-treatment in Black men [13–15].

Genetic Variants and Prostate Cancer Risk

There are increasing amounts of data suggesting associations between the presence of specific alterations in the human genome and the presence of cancerous prostate tissue in specific individuals. Indeed, there are well over 20 single nuclear polymorphisms (SNPs) that have now been associated with risk for prostate cancer. Genome Wide Association Studies (GWAS) have confirmed that specific variants mainly on 8q24 and 17q were associated with the prostate cancer risk [16]. The problem, which remains is that each SNP has only a moderate association, although when SNPs are combined, the association may be stronger but very few individuals carry all SNPs.

Interestingly enough, studies carried out in Europe, North America or Asia all confirmed that the 8q24 gene was associated with prostate cancer [17–20]. Variants of the hK2 protein gene (KLK2) and hK3 (PSA) have also been shown to predict the presence of prostate cancer at biopsy [21, 22]. However, most markers have not been prospectively validated for providing useful prognostic or predictive information or improvements upon clinicopathologic parameters already in use. Despite these studies, the US Food and Drug Administration (FDA) has therefore issued letters to companies marketing tests designed to provide consumers with information about their genetic profile and their risks for certain types of disease. The letters basically ask the companies to justify why they are marketing these tests in the absence of data demonstrating their clinical utility.

Novel Biomarkers

Given the lack of specificity and unclear mortality benefit of PSA testing, methods to improve the management of elevated PSA are clearly needed. Several novel biomarkers have been detected and studied in recent years [23]. There is a plethora of promising blood and urine based biomarkers nowadays. Among those biomarkers, the prostate-specific non-coding mRNA marker PCA3 is the most intensively investigated [24]. The PCA3 score is obtained from PCA3 mRNA normalized against PSA mRNA measured in the urine after a prostatic massage. It has been shown that the PCA3 score, integrated into nomograms, can be helpful in the decision of whether to perform a first or repeat prostate biopsy. The higher the PCA3 score, the greater the probability of a positive repeat prostate biopsy [25]. The usual cut-off score is 35. However, a significant association with tumor aggressiveness was not consistently detectable, although higher PCA3 scores seem to correlate with more aggressive disease and adverse pathological outcome at radical prostatectomy [26]. Further large-scale studies are needed to evaluate if PCA3 or any other novel biomarker has the potential to confirm whether this test can predict final pathological stage or treatment outcome.

TMPRSS2:ERG gene fusion has also been found as a promising prostate cancer specific biomarker. Greater than 50 % of PSA-screened prostate cancers harbor fusions between the transmembrane protease, serine 2 (TMPRSS2) and the ER genes. Urine TMPRSS2:ERG, in combination with PCA3, enhances the utility of serum PSA for predicting prostate cancer risk and clinically relevant cancer on biopsy [27]. When combined with PCA3, most of the false-negative results of the PCA3 test were corrected by TMPRSS2:ERG (57 %) and the combination of both had a higher sensitivity for PCa diagnosis [28].

Nomograms/Risk Calculators

Many nomograms and risks calculators have been proposed in the last years. Nomograms are multivariate models based on the clinical and pathological data at presentation calibrated and validated to evaluate their accuracy. Nomograms take a panel of preoperative parameters into account to increase the predictive value of each individual parameter. There are very good data to support adding nomograms to the traditional decision-making process. The first tool to predict prostate cancer risk was the PCPT prostate cancer risk calculator, developed from data collected in the Prostate Cancer Prevention Trial [29].

The Sunnybrook prostate cancer risk calculator (SRC) (http://sunnybrook.ca/content/?page= OCC_prostateCalc), developed by Nam et al. is the second online prostate cancer risk assessment tool that allows a man to assess his risk for prostate cancer in consultation with his primary care physician. In addition to PSA and DRE results, the nomogram is based on knowledge of the following patient characteristics: age, family history of prostate cancer, ethnicity, urinary voiding

symptoms, and free:total PSA ratio. The SRC performed better than the PCPT-RC, but neither one added clinical benefit for risk thresholds of less than 30 % [30].

The European Randomized Study of Screening for Prostate Cancer Risk Calculator (ERSPC-RC), another tool to predict prostate cancer risk, was compared to the PCPT risk calculator in a Canadian population. The ERSPC-RC outperformed the PCPT-RC (ERSPC-RC, AUC = 0.71, PCPT-RC, AUC = 0.63 and PSA, AUC = 0.55), for prostate cancer prediction [31].

The major problem of these different risk calculators and nomograms is the absence of validation across different patient populations and contemporary patients are now sampled by extended biopsy schemes, which differ from that in PCPT, for instance.

Prostate Imaging

Traditionally, imaging has played a relatively minor role in the management of localized prostate cancer, including its detection. TRUS was the only technique reliably used during diagnosis and it was used mainly for guiding biopsies. However, the advent of new modalities including multiparametric MRI, functional MRI and PET, may lead to significant improvements in lesion detection and staging and are likely game changers. Imaging plays an increasingly important role in the detection, localization, and staging of prostate cancer and some argue it may supersede biological markers as first-line detection tool. Indeed technological advances over the past 5 years demand a re-evaluation of the role of imaging, MRI in particular. Some groups propose and investigate an increased use of MRI, not only in those with a diagnosis of prostate cancer but also for men before a prostate biopsy [32].

Transrectal Ultrasound Biopsy of Prostate (TRUS)

Transrectal ultrasonography (TRUS) is an outpatient procedure that requires no sedation or analgesia and is relatively well tolerated by most men. TRUS is not recommended as a primary screening test for prostate cancer because of its low sensitivity and positive predictive value. The main role of TRUS is to provide visual guidance for the needle biopsy. It is not particularly helpful as a tool for local staging of prostate cancer and should not be relied for staging on its own.

TRUS has a limited capacity to identify prostate cancer due to variability in the ultrasonic appearance of cancers and lack of specificity. In addition to biopsying, TRUS guidance is also used in brachytherapy, cryotherapy, high-intensity focused ultrasound (HIFU), and more recently in focal therapy. TRUS is increasingly used to fuse images with MRI, especially for anterior tumours.

Considerations About TRUS Biopsies

An editorial has been recently written urging urologists and physicians to think twice when recommending prostate biopsies [33]. Prostate biopsy, generally considered a safe procedure although beset by rare albeit worrisome major complications, has changed quite dramatically over the past two decades. A sharp increase in the number of biopsies performed as compared to the sextant scheme has taken place with the most extreme schemes (saturation) including over 50 biopsies [34]. This inflation in the number of biopsies has come with a cost. A significant number of cancers very unlikely to ever become life-threatening are diagnosed. This has a profound impact on both patients and their physicians as the best management and course of action for these "indolent" cancers remains unclear at the present time. Despite this increased number of biopsy samples, some clinically significant prostate cancers are still missed.

In addition to the huge burden on our health systems and on patients produced by the detection of so many low risk cancers, prostate cancer biopsies are associated with inherent risks [35]. Because they are performed through the transrectal route, and despite prophylactic antibiotics, the infectious risk associated with them seems to have increased over time. Whether this is due to the increased number of biopsies performed, the liberal use of local anaesthesia, the growing resistance to quinolone based antibiotics, or a combination of these factors is not completely established. What is clear is that when counselling a patient and advising him to undergo prostate biopsies, the risks vs. benefits discussion should not be neglected. As urologists, we should remain on the side of caution as it is easy to become desensitized to the potential risks to our patients.

Contrast Enhanced Ultrasonography (CEUS) of Prostate Cancer

Contrast-enhanced ultrasound (CEUS) is a real-time imaging technique with the capability of visualizing perfusion patterns. Since tumour growth is associated with changes in vascularisation, this modality is under research for imaging of prostate cancer. In four European centres investigating CEUS of the prostate, prostate cancer could be visualized and localized in up to 78 % [36]. Research in refinements of this technology is ongoing.

Elastography

There is basic evidence that the elasticity of prostate tumour and BPH/normal tissue are different. This results in a different colour signal on the screen. The prostate cancer detection rate seems significantly higher in patients who undergo biopsy with the real-time elastography guided approach compared to the gray scale ultrasound

guided biopsy at 51.1 % vs. 39.4 % [37]. Overall sensitivity and specificity to detect prostate cancer is around 60 and 70 % for real-time elastography compared to 44 and 92.3 % for gray scale ultrasound, respectively. However, its suboptimal sensitivities and specificities around still limit the widespread use of elastography.

Magnetic Resonance Imaging of the Prostate

Magnetic resonance imaging (MRI) is fast becoming a multipurpose imaging modality and might soon change the way we think and diagnose prostate cancer. MRI has been used to evaluate prostate anatomy and prostate diseases since 1982. MRI-compatible robotics for prostate biopsies is currently evaluated around the globe. MRI is able to provide detailed anatomical images, particularly of soft tissues, at high spatial resolution, and when combined with the ability to provide functional measurements has lead investigators to extensively explore the role of MRI in diagnosis and staging of prostate cancer. Different sequences (the manner in which the magnet creates pulses and interfaces with the data collected) have been manipulated and even combined to give the greatest information (e.g. contrast-enhanced imaging combined with magnetic resonance spectroscopy).

Multiparametric MRI is also increasingly used to rule out clinically significant prostate cancer.

Magnetic Resonance Spectroscopy (MRS)

Magnetic resonance imaging and magnetic resonance spectroscopy imaging (MRI + MRSI) holds great potential for predicting the presence or absence of high-grade tumors in men with elevated PSA. MRS is an advanced form of MRI in that it uses the property of hydrogen ions known as chemical shift. The MRI uses strong magnetic fields to induce spinning of hydrogen protons, generating a map of proton signal intensity. The hydrogen protons in different molecules have different frequencies—the chemical shift. The main advantage of MRS is supposed to be its increased staging accuracy for less experienced readers and reduction of interobserver variability [38].

Indications for TRUS-Guided Prostate Biopsy

PSA

Serum total PSA (tPSA) levels 4.0 ng/mL have been traditionally considered as an indication for biopsy since 1990 but ironically this cut-off was based on an extremely limited series [39]. Which PSA cut-off to use when deciding to biopsy is still much debated although there is growing evidence to suggest that there is

no definite cut-off point for PSA as a significant number of men with PSA values below the level of 4 ng/mL (or whatever cut-off would be chosen) has prostate cancer. In the Prostate Cancer Prevention Trial (PCPT), Thompson et al. [40] found an incidence of 15 % in men with PSA levels below 4.0 ng/mL and 15 % of these men had Gleason scores of 7 or higher. Similar findings were noted in the European Randomized Study of Screening for Prostate Cancer (ERSPC), which originally adopted 4.0 ng/mL as a threshold PSA level for biopsy. It is now reduced to 3.0 ng/mL. In other studies on men with a tPSA range of 2.6–4 ng/mL, the incidence of cancer was 25 % [41, 42].

Abnormal Digital Rectal Examination

As already mentioned, an abnormal nodule/area on the prostate should be considered as an important indication for biopsy even if the PSA is within normal limits. The role of DRE was investigated in the Rotterdam arm of the large ERSPC trial. At initial and subsequent screenings, the chance of having cancer at biopsy was higher in men with a suspicious DRE compared to men with a normal DRE. At initial screening, the positive predictive value of a suspicious DRE, in conjunction with an elevated PSA level, to detect PC was 48.6 % compared to 22.4 % for men with a normal DRE. Interestingly, an abnormal DRE was associated with a significantly increased risk of very high-grade disease during all screening rounds, indicating that it provides useful additional prognostic information. This study adds to a considerable body of evidence supporting a role for DRE in early detection of prostate cancer [43].

The role of DRE has been assessed in conjunction with risk calculators (RC) and it was suggested that RC should contain volume estimates based either on TRUS or DRE to improve their usefulness [44]. DRE therefore is of utmost importance no matter what PSA level is considered.

Repeat Biopsies for Prostatic Intraepithelial Neoplasia or Atypical Small Acinar Proliferation

The recognition of high-grade prostatic intraepithelial neoplasia (HGPIN) is clinically important because of its strong association with prostatic adenocarcinoma. The predictive value for cancer of an initial diagnosis of HGPIN on needle biopsy has substantially declined compared to initial reports 15 years ago. Historically, HGPIN usually prompted repeat biopsies within 6 months, but values nowadays have fallen from 36 to 21 %. A major factor contributing to this decline is related to the increased use of needle biopsy core sampling, which has provided the means for many cancers associated with HGPIN to be detected on initial biopsy. Repeat biopsy, even with good sampling, does not detect many additional cancers [45]. HGPIN was followed by prostate cancer on repeat biopsy in 16.8 % of patients, and atypical small acinar proliferation (ASAP) in 26.7 % [46].

Table 40.1 Saturation biopsies studies in patients undergoing re-biopsy

Author	Year	N° pts	PSA (mean; ng/ml)	N° cores	Cancer detection rate (%)
Borboroglu et al. [48]	2000	57	8.6	22.5	30
Stewart et al. [49]	2001	224	8.7	23	34
Fleshner and Klotz [50]	2002	37	22.4	32–38	13.5
Rabets et al. [51]	2004	116	9.2	22.8	29
Patel et al. [52]	2004	100	9.4	20–24	25
Pinkstaff et al. [53]	2005	210	13.6	21.2	37
Walz et al. [54]	2006	161	9.4	24.2	41

Adapted from Scattoni et al. [34]. With permission from Elsevier

Whereas ASAP is still considered as a factor that should prompt repeat biopsies, this is not the case of HGPIN anymore. Patients with HGPIN on first biopsy should be managed independently of this finding, according to other risk factors. The term ASAP was originally used by Iczkowski et al. [47], and it refers to minute tumor foci, a small lesion that disappears in other sectioning levels, or the absence of categorical cytological criteria for establishing the diagnosis of carcinoma. It is not consensually used.

Age-Adjusted PSA Levels (See Table 40.1), Free PSA, PSA Density, PSA Density of the Transition Zone and Other PSA Parameters

As PSA has a sensitivity of about 21 % only and a specificity of 60–70 % at the cut off 4 ng/mL, any avenues have been explored to improve its sensitivity. These include a lower cut off, age-specific or age-adjusted PSA, PSA density (PSAD), PSAD density transition zone (PSA-TZ), PSA velocity (PSAV), free PSA/ total PSA, % free PSA and various PSA molecular forms [55].

Percent-Free PSA

PSA occurs in two major forms in the blood. One form is attached to blood proteins while the other circulates free (unattached). The percent-free PSA (fPSA) is the ratio of free PSA circulates compared to the total PSA level. Percent free PSA has been demonstrated to improve PSA usefulness both in the grey zone (PSA 4–10 ng/ml) and from 2.5 to 4 ng/ml [56]. The recommended cut-off to recommend prostate biopsies is 10 % or less, although men should be cautious if it is between 10 and 25 % as this is considered the grey zone. The major problem of free PSA is that its value is influenced by prostate volume and associated prostatitis. Furthermore, the cut-off of 25 % is far from being universally agreed upon.

PSA Density

PSA levels are higher in men with larger prostate glands [57]. The PSA density (PSAD) is sometimes used for men with large prostate glands to try to adjust for this observation. The classical cut-off is 0.15 ng/ml/cc. PSA density has not been shown to be as useful as the percent-free PSA test in clinical practice although it is integrated sometimes in risk calculators.

PSA Density of the Transition Zone

PSA adjusted for transition zone volume (PSA density of the transition zone) has been shown to be more accurate than the prostate-specific antigen density in distinguishing prostate cancer from benign prostatic hyperplasia in men with intermediate serum prostate-specific antigen of 4.1–10.0 ng/mL, from 2.5 to 4 ng/ml and in men with initial negative biopsies. Limitations to its widespread use include the variability of the transition zone measurement by TRUS [56, 58, 59].

Age-Specific PSA Ranges

PSA levels are normally higher in older men than in younger men, even when there is no cancer. This is because a major source of PSA leakage comes from the transition zone of the prostate which enlarges as men age. However, due to the usefulness of age-specific PSA ranges is not well proven, most authors do not recommend their use at this time outside of being integrated in risk calculators or nomograms.

PSA Velocity

PSA increases more rapidly in men with prostate cancer than in healthy men. The Baltimore Longitudinal Study of Aging (BLSA) found that men with a PSA rate of change (PSA velocity) greater than 0.75 ng/mL/year were at an increased risk of being diagnosed with prostate cancer and that PSA velocity was more specific than a 4.0 ng/mL PSA cutoff (90 versus 60 % specificity). The study results, though, were based on analyzing the banked serum of only 18 cancer cases, PSA velocity and its cut-off [60].

Data from the Rotterdam arm of the ERSPC trial found that PSA velocity was significantly higher in men with prostate cancer than in men with a negative biopsy (0.62 vs. 0.46 ng/mL/year). However, PSA velocity did not independently predict cancer after adjusting for PSA level [61].

Repeat TRUS Biopsy

Urologists are frequently faced with the dilemma of treating a patient with a high index of suspicion for prostate cancer, but with an initial set of negative biopsies. Negative biopsy does not ensure the absence of disease [62]. Whatever parameter is used to determine the need for a repeat biopsy, it is important to have a look at first the initial biopsy. Factors to consider include the location and number of cores taken as well as the size of the prostate.

If the prior negative biopsy was a sextant scheme, the cancer detection rate may be as high as 39 % with a repeat extended biopsy, whereas if the prior negative biopsy was an extended scheme, the cancer detection rate is usually much lower between 15 and 30 %. Saturation biopsy techniques and transperineal templates have also been proposed but supplanted nowadays by imaging techniques like MRI [34]. The variability in cancer detection rates does not justify its invasiveness (Table 40.1). Others have proposed up to 21 biopsies in previously negative biopsies [63].

Prostate Biopsy After Radiotherapy

Post-radiotherapy (RT) prostate biopsies are likely to pose problems in histological interpretation. False negatives due to sampling error, false positives due to delayed tumour regression, and indeterminate biopsies showing radiation effect in residual tumour of uncertain viability are common occurrences [64]. However, with very experienced uro-pathologists, these limitations can be minimized.

Predictors of a Positive Biopsy

The main aims of the TRUS biopsy are not only to diagnose prostate cancer but also to determine its aggressiveness. This is especially true at a time of increased complication risks after TRUS biopsies and with the dilemma posed by low volume, low grade prostate cancer. Nomograms are often used to predict the likelihood of a positive biopsy and several have now incorporated more extended biopsy schemes in their calculations, including for repeat biopsies [65].

Prostate Biopsy Technique

Transrectal ultrasound (TRUS)–guided biopsy is the preferred method except in patients who had the rectum and anus excised, in which case the biopsy is performed by the transperineal route. TRUS is carried out by using a 5- to 8-MHz

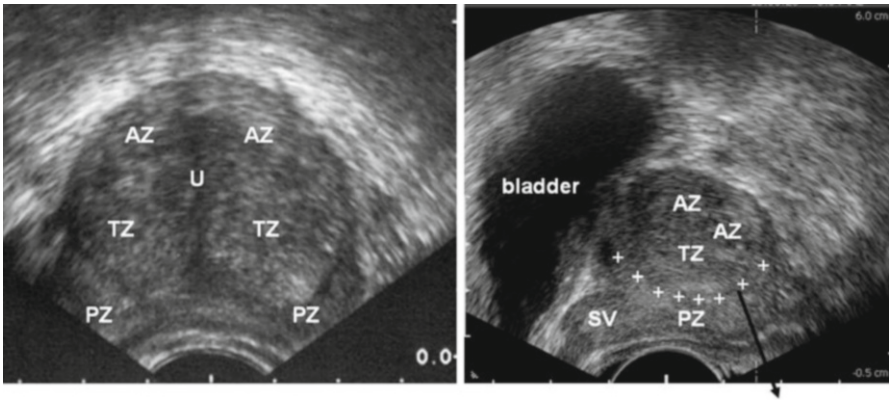

Fig. 40.1 Transverse and sagittal view of prostate during Ultrasound. *AZ* anterior zone, *U* urethra, *TZ* transitional zone, *PZ* peripheral zone, *SV* seminal vesicles

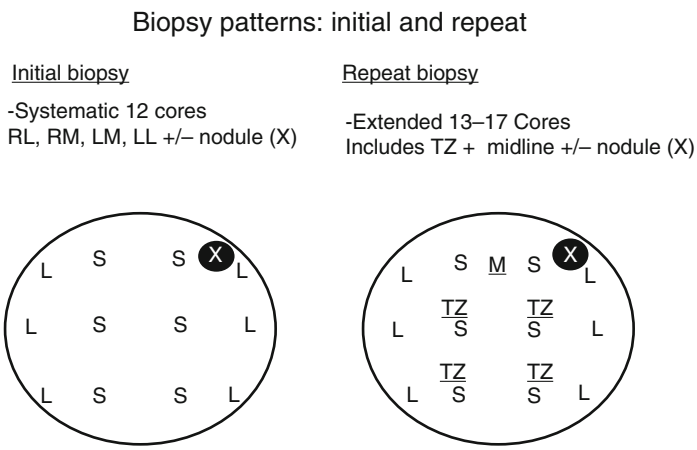

Fig. 40.2 Initial and repeat biopsy schemes at UHN, Toronto (Courtesy of Dr. Ants Toi, University Health Network, Toronto, Canada)

handheld high-resolution probe with capabilities of sagittal and transverse (coronal) imaging (Fig. 40.1). A disposable adaptor is fitted on the probe that will direct the biopsy needle into various regions of the prostate as guided by ultrasound imaging. Currently, extended schemes consisting of at least 10–12 biopsies including lateral biopsies, but without transition zone biopsy, is now considered as the diagnostic gold standard (Fig. 40.2). Some authors have argued that more extended schemes minimize the risk of missing an aggressive disease but this remains debated [66]. Extended schemes decrease the grade discordance between biopsy and prostatectomy specimens but increase the risk of detecting insignificant prostate cancer.

Principles of the TRUS Examination

Informed Consent

Alternatives, consequences, and complications of biopsy are discussed prior to the procedure. Patients should have clear directions in dealing with the complications of a TRUS biopsy, including risk of hospitalization and sepsis.

Antibiotic Prophylaxis

Oral aminoquinolones in the form of ciprofloxacin or norfloxacin are sufficient in uncomplicated cases but cases of resistance to quinolones are the source of increasing concern. It is important for centers to be aware of local microbiological trends and antibiotic resistance. Standard rectal swabs are not performed beforehand and there are logistical difficulties in trying to do them, however, with infection rates rising, the findings of rectal swabs may become more and more important in the future. Patients with cardiac valve problems should receive intravenous antibiotics although this is not universally agreed upon. Meropenem should be considered for post-biopsy urosepsis [67].

Anticoagulation

These medications are discontinued for several days prior to the biopsy although aspirin can be continued. In high risk patients, hospitalization and parenteral heparin cover may be necessary.

Digital Rectal Examination

Digital rectal examination should be performed prior to the biopsy to make sure that rectum is empty and to rule out rectal pathology. In some centers, an enema is routine prior to TRUS biopsy. In addition, DRE will help to note any abnormal areas in the prostate and the presence of a nodule. These areas are included in the biopsies.

Pain Relief

Patients feel pain and discomfort because of the ultrasound probe and needle passage through the prostate gland, particularly below the dentate line in the anorectum [68]. Patients also experience considerable psychological stress because of the fear of impending cancer diagnosis. The pain induced during the procedure can lead to contraction of pelvic floor muscles causing exacerbation of pain. Periprostatic infiltration with 1–2 % lignocaine significantly decreases the pain during the procedure [68].

Biopsy

The anatomy of the prostate, bladder, seminal vesicles, and ampulla of vas is examined for asymmetry and distortion. This is followed by examination of the prostate for abnormal shadows, hypoechoic areas, erosion of capsule, and volume measurement. The gland is scanned in both the sagittal and coronal planes. The width of the prostate is measured in the axial (coronal) plane and the length of the prostate is measured in the sagittal plane, including the transition zone of the prostate. Most of the TRUS machines have the capability for calculation of volume.

The zonal anatomy of the prostate is described in Chap. 39. As 70 % of cancers occur in the peripheral zone and nearly 25 % occur in the central zone, biopsies of the posterior part of the prostate seem logical, and for biopsy purposes, the prostate gland can be divided into base, midregion, and apex. The transition zone is included in repeat biopsies. The needle tip is placed near the region of the intended biopsy and the gun is fired to get the sample. The length of the biopsy core also determines the detection rate, particularly at the apex, with a longer core giving higher detection rates. Each core is sent to the laboratory in a separate container properly libelled for histological diagnosis.

Role of Transition Zone Biopsies

In men with previously negative biopsies, TRUS-guided TZ biopsy should be done to exclude the cancer. Also with the increasing use of MRI and fusion MRI and TRUS, the TZ may be specifically targeted. There is no demonstrated role of TZ biopsies on the initial biopsies though.

Role of Real-Time MRI-TRUS Fusion for Guidance of Targeted Prostate Biopsies

The current biopsy process is blind, involving 12 or more random needle samples but new technology such multi-parametric magnetic resonance imaging (MRI) coupled with transrectal ultrasound (TRUS) guided biopsy (called fusion technology) can accurately identify men with prostate cancer who are at risk of developing aggressive disease or target lesions not identified on TRUS examination, often in the anterior zone of the prostate [69–71].

Complications

Transrectal guided prostate biopsy is not without risks and complications. Taking more biopsy cores does not necessarily increase the complication rates [72]. Most of the following complications are minor and self-limiting but can cause considerable

anxiety to the patients. Bleeding: urethral bleeding/hematuria (35 %), hematochezia (9 %), and hematospermia (5 %) are usually self-limiting and do not need any active treatment. Infections: prostatitis, epididymitis, and septicemia; sepsis is the most dangerous complication as it can be life-threatening in elderly patients. Outflow symptoms: painful micturition. Urine should be tested for infection and appropriate antibiotics usually improve symptoms. Urinary retention could be precipitated by the biopsy due to hemorrhage and edema. Catheterization is done to relieve the obstruction and a trial removal can be done a couple of days later.

Staging Investigations

Prostate cancer spreads locally within its zones and into the ejaculatory ducts, seminal vesicles, and neurovascular bundles. Distal spread includes lymphatic (to internal iliac lymph nodes) and hematogenous routes to bones, lungs, and other organs. The bony metastasis involves bones of the axial skeleton. Visceral metastasis is rarely seen in newly diagnosed patients and rarely seen even in patients dying of prostate cancer [73].

For clinical staging the extent of the prostate cancer is assessed by DRE, PSA, TRUS, and Gleason histological grading. For example, in patients with stage T1c or less disease with a total Gleason Score of 6 and a PSA of less than 10 ng/mL, no further staging investigations would be required unless there is a specific indication, like symptoms [74]. Selective cross-sectional imaging modalities like computed tomography (CT), MRI and bone scan help to assess the extent of spread and are mainly performed for the following reasons:

1. To determine lymph node status in high-risk patients as well as bone metastases
2. Apical disease to guide for surgical management
3. Suspected locally advanced disease
4. Prior to radiotherapy

The risk of metastasis can be quantified by PSA levels, number of positive cores and clinical and TRUS biopsy findings. Noteworthy, in contemporary patients with PCa, the accuracy of CT scan as a preoperative nodal-staging procedure is poor, even in patients with high risk of lymph node involvement [75].

Magnetic Resonance Imaging for Prostate Cancer Staging

Magnetic resonance imaging has a number of advantages over CT in prostate cross-sectional imaging. It helps in the detailed evaluation of prostatic, periprostatic, and pelvic anatomy and therefore mostly is used as a staging study in men with biopsy-proven prostate cancer. T1 corresponds to haemorrhage, lymph nodes, bone

metastasis, short T1 inversion recovery investigates bone metastasis, T2 defines prostate structure, tumour and capsule. Importantly, it is recommended to wait 3 months after prostate biopsies before performing MRI of the prostate (for local staging purposes) as biopsy induces artefacts.

MRI findings in extracapsular extension include a focal irregular capsular bulge, asymmetry or invasion of neurovascular bundles, and obliteration of rectoprostatic angle [76]. The sensitivity of MRI for SV involvement is unfortunately extremely variable (from 20 to 80 %) whereas its specificity is much better, over 80 %.

Bone Scan

Serum PSA levels can predict the results of radionuclide bone scan in newly diagnosed patients. In patients with a PSA of <20 ng/ml and no bony pain, the likely chance of bony metastasis is less than 0.3 %. In 853 consecutive patients diagnosed with prostate cancer between 2003 and 2008 at a single centre who all underwent bone scan using technetium Tc at diagnosis, results confirmed that staging bone scans might be considered only for patients with a biopsy Gleason Score >7 or with a PSA >10 ng/ml and palpable disease (cT2/T3) prior to treatment [77].

PET/CT

Molecular imaging techniques, such as positron emission tomography (PET), may be of help in prostate cancer management and staging. PET can be combined with CT (PET/CT) to produce high-resolution images. Positron emission tomography, a functional imaging test uses a small amount of radioactive material to reveal how tissues and organs are functioning. The most commonly used PET tracer, Fluorodeoxyglucose presents limitations in imaging prostate cancer patients because most prostate cancers are not very ^{18}F-FDG avid, therefore, several alternative PET tracers either Choline (^{11}C) or Citrate have been proposed to evaluate by PET these patients, with promising results.

Recent studies have suggested that ^{11}C PET/CT fusion scans can be utilized as a staging tool in prostate cancer. Metabolite level measurements in normal prostate tissue demonstrate that glandular cells of the prostate tissue contain 10–60 higher citrate level than any cells in the human body.

A ^{11}C PET scan involves the IV injection of a small amount of ^{11}C. Clinicians then use a scanner and computer to make detailed pictures of areas where the ^{11}C collects. Since cancer cells, because of rapid cytokinesis, take up more ^{11}C than normal cells, high choline levels are found on functional imaging. In contrast, tumour cells need increased energy and citrate oxidation leads to low citrate levels. ^{11}C-acetate PET may be valuable in the early evaluation of prostate cancer relapse (See Table 40.2).

Table 40.2 Different imaging techniques for Prostate Cancer diagnosis and staging

	Diagnosis (D)/Staging (S)	Staging local (L)/ distant (D)	Sensitivity[a] (%)	Specificity[a] (%)	Strength	Estimated impact in the future[b]
Ultrasound						
(a) TRUS	D (S)	L	44–90	30–74	BG (CD/ CE)	++
(b) Doppler US	D (S)	–	27–92	46–84	CD	+
(c) CEUS	D	–	40–93	79–87	CD (CE)	+
(d) 3D ultrasound	D (S)	L	38–88	57–80	CD/CE	+
(e) Elastography	D	–	60–90	70–76	CD	+
CT	S (D)	D (L)	–	–	LM/BM	++
MRI	S (D)	L / D	50–97	58–87	BG/CD CE/LN	+++
PET	S (D)	D/L	70–100	57–62	CD/LN/ BM	++
Bone scan	S	D	–	–	BM	++

TRUS transrectal ultrasound, *US* ultrasound, *CEUS* contrast enhanced ultrasound, *3D* three-dimensional, *CT* computed tomography, *MRI* magnetic resonance tomography, *PET* positron emission tomography, *BG* biopsy guidance, *CD* cancer detection, *CE* cancer extension, *LN* lymph node metastasis, *BM* bone metastasis

[a]For prostate cancer diagnosis

[b]+ low, ++ intermediate, +++ high estimated impact

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Chapter 41
Expectant Management of Localized Prostate Cancer

Maria Carmen Mir and Andrew J. Stephenson

Rationale for Expectant Management

In 2014, an estimated 233,000 men in the United States will be diagnosed with prostate cancer, the majority of whom will be diagnosed by opportunistic PSA screening [1]. Since the PSA test was made commercially available in the late 1980's, the incidence rate of prostate cancer has increased by roughly 33 % (from 120 to 160 per 100,000 population) and a man's lifetime risk has more than doubled (from 7.3 % in 1975 to 18 % in 2012) [1]. PSA screening preferentially detects cancers of low-grade and low-stage that may pose a limited threat to a man in terms of longevity and quality-of-life. As a result, the majority of men diagnosed with prostate cancer have low-risk tumors, defined as PSA <10 ng/mL, biopsy Gleason score 2–6, and clinical T2a or less [2].

Estimates from the European Randomised Screening Trial for Prostate Cancer and the U.S. Surveillance, Epidemiology, and End Results (SEER) registry indicate that 25–50 % of cancers detected through screening represent over diagnosis, defined as tumors that would have gone undiagnosed over a man's lifetime in the absence of screening [3, 4]. In older men, prostate cancer is ubiquitous, as approximately 60–70 % of men dying from non-prostate cancer causes will have histological evidence of prostate cancer in autopsy series [5]. While a 35 % reduction in prostate cancer-specific mortality in the U.S. has been observed since the early 1990's (of which 45–70 % may be attributable to screening) [6], it is estimated that the vast majority of excess men diagnosed as a consequence of opportunistic PSA testing

M.C. Mir, MD
Department of Urology, Cleveland Clinic, Cleveland, OH, USA

A.J. Stephenson, MD, FACS, FRCS(C) (✉)
Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH, USA
e-mail: stephena2@ccf.org

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were over-treated and did not benefit from early detection [7]. The issue of over-treatment is particularly relevant for prostate cancer as all treatments (surgery and radiation therapy) may negatively impact urinary, bowel, and sexual function (even when performed at high-volume hospitals), each is associated with a small but definable risk of treatment-related mortality, and many men will live decades with the sequelae of the treatments they have received [8]. The issues of over diagnosis and over-treatment were largely behind the recent U.S. Preventive Services Task Force's grade D recommendation for PSA screening, indicating that there is a moderate-to-high certainty that the screening has no net benefit or that the harms outweigh the benefits [9].

While a strong rationale can be made that the majority of men diagnosed with screen-detected prostate cancer do not need immediate radical therapy (particularly for those with life expectancy <10–15 years due to advanced age and/or comorbid medical illness), the vast majority of American males receive some form of definitive local therapy. Data from the combined, linked SEER-Medicare registry of men over 65 years of age suggest that 75–84 % of elderly men diagnosed with localized prostate cancer receive surgery or radiation therapy [7, 10]. Expectant management rates for men with low-risk prostate cancer in the CaPSURE registry are only 6–8 % and these rates appearing to be decreasing over time [11, 12]. Similarly low rates of surveillance among low-risk patients has been reported from high-volume, academic centers [13, 14].

It is likely that both patient- and physician-related factors have contributed to the low utilization of expectant management for prostate cancer in the United States, such as anxiety and loss of control for the patient, and financial disincentives and medicolegal concerns for the physician. One of the major factors that has contributed to the low acceptance of this approach is concern by the patient and physician that the threat a cancer poses to an individual may be underestimated by the PSA, clinical stage, biopsy Gleason score, and other information from the diagnostic biopsy (e.g. number of positive and negative cores, percentage of cancer within the biopsy specimens). Data from conservatively-treated patients from the pre-PSA era have suggested rates of prostate cancer-specific mortality at 15 years of 20–25 %, 65–75 %, and 80–90 % for men with biopsy Gleason score 6, 7, and 8–10 cancers, respectively [15]. As such, expectant management has largely been restricted to those with a high probability of indolent cancer (defined as tumor volume <0.5 cc, absence of Gleason pattern 4, and no evidence of pathologically advanced cancer features such as extra-prostatic extension or seminal vesicle invasion) as these features are associated with cancers detected at autopsy and, with exceedingly rare exceptions, all these men are cured by radical therapy [5, 16]. Various clinical criteria and nomograms have been developed to predict which men have a high probability of having indolent prostate cancer for whom expectant management is a safe approach [17–20]. However, fewer than 15 % of patients from screening and surgical series meet pre-treatment criteria for indolent prostate cancer [21–23], and thus likely under-estimate the proportion of men who may be eligible for active surveillance.

For various reasons, the outcomes of conservatively managed patients from the pre-PSA era may not be applicable to contemporary patients to determine who should and should not be considered for expectant management. First, PSA screen-

ing is associated with a lead-time of 5–12 years in the diagnosis of prostate cancer [24]. Second, patients treated in the pre-PSA era may not have been appropriately staged at diagnosis as bone scintigraphy and computed tomography (CT) imaging were in their infancy and many of these men may have had metastatic disease at diagnosis. Third, many of these men were diagnosed by TURP (which largely samples the transition zone) and thus index tumors that largely develop in the peripheral zone may not have been adequately sampled. Lastly, substantial changes to the Gleason scoring system have taken place which culminated in a modification of the Gleason scoring system such that many tumors of lower grade in years past would now be classified as high-grade cancers [25, 26].

In summary, the rationale for expectant management of localized prostate cancer is based on the fact that the majority of men with prostate cancer will die with their disease rather than from their disease; estimates from various sources suggest the number of men needed to be treated to prevent one prostate cancer death ranges from 18 to 48 [7, 27, 28]. As treatment may be associated with important impacts on quality-of-life, an observational strategy has the potential to reserve treatment for those who it need and avoid unnecessary treatment for those that do not, thus preserving quality-of-life without compromising survival.

Expectant Management: Watchful Waiting vs. Active Surveillance

Expectant management of prostate cancer may take one of two forms: watchful waiting and active surveillance. Watchful waiting involves less intensive monitoring with periodic clinical assessment with or without PSA testing and imaging where treatment (usually in the form of androgen deprivation therapy) is typically administered with palliative intent for symptomatic local or systemic progression. Active surveillance involves intensive monitoring with PSA testing and surveillance prostate biopsies at periodic intervals and intervention with curative intent is recommended when evidence of more important cancer is detected (either cancer of higher grade, increasing cancer burden on biopsy or prostate exam, or changes in PSA). It is anticipated that the risks of clinical progression and prostate cancer-specific mortality will be less with an active surveillance strategy compared to watchful waiting (though the probability of receiving radical treatment will be higher). As such, active surveillance has emerged as the preferred observational strategy by clinicians and patients for those with life expectancy >10 years who would otherwise be candidates for definitive local therapy.

Watchful Waiting

The rationale behind watchful waiting is the observation that localized prostate cancer often progresses slowly and relatively few men with life expectancy <10 years due to advanced age and/or comorbid illness will suffer symptoms or die from

prostate cancer over their anticipated life expectancy. As mentioned, watchful waiting has been the most frequently used observational strategy in the past but currently favored only for those with limited life expectancy. While watchful waiting may be associated with a lower probability of treatment and higher cost compared to active surveillance, it may also be associated with higher risks of prostate cancer mortality (though this has yet to be proven).

The strongest evidence in favor of expectant management is for watchful waiting, and this comes from two randomized trials of radical prostatectomy vs. watchful waiting, one from a cohort of men with clinically-detected prostate cancer and the other from a cohort with screen-detected prostate cancer [29, 30]. Scandinavian Prostate Cancer Group-4 (SPCG-4) randomized 695 men with clinically-detected prostate cancer (only 5 % of whom were diagnosed as a consequence of PSA screening) between 1989 and 1999 and reported a statistically significant 6.6, 6.1, and 11.7 % absolute reduction in all-cause mortality, prostate cancer-specific mortality, and distant metastasis, respectively among men treated by radical prostatectomy versus watchful waiting at a median follow-up of 15 years [29]. What is notable from this study is that, theoretically, only 12 % of men benefited from radical prostatectomy in terms of preventing distant metastasis or death from prostate cancer death and 88 % were treated unnecessarily; 22 % developed metastasis despite therapy and 66 % did not experience clinical disease progression. In terms of local progression (defined as biopsy-proven local recurrence in the radical prostatectomy arm and palpable transcapsular tumor growth or with symptoms of urinary obstruction that necessitated intervention in the watchful waiting arm), the difference in the absolute risk reduction associated with radical prostatectomy after 10 years was 25 % (19 % vs. 44 %), corresponding to a relative risk with radical prostatectomy of 0.33 (95 % CI: 0.25–0.44) [31].

In an unplanned subset analyses, SPCG-4 reported no significant reduction in mortality or metastasis among men aged 65 years or older. Given the lead-time of 5–11 years in the diagnosis of prostate cancer by screening, these results suggest that watchful waiting may be a reasonable strategy for men as young as 55–60 years of age who have screen-detected cancers [4, 32].

The recently-published Prostate Cancer Intervention Versus Observation Trial (PIVOT) randomized 731 American veterans with screen-detected prostate cancer between radical prostatectomy and watchful waiting and reported no difference in all-cause (HR 0.9; 95 % CI: 0.7–1.1) or prostate cancer-specific mortality (HR 0.6; 95 % CI: 0.4–1.1) at a median follow-up of 12 years [30]. The trial closed prematurely due to poor accrual (initial planned sample size was 2000) and a lower-than-expected mortality rate was observed among the men randomized and thus may have been inadequately powered to detect survival differences. The trial reported a non-significant 15 % relative increase in all-cause mortality among men treated by radical prostatectomy and non-significant reductions in all-cause mortality among those with intermediate- and high-risk features. In terms of prostate cancer-specific mortality, only those patients with high-risk features on the basis of PSA, biopsy Gleason score, and/or clinical stage appeared to benefit from radical prostatectomy. What are notable from this trial are the low rates of prostate cancer-specific

mortality at 12 years with watchful waiting among all patients (7.4 %) and those with low-risk (4.1 %) and intermediate-risk (4.3 %) features, all of which are substantially lower than those reported from observational studies in the pre-PSA era.

In terms of observational studies, in a pooled analysis of 828 patients managed by watchful waiting in six non-randomized studies, Chodak et al. reported 10-year cancer-specific survival and metastasis-free survival of 87 and 81 %, respectively for grade 1 tumors versus 34 and 26 %, respectively for grade 3 tumors [33]. In a population-based study of 14,516 patients treated conservatively between 1992 and 2002 from the SEER-Medicare database, the 10-year risk of prostate cancer-specific mortality and death from competing causes was 8.3 and 60 % for well-differentiated tumors, 9.1 and 57.2 % for moderately-differentiated tumors, and 25.6 and 57 % for poorly-differentiated tumors [10]. The authors note that cancer mortality rates observed were substantially lower than the pre-PSA era. Albertsen et al. used data from 19,639 men 66 years of age and older identified by the combined SEER-Medicare registry to estimate 10-year risks of prostate cancer-specific mortality and all-cause mortality based on tumor grade and stage, age and comorbidity to better select patients for expectant management. During the first 10 years after diagnosis, men with moderately- and poorly-differentiated prostate cancer were more likely to die from causes other than their disease. Depending on patient age, clinical stage, Gleason score, and number of comorbid illnesses present at diagnosis, 10-year all-cause mortality rates ranged from 29 to 94 %, and prostate cancer-specific mortality rates ranged from 2 to 28 % [34].

In summary, evidence from randomized trials and observational studies demonstrate that the risks of prostate cancer-specific mortality and metastatic progression associated with watchful waiting are substantially less than that reported for patients diagnosed in the pre-PSA era before the availability of standard contemporary imaging modalities for prostate cancer staging. Over a time period of 10–15 years, the risk of mortality from competing causes is far greater than prostate cancer-specific mortality among all tumor grades. For clinically detected prostate cancer, the benefit of radical prostatectomy was apparent only for those men less than 65 years of age at diagnosis (this may translate into 55–60 years of age or less for screen-detected prostate cancer). For screen-detected prostate cancer, no benefit of radical prostatectomy was observed overall, though there was a suggestion that those with high-risk features may have a reduced all-cause and prostate cancer-specific mortality. As such, there is strong evidence that watchful waiting may be a suitable strategy for all patients except those with long (>15–20 year) life expectancy and/or high-risk features.

Active Surveillance

As mentioned, active surveillance is the preferred observational strategy for men with life expectancy >10 years who would otherwise be candidates for definitive local therapy as it is theoretically associated with lower risks of clinical progression

and prostate cancer mortality since men are not denied curative therapy who would benefit from it. The current data in support of active surveillance is limited to single-arm, observational studies and thus is not as robust as the data for watchful waiting. An international randomized trial of surveillance vs. radical therapy was opened in 2006 (START, Surveillance Therapy Against Radical Treatment) but was closed due to poor accrual. The ProtecT (Prostate testing for cancer and Treatment) study is a randomized trial in the United Kingdom where men with screen-detected prostate cancer are randomly assigned to surgery, external-beam radiation or surveillance, but results from this trial are not anticipated to be available for many years [35].

There are no standardized schedules for how patients should be selected, how they should be followed, and what criteria should be used to recommend definitive treatment. Active surveillance involves a repeat biopsy shortly after diagnosis (typically within 6 months) to confirm the presence of favorable clinical and pathological features with or without adjunctive tests such as free: total PSA measurements, urine PCA3, and/or multiparametric magnetic resonance (MR) 1.5-3-T prostate imaging (with or without endorectal coil, spectroscopy or dynamic contrast-enhanced sequences).

Eggener et al. have previously reported that the presence of cancer on the repeat biopsy was significantly associated with the need for intervention [36]. The rate of re-classification to a more aggressive cancer by repeat biopsy has consistently been reported in this and other studies to be between 20 and 30 % [36–38]. Of all low-risk patients eligible for surveillance who are found to adverse features on subsequent evaluations, 80 % are identified at the initial repeat biopsy, which emphasizes the importance of initial repeat biopsy in patient selection. In the authors' practice, the recommendation to proceed with therapy is individualized and generally advised for patients with a substantial amount of Gleason pattern 4 (either Gleason 4 + 3 or greater or multiple cores showing Gleason 3 + 4) or a substantial increase in the amount of cancer in biopsy specimens (either based on the number of positive cores or the % cancer in a core).

Once favorable clinical parameters are confirmed, patients are typically followed at 3- to 6-month intervals with PSA and clinical assessment and repeat prostate biopsy every 1–3 years (the authors' practice is to perform a repeat biopsy using an extended biopsy scheme (12-cores or more) at year 2 and 4 and 2–4-year intervals thereafter). Surveillance biopsies may be performed sooner if a change in other clinical parameters warrants it. Adjunctive tests such as prostate MRI may be considered if there is discordance between biopsy findings and clinical parameters such as PSA and prostate examination. There are no uniform criteria for recommending treatment. PSA alone is seldom used to recommend abandoning active surveillance in the absence of other findings suggesting important disease reclassification as a poor correlation between rising PSA levels and adverse biopsy features among active surveillance patients has been reported [39].

The use of 5-alpha-reductase inhibitors (5ARI) in patients on surveillance is highly controversial. A randomized trial of dutasteride vs. placebo in 302 patients followed for 3 years on active surveillance (with repeat biopsy at 18 months and

3 years) showed a significant reduction in the need for treatment and biopsy progression (HR 0.6; 95 % CI: 0.4–0.9; $P=0.009$) [40]. The use of 5ARI may also improve the ability of currently available tests to monitor patients on surveillance as these drugs increase the performance characteristics of PSA, digital rectal examination, and prostate biopsy to diagnose prostate cancer [41–43]. However, the appeal of 5ARI in the active surveillance population is limited by the possible association with the development of high-grade prostate cancer [44].

The feasibility and safety of surveillance in appropriately selected patients has been demonstrated in multiple single-arm cohort studies. Klotz et al. recently published their updated experience in 450 patients on surveillance and reported a 97 % 10-year cancer-specific survival and the hazard ratio of deaths from competing causes vs. prostate cancer was 18.6 [45]. A treatment rate of 30 % was reported in this study, which is consistent with the 20–40 % rate reported in most series, though one study reported a 4-year intervention rate of 73 % [13, 14, 36, 38, 40, 45–49]. While a 50 % biochemical recurrence rate after deferred radical therapy was reported for patients in the Klotz et al. series, most series have reported successful salvage in 87 % or more of patients over short (<5 years) follow-up [36, 45, 50, 51]. Of the men on active surveillance who undergo deferred radical prostatectomy, 85 % or more have organ-confined cancer in most series (this rate was only 65 % in the Johns Hopkins series) and rates of seminal vesicle invasion and lymph node metastasis are less than 5 % [36, 50–53].

In most surveillance series, patients who are found to have adverse features on subsequent evaluations and proceed to definitive local therapy are defined as having "progression". It may not be appropriate to define this event as "progression" as the vast majority of patients who "progress" in the published series have organ-confined cancers and are cured by deferred therapy. Advanced pathological features (such as seminal vesicle invasion, lymph node metastasis, or pathological Gleason score 8–10) are identified in fewer than 5 % of these patients. Thus, we prefer to define this endpoint as rate of intervention recommendation rather than progression as there is little evidence that patients have developed an incurable form of cancer while on surveillance. This suggests that the surveillance procedures and triggers for intervention that we and others have employed are safe, at least over short-term intervals. Patient anxiety plays a major role in limiting the proportion of patients who accept an observational approach and remain on active surveillance. In one cohort study, increasing cancer anxiety was the strongest predictor, aside from PSA kinetics, of active treatment among men managed expectantly [54]. In fact, the majority of patients who ultimately receive deferred radical therapy choose to come off surveillance voluntarily without evidence of worsening disease by histopathological criteria.

It is anticipated that a surveillance approach will have a less impact on a man's urinary, bowel, and sexual function compared to radical therapy (surgery or radiation therapy) although this has yet to be definitively proven. In a cross-sectional health-related quality-of-life study of participants in the SPCG-4 trial, a high-degree of self-assessed quality of life was reported by 35 % men allocated radical prostatectomy vs. 34 % in the watchful waiting arm [55]. Anxiety was higher in the

SPCG-4 groups (43 % in both arms) than age-matched controls. Prevalence of erectile dysfunction was 84 and 80 % and urinary leakage was 41 and 11 % in the radical prostatectomy and watchful waiting groups, respectively. Distress caused by these symptoms was reported significantly more often by men allocated radical prostatectomy than by men assigned to watchful waiting. In an unpublished analysis of 420 patients managed by either radical prostatectomy, brachytherapy or active surveillance from a prospective, longitudinal health-related quality-of-life protocol at our institution, significant differences in urinary and sexual function at 2 years compared to baseline function were observed for those patients receiving radical therapy but not for men on active surveillance. In multivariable analysis, no significant differences between urinary function ($P = 0.5$) and sexual function ($P = 0.07$) at 2 years were observed between brachytherapy and active surveillance patients, but radical prostatectomy patients had significantly decreased urinary and sexual function compared to active surveillance ($P < 0.001$ for both) [56]. While further confirmatory studies with mature follow-up are needed, it appears that men on active surveillance have the highest probability of maintaining urinary and sexual function over short-term (<5 year) intervals.

Patient Selection for Expectant Management

As mentioned, active surveillance is the preferred observational strategy for men with life expectancy greater than 10 years who are otherwise candidates for definitive local therapy. Watchful waiting or active surveillance may be considered for men with a life expectancy less than 10 years. In the past, active surveillance for healthy men with long life expectancy was limited to those with clinical features associated with a high probability of indolent prostate cancer. The Epstein criteria is the most frequently used parameters for identifying men with very low-risk prostate cancer and is defined by: PSA <10 ng/mL, clinical stage T1c, biopsy Gleason score 2–6, PSA density <0.15 ng/mL/g, ≤ 3 positive cores, ≤50 % cancer in any single core [17, 20]. The National Cancer Comprehensive Cancer Network guidelines suggest active surveillance is an appropriate strategy only for men with life expectancy >20 years who meet Epstein criteria, men with life expectancy <20 years who have low-risk prostate cancer (T1c-T2a, PSA <10 ng/mL, biopsy Gleason score 2–6), and men with life expectancy <10 years with intermediate-risk prostate cancer (T2b, PSA 10.1 ng/mL, biopsy Gleason score 7) [57]. The available evidence from SPCG-4 and PIVOT suggests these guidelines under-estimate the true number of men who may be candidates for active surveillance.

In the authors' opinion, an observational strategy is reasonable to consider for men with life expectancy <10 years with non-metastatic prostate cancer (regardless of PSA, clinical stage, and biopsy Gleason score), men with life expectancy <20 years with low- and favorable intermediate-risk prostate cancer (defined as low volume, Gleason 3 + 4 disease), and men with life expectancy >20 years who have

low-risk disease (not necessarily restricted to those meeting Epstein criteria). These recommendations are based on a repeat biopsy shortly after diagnosis, which the authors' consider to be a prerequisite to going on any observational strategy. The available evidence suggests the outcomes of active surveillance are similar for those with low- and intermediate-risk features [49]. New biomarkers such as PCA3 may help in better selecting patients and several prognostic novel molecular signatures as commercially available tests are currently in various stages of development and validation. It is anticipated that the acceptance of expectant management as a reasonable strategy for these patients will significantly impact the problem of overtreatment and reduce the monetary, psychological, and physical costs of treatment for this disease without compromising patient survival.

Conclusions

Among urologic cancers, surveillance is widely embraced as the preferred management strategy for men with clinical stage I nonseminoma and seminoma based on long-term survival rates of 98 % or greater, which avoids treatment in 70–90 % of patients [58, 59]. These results are almost identical to that of expectant management of prostate cancer yet this approach has failed to gain widespread acceptance despite the substantial differences in years of potential life lost per prostate cancer death (average 5.66; most of which include an individual's least productive and functional years) compared to testis cancer (32.6; most of which include an individual's most productive and functional years) [60]. It is anticipated that recent randomized trials attesting to the safety of expectant management and improvements in prognostication (with biomarkers and imaging) will increase its acceptance. In our recent institutional experience, we reported a 59 % acceptance of active surveillance among men with low- and intermediate-risk prostate cancer, which is substantially higher than that reported previously [38]. This suggests an increasing acceptance of active surveillance among healthy American men when counseled using the available evidence.

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Chapter 42
External Beam Radiation Therapy for Clinically Localized Prostate Cancer

Bridget F. Koontz and W. Robert Lee

Introduction

Radiation Therapy

Radiation therapy is used as definitive therapy in about one-third of patients diagnosed with prostate cancer [1]. The use of external beam radiotherapy (EBRT) over brachytherapy (BT) increases with both risk and age [2]. External radiotherapy can be delivered by photon or protons over an extended (approximately 2 month) or limited (2 week) time period. It is utilized as monotherapy for low risk prostate cancer, in conjunction with androgen deprivation and/or brachytherapy for intermediate and high risk cancers, and after prostatectomy for patients with high risk features or a detectable prostate specific antigen (PSA).

The purpose of this chapter is to discuss the role of external radiation therapy in the management of clinically localized prostate cancer as definitive therapy and as an adjuvant therapy following radical prostatectomy (RP). Expectant management, surgery, brachytherapy, and management of metastatic disease will be discussed elsewhere.

Statement of Data

Randomized clinical trials (RCT) are the "gold standard" of evidence based medicine and where data from RCTs are available, special emphasis will be given. Absent data from RCTs, non-randomized prospective and retrospective data will be

B.F. Koontz, MD (✉) • W.R. Lee, MD
Department of Radiation Oncology, Duke University Medical Center,
Durham, NC, USA
e-mail: bridget.koontz@duke.edu

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Table 42.1 D' Amico risk group definitions

Risk group	Combination of pretreatment variables
Low	≤T2a *and* PSA ≤10 ng/ml *and* GS ≤6
Intermediate	T2b *or* PSA 10.1–20 ng/ml *or* GS = 7
High	≥T2c *or* PSA >20 ng/ml *or* GS ≥8

GS Gleason score

provided along with appropriate cautions regarding interpretation. RCTs have been reported addressing the role of radiation dose escalation, the addition and timing of androgen deprivation therapy to radiation, and post-operative radiation. No contemporary RCT of radiation versus surgery or external radiation versus brachytherapy has been reported.

Risk Group Definitions

A number of variables have been consistently reported as independent predictors of biochemical relapse-free survival (BRFS) following radiation therapy for clinically localized prostate cancer. These variables include Gleason score, pretreatment PSA level, and clinical T stage. These variables have been combined by various authors to form risk groupings that predict BRFS. The most commonly used risk stratification schema was first described by D'Amico [3]. Patients are classified as low, intermediate, or high-risk (Table 42.1). This classification has been shown to provide accurate assessments of BRFS for patients regardless of treatment (RP, EBRT, or brachytherapy) and to correlate with prostate cancer specific survival. When possible, the results of radiation therapy will be discussed in the context of these risk groupings.

Using PSA to Define Freedom from Recurrence

Due to the long natural history of prostate cancer, it is difficult to demonstrate a beneficial effect of any therapeutic intervention. D'Amico quantified prostate cancer specific mortality (PCSM) in men with clinically localized T1-2 prostate cancer treated with RP or EBRT in the PSA era [4]. This analysis included more than 7,000 men from 44 different institutions. The rate of PCSM was dependent on risk groupings and primary treatment. In men treated with EBRT and with low-risk disease, the 8 year rate of PCSM was <5 % and approximately 10 % for intermediate risk patients. If aggressive local therapy is to impact survival, especially for low-risk patients, large patient numbers with long follow-up will be required. Additionally, many men are diagnosed with prostate cancer beyond the age of 65 and thus have competing medical co-morbidities; likely making detection of treatment-related improvements difficult. More than 50 % of men treated on cooperative group clinical trials of prostate cancer between 1975 and 1992 died of non-prostate causes.

For these reasons, researchers have sought a surrogate for survival when conducting clinical research. Using the post-treatment PSA level as a surrogate has gained acceptance and the biochemical relapse-free survival is the most commonly reported end-point used.

The Phoenix definition [5] is the current standard for defining biochemical failure after definitive radiotherapy and replaces the American Society of Radiation Oncology (ASTRO) Consensus definition which had been in use since 1997 [6]. Phoenix defines biochemical failure as a rise in serum PSA of more than 2 ng/ml above the post-radiotherapy nadir. The previous ASTRO definition required three consecutive rises in PSA but the date of failure was then backdated to midway between the PSA nadir and the first PSA rise. The advantages of the Phoenix definition are that it eliminates the backdating artifact of ASTRO and false positives due to hormone therapy use; the negatives are that it relies on sufficient follow-up. This chapter will preferentially report the Phoenix definition of biochemical failure but will report the ASTRO Consensus definition in older studies.

Definitive External Beam Radiotherapy

Monotherapy

EBRT as monotherapy is appropriate for men with most men with low-risk disease and some men with low-volume intermediate-risk disease. It is not appropriate, however, for men with high-risk or locally advanced cancer unless there is concern for competing comorbidities. In men with low-risk disease EBRT monotherapy is associated with 10-year BRFS of 80–90 % [7–9]. Men with intermediate- and high-risk features experience 10-year BRFS of approximately 65 and 25 % respectively when treated with EBRT alone [10, 11].

Combination EBRT and Androgen Deprivation Therapy (ADT)

The addition of androgen deprivation to radiotherapy improves overall survival for both intermediate and low risk disease [10, 12]. For intermediate disease 6 months ADT appears to be sufficient [13, 14], while survival for high risk is improved by long-term ADT (~3 years) [15]. The details and results of the following RCTs are detailed in Table 42.2.

1. **EORTC 22863**: This study included high-grade T1-2 or T3/T4 disease. Approximately 90 % of the patients had ≥ T3 disease and 10 % had high-grade T1-2 disease
2. **RTOG 85–31**: Inclusion criteria included clinical T3 disease or regional lymphatic involvement or pathologic T3a or T3b disease post-prostatectomy

Table 42.2 Randomized controlled trials of EBRT and ADT

Study	N	Length of ADT (months)	EBRT (Gy)	Median follow-up (years)	Results
EORTC [10]	415	36 vs 0	50 WP 70 P	9.1	10-year OS increased from 40 to 58 % with ADT
85–31 [16]	977	24 vs 0	44–46 WP 65–70 P	7.6	10-year OS increased from 39 to 49 % with ADT
86–10 [11]	456	4 vs 0	44–46 WP 65–70 P	12.5	10-year DSM decreased from 36 to 23 % with ADT
D'Amico et al. [17]	206	6 vs 0	70 P	7.6	8-year OS increased from 61 to 74 % with ADT
94–08 [12]	1,979	4 vs 0	46.8 WP 66.6 P	9.1	10-year OS improved from 57 to 62 % with ADT
92–02 [18]	1,554	28 vs 4	44–46 WP 65–70 P	11.3	10-year DSM decreased from 16 to 11 % with longer ADT. OS benefit only seen for GS ≥ 8 with longer ADT
EORTC 22961 [15]	970	36 vs 6	50 WP 70 P	6.4	5-years OS improved from 81 to 85 % with longer ADT

These studies typically provided an initial lower dose to the prostate, seminal vesicle, and pelvis lymph nodes ("whole pelvis" or WP) followed by additional dose to the prostate (P). Here we have listed both the initial dose prescribed to the WP and the final dose the prostat e received
EBRT external beam radiotherapy, *ADT* androgen deprivation therapy, *WP* whole pelvis, *P* prostate, *OS* overall survival, *DSM* disease-specific mortality

3. **RTOG 86–10**: Eligibility included patients with T2-4 disease with or without positive pelvic lymph nodes.
4. **D'Amico**: This single institution RCT included men with PSA >10 ng/ml, or GS ≥ 7, or had radiographic evidence of extraprostatic disease.
5. **RTOG 94–08**: This study primarily enrolled low and intermediate risk patients. Its eligibility included T1-2b with a PSA ≤ 20 ng/ml. One third were considered low risk and ~50 % were intermediate risk.
6. **RTOG 92–02**: Patients with T2c-4 disease and PSA <150 ng/ml were eligible. Fifty-five percent of patients had ≥ T3 disease with a median PSA of 20 ng/ml
7. **EORTC 22961**: This non-inferiority study allowed pathologically node positive or T2c-4 node negative patients with a PSA up to 40× upper limit normal.

External Beam Dose Escalation

With the evolution of radiotherapy technology, data has emerged that supports the concept that higher radiation doses will yield better clinical outcomes with acceptable toxicity profiles. A meta-analysis including seven RCT and 2,812

patients showed that all categories of risk benefited in biochemical control from dose escalation, although there was no change in overall survival or disease-specific survival observed to date [19]. Current recommendations are for doses of 75.6 Gy or higher when conventional fractionation (1.8–2 Gy/fraction) is used. External beam radiation therapy and brachytherapy have been combined in the treatment of prostate cancer as a method of dose escalation beyond what external techniques alone can deliver. Institutional series have shown promising biochemical control of high risk disease using combined EBRT and brachytherapy in conjunction with ADT. Institutional series from Duke [20] and Mt Sinai [21] state 5-year biochemical control of 80 %, although 15-year outcome drops to 68 % [22]. The RTOG has conducted two phase II trials of combination external beam and brachytherapy, either permanent interstitial (0019) or high dose rate (0321). RTOG 0019 enrolled 138 intermediate-risk patients and resulted in 4-year biochemical relapse rate of 14 % but a high GU/GI combined grade 3+ morbidity rate of 15 % [23]. Preliminary results for 0321 show low rate of grade 3+ toxicity (3 % at 18 months) but will need to be evaluated at longer followup [24].

Hypofractionation

The advent of improved prostate localization and high precision radiotherapy made it possible to deliver shorter courses using higher dose per fraction. Two methods of hypofractionation have resulted: moderate hypofractionation (4–5 weeks of daily treatment) and extreme hypofractionation (4–5 treatments over 1–2 weeks). The results of three RCTs examining moderate hypofractionation have been published, although two used doses that are much lower that contemporary standards [25, 26]. The third RCT compared 80 Gy in 40 fractions over 8 weeks versus 62 Gy in 20 fractions over 5 weeks. With short follow-up, 3 year freedom from biochemical failure was 87 % in the hypofractionated arm compared to 79 % in the conventional arm ($p=0.035$) with similar late toxicity rates [27]. Other moderate hypofractionation trials have been reported in abstract form [28, 29]. Three very large studies of moderate hypofractionation with non-inferiority hypotheses containing more than 5,000 patients have recently been completed. The results are expected in 2–3 years and will inform subsequent decision-making.

The results of extreme hypofractionation (4–7 fractions over 1–2 weeks) have also been reported. Prospective cohort data has achieved follow-up of 3–5 years, however less than 20 patients have been followed beyond 5 years [30]. Extreme hypofractionation requires accurate positioning and tight margins on the prostate to avoid the rectum and bladder. The studies reported to date have included mostly patients with low risk disease. The follow-up is short (median usually 3–4 years) with reported rates of biochemical progression-free survival of 90–95 % [30, 31].

Post-prostatectomy EBRT

Adjuvant Radiotherapy

Approximately 80,000–100,000 RPs are performed in the US per year and ~30,000 will have a PSA failure [32]. The risk factors for local failure after prostatectomy include positive surgical margins, extracapsular extension, seminal vesicle invasion. The risk factors have been used as eligibility criteria for three randomized trials of adjuvant EBRT (Table 42.3).

These trials have all found an improvement in biochemical relapse- and disease-free survival, and one has shown a significant overall survival benefit to adjuvant radiotherapy for men with pathologic high risk features. However, debate still exists as to whether certain subgroups, particularly those with pT3a negative margin or seminal vesicle-positive disease, benefit from adjuvant radiotherapy compared to early salvage [36].

The EORTC performed a RCT of observation versus immediate RT for high risk post-prostatectomy prostate cancer patients [37]. Eligibility included clinical T1-3N0M0, age <75 years old and a good performance status. Pathologic risk factors were: capsule invasion, positive margins or SVI. EBRT (60Gy) had to start within 4 months of surgery. One thousand and five patients accrued between 1992 and 2001 with a median age 65, median pre-tx PSA 12.3, and median post-op PSA 0.2. The 10-year BFS rate was 61 % versus 41 % in favor of RT ($p < 0.0001$). Clinical progression-free survival and local control were also improved with RT, but overall survival was not significantly different (77 % v 81 %, $p > 0.1$) [33]. Unplanned sub-analysis found that when pathology was centrally reviewed, extracapsular extension in the setting of negative margins did not have a statistical benefit from adjuvant EBRT [38]. While seminal vesicle invasion is commonly thought to be a harbinger of distant metastatic disease, the same study showed that adjuvant RT does benefit those with seminal vesicle involvement [38].

Table 42.3 Randomized controlled trials of adjuvant EBRT versus observation

Study	N	Percentage undetectable post-operative PSA (%)	EBRT (Gy)	Median follow-up (years)	Results
EORTC [33]	1,005	69	60 P	10.6	10-year BRFS improved from 41 to 61 % with adjuvant EBRT
SWOG [34]	425	66	60–64 P	12.6	10-year OS improved from 66 to 74 % with adjuvant EBRT
German [35]	385	100	60 P	4.5	5-years BRFS improved from 54 to 72 % with adjuvant EBRT

EBRT external beam radiotherapy, *P* prostate bed, *BRFS* biochemical relapse-free survival, *OS* overall survival

The Southwest Oncology cooperative group (SWOG) conducted a RCT of 425 men with extracapsular extension (ECE), seminal vesicle invasion (SVI), or positive margins, with arms of immediate 60–64 Gy to the prostate bed or observation. Overall survival, as well as metastasis-free and PSA relapse-free survival, were improved with adjuvant therapy [34, 39]. This benefit was seen in subsets of PSA stratification (both less than and greater than 0.2 ng/ml), high gleason grade, ECE/positive margin, and SVI-positive patients [34]. The authors calculate that the number needed to treat with adjuvant EBRT to prevent one death was 9.1.

Finally, Weigel published a trial from Germany randomizing men with pathologic T3 disease and undetectable post-operative PSA to adjuvant radiotherapy (60 Gy) or observation. With follow-up just under 5 years, the authors confirmed a biochemical progression-free survival benefit to adjuvant EBRT in undetectable PSA population [35].

Salvage Radiotherapy

If patients are observed, the PSA should be undetectable by 1–2 months post-prostatectomy. Salvage radiation therapy is given in response to a rising PSA after radical prostatectomy. Data suggests early salvage therapy (when PSA is under 0.5 ng/ml) is much more likely to be effective that late salvage radiotherapy [40–42]. PSA reduction occurs in 80 % of patients treated w/ EBRT after RP and remains undetectable in 30–50 %. Several publications attempt to stratify which patients are most likely to benefit from salvage radiotherapy. Stephenson et al. performed a retrospective review of 1,540 patients who received salvage EBRT for rising PSA after RP from 1987 to 2005. Updating a previous multivariate analysis which showed that Gleason score 8–10, Pre-RT PSA level > 2 ng/ml, negative surgical margins, SVI, and PSA doubling time < 10 months were independently associated with an increased risk of PSA progression [43], the authors published a nomogram based on these factors predicting progression-free probability. A patient with no adverse features based on the above factors has a 69 % 4-years progression-free survival rate. This drops to 30 % for those with the highest risk factors [41]. Others have found a benefit to salvage EBRT even in the setting of short PSA doubling time, as long as treatment is given within 2 years of PSA rise [42].

Proton Therapy

Proton therapy has been debated more recently as it has become more readily available [44]. The theoretical advantage is due to the physics of proton particle therapy, where no dose is delivered beyond the beam's range. However, clinical advantages to proton therapy for prostate cancer (improved efficacy or decreased toxicity) over traditional photon external beam have not been shown. No clinical trials exist comparing protons to intensity-modulated radiotherapy (IMRT) head to head, but large cohort studies suggest similar efficacy and toxicity [45].

Treatment Planning Considerations

Target Definition

The International Commission of Radiation Units (ICRU) has developed standardized definitions of volumes to be used in external radiotherapy planning. The gross tumor volume (GTV) is defined as the tumor which is palpable or visible on imaging and in most cases of prostate EBRT is considered the entire prostate or prostate bed. The clinical target volume (CTV) includes the GTV plus any additional areas that are felt to be at risk for microscopic involvement (i.e. seminal vesicles, pelvic lymph nodes). The planning target volume (PTV) includes the CTV plus an expansion to account for organ motion and daily set-up uncertainties (Table 42.4).

Many clinicians will use non-uniform margins with the smallest CTV to PTV margins posteriorly in the vicinity of the rectum. A variety of beam arrangements have been described ranging from a coplanar, four-field technique to a non-coplanar seven-field approach. Immobilization devices are commonly used to decrease set-up error, reducing the CTV to PTV margin. In an attempt to reduce the CTV to PTV margin further, a number of investigators have localized the prostate daily prior to delivering treatment. Common techniques include transabdominal ultrasound localization of the prostate and the use of implanted fiducial markers.

Three Dimensional Conformal Radiation Therapy (3D-CRT) and Intensity Modulated Radiation Therapy (IMRT)

3D-CRT requires a CT of the treatment area and specialized treatment planning software to customize treatment to an individual's anatomy, thus more accurately targeting prostate and avoiding bladder and rectum than older non-conformal techniques. The basic process involves obtaining a CT scan with the patients immobilized in the treatment position. The prostate and surrounding tissues are then segmented and the data is reconstructed in to high resolution 3D images.

IMRT is a type of 3D-CRT that uses relies on volumetric imaging to deliver thousands of tiny radiation beamlets that enter the body from many angles and all intersect at the tumor. The intensity of each beamlet (as opposed to each beam in standard 3D-CRT) can be controlled and thus the radiation dose can conform around

Table 42.4 Volume recommendations of the International Commission of Radiation Units and Measurements (ICRU Report 50)

Parameter	Definition
Gross tumor volume (GTV)	Palpable or visible extent of tumor
Clinical target volume (CTV)	GTV + margin for subclinical disease
Planning target volume (PTV)	CTV + margin for organ motion and daily set-up error

normal tissue, create concave shapes and have rapid falloff. The aim is to deliver a higher radiation dose to a tumor with less damage to nearby healthy tissue. The improved conformality of IMRT compared to 3D-CRT offers the possibility of dose escalation without an increase in normal tissue injury. The ability of IMRT to minimize normal tissue irradiation is aided by image guidance, or IGRT, which by implanted fiducials, GPS tracking devices, or pelvic ultrasound localizes the prostate prior to each treatment and minimizes the planning margins needed to ensure adequate coverage due to setup error.

While there are no head-to-head trials comparing IMRT to 3D-CRT for prostate radiotherapy, institutional series comparing serial cohorts have shown that when both IMRT and 3D-CRT use the same total dose, there is (1) no difference in cancer control [46, 47] and (2) significant decrease in late rectal toxicity using IMRT. [48–50] Zelefsky reports on 830 patients with median 10 year following that actuarial grade 2+ gastrointestinal toxicity with IMRT was 5 % versus 135 FOR 3D-CRT ($p<0.001$) [51]. Martinez reported similar toxicity rates [49]. However, most studies do not show a benefit in late urinary toxicity, and in fact, Zelefsky noted an increase in grade 2+ urinary toxicity in IMRT patients (20 versus 12 %, $p=0.01$) [51].

Radiation Complications

The complications of EBRT for prostate cancer depend upon the dose and volume of tissue irradiated. The four main categories of complications are gastrointestinal, urinary, sexual, and other and these each are divided into acute and late phases.

1. Acute intestinal toxicity can manifest during EBRT as enteritis and is dependent on the volume of bowel irradiated with symptoms resolving typically by 6 weeks. Symptoms (diarrhea, tenesmus, rectal/anal strictures, and/or hematochezia) will persist in approximately 3 % and be labeled chronic radiation proctitis [8, 51].
2. Acute urinary toxicity (urinary frequency, dysuria, and urgency) will manifest in most patients during RT and usually resolve by 3 weeks after completion. Late genitourinary (GU) toxicity is rare with modern techniques with approximately 5 % of men developing urethral stricture, cystitis, hematuria, or bladder spasm. About half of late GU toxicities are strictures that can be managed with outpatient dilatation. The rate of urinary incontinence has been reported at 0.3 % following EBRT.
3. Sexual function following treatment of prostate cancer depends upon the treatment, baseline potency, and age of the patient. Modern series have reported that approximately one-third of men who are potent pre-radiation will develop impotency after EBRT, with frequency increasing over time.
4. Radiation induced secondary malignancies are potentially the most important complication following EBRT to the prostate. The incidence of rectal cancer is increased in men treated with EBRT compared to men treated with radical prostatectomy. This increased risk is equivalent to having a first degree relative diagnosed with rectal cancer. Radiation induced bladder cancers and sarcomas are also possible.

Summary

A. EBRT alone (utilizing IMRT techniques) is an acceptable treatment for men with low-risk prostate cancer.
B. RCT support the use of higher than conventional doses (>74 Gy) in men treated with EBRT.
C. Randomized trials support the use of ADT + EBRT in men with intermediate or high-risk disease.
D. RCT support the use of post-prostatectomy EBRT in men with adverse pathologic risk factors.

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Chapter 43
Brachytherapy for Prostate Cancer

Albert A. Edwards, Robert W. Laing, and Stephen E.M. Langley

Brachytherapy places sealed radioactive sources close to or within a tumour, delivering tumoricidal radiation dose while sparing surrounding normal tissues. Successive technological advances throughout the twentieth Century have led to improvements in the safety, accuracy and flexibility of brachytherapy.

Prostate brachytherapy is divided into low-dose rate (LDR) brachytherapy (permanent seed implantation) and temporary high-dose rate (HDR) brachytherapy implants. Either type of implant may be combined with treatment approaches such as hormone therapy and external beam radiotherapy, depending on the prognostic group.

Brachytherapy is a popular treatment choice for prostate cancer in North America and Europe, particularly in the United Kingdom and Spain, where its use is increasing [1, 2]. Delivering prostate brachytherapy safely depends on the coordinated activities of a large skilled team including clinicians, medical physicists, dosimetrists, nurses, anaesthetists and radiographers. Ongoing quality assurance is required to ensure that each treatment centre is achieving satisfactory clinical outcomes.

Important Definitions

LDR: Low dose rate sources deliver dose rates less than 2 Gy per hour [3]. It is a common misconception that low dose rate brachytherapy delivers low doses to the prostate. In fact, LDR brachytherapy typically delivers higher total doses than HDR

A.A. Edwards, FRCR (✉) • R.W. Laing, FRCP
Department of Oncology, St. Luke's Cancer Centre, Royal Surrey County Hospital, Guildford, UK
e-mail: albert.edwards@nhs.net

S.E.M. Langley, FRCS (Urol)
Department of Urology, Royal Surrey County Hospital, Surrey, UK

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brachytherapy. The rate at which dose is delivered affects the radiobiological response of tumour and normal tissues.

HDR: HDR treatment units deliver dose rates above 12 Gy/h (or 20 cGy/min) [3].

Interstitial therapy: Interstitial implants are placed within or near to a tumour, rather than in a body cavity.

Sealed source: Brachytherapy sources are doubly encapsulated within sealed containers to minimise the risk of dispersion of radioactive material.

Applicator: A non-radioactive metal or plastic structure, such as a needle or catheter, which is implanted into the target. The sealed source is later inserted into the applicator, reducing the radiation exposure to staff during the procedure.

Remote afterloading: The clinician implants applicators within the target tissue and connects them to the HDR afterloading unit. Once staff have left the room, the HDR unit drives the source out of its shielded safe under remote control to dwell within the applicators and deliver the planned radiation dose distribution.

Half-life: The nuclei of radioactive isotopes are unstable. They decay in an exponential fashion, releasing radiation in the form of electromagnetic radiation (such as gamma rays) and or sub-atomic particles. The half-life of a radioactive isotope is the time required for the number of the radioactive nuclei to decay to half of their initial value. The shorter the half-life, the faster the rate of radioactive decay.

Half-value layer: This is defined as the thickness of a specified absorbing substance that is required to reduce the intensity of a beam of photons (such as emitted gamma rays) to half its original value. The intensity of a photon beam travelling through an absorber reduces exponentially. Higher energy photons beams require thicker half-value layers.

Artificial Isotopes

Radium-226 (^{226}Ra) and its decay product, Radon-222 (^{222}Rn), were the only radioactive sources used clinically for brachytherapy until artificial radioisotopes became available in the 1960s. Thick shielding was required to protect staff from their high-energy photons and there was a substantial danger of contamination through the release of gaseous radioactive products if the source tubes became damaged.

Modern artificial radioisotopes are non-dispersible, insoluble and have no decay products in liquid or gaseous form. Their emitted photon radiation is usually of an energy sufficient to reach and treat the target tissue, but not high enough to require prohibitive radiation shielding. Long-standing sources, such as those used for HDR afterloading units, do not need to be replaced frequently because they have long half-lives. The properties of the radioisotopes commonly used in prostate brachytherapy are detailed in Table 43.1.

Iridium-192 (^{192}Ir) emits a spectrum of photons of different energies. It is used in the form of an iridium/platinum alloy wire enclosed by a thin platinum sheath. Its half-life is relatively long (73.8 days), which is convenient for the transport and

Table 43.1 Physical characteristics of artificial radioisotopes used in prostate brachytherapy

Radionuclide	Half-life (days)	Emitted energy spectra (weighted average MeV)	Half-value layer of lead (mm)
^{125}I (Iodine)	59.4	0.028	0.025
^{103}Pd (Palladium)	17.0	0.021	0.008
^{131}Cs (Caesium)	9.7	0.030	0.022
^{192}Ir (Iridium)	73.8	0.38	2.5

Fig. 43.1 RapidStrand containing Model 6711 seeds (Courtesy of GE Healthcare/Oncura, NY, USA)

storage of sources. This is the most common radioisotope employed in HDR afterloading units.

Permanent LDR seed implants are made from radioisotopes with relatively short half-lives which emit photons of energy low enough that the patient does not pose a significant risk of irradiating others nearby. A typical example of an Iodine-125 seed is the model 6711 seed (GE Healthcare/Oncura). It contains a silver wire with the silver iodide of ^{125}I adsorbed onto its surface. This is encapsulated within a 0.05 mm thick titanium cylinder that is welded at both ends. The silver wire has the advantage of being radiographically distinctive. Seeds may be inserted individually using a Mick applicator or preloaded into a needle. Figure 43.1 shows a central strand of model 6711 seeds spaced regularly along a braided carrier. Before insertion, the strand of seeds is cut to the required length and loaded into a needle.

^{103}Pd seeds contain graphite-pellets plated with ^{103}Pd and lead radiographic markers sealed within a titanium capsule. It was hoped that the shorter half-life of ^{103}Pd might offer a radiobiological advantage over ^{125}I, but this has not been shown to be clinically significant in trials [4, 5]. ^{131}Cs is a newer radioisotope that is used by some practitioners in permanent seed implantation [6, 7].

The Development of Modern LDR Prostate Brachytherapy

Permanent prostate implantation was explored at the Memorial-Sloan Kettering Cancer Center in the 1970s [8]. They performed bilateral pelvic lymphadenectomies and implanted ^{125}I seeds within the prostate using an open retropubic approach in a series of patients, several of whom had pelvic lymph node metastases. This technique was abandoned due to poor results and excessive morbidity. In the 1980s, the modern non-surgical technique of seed implantation was developed. Holm described a technique for guiding transperineal prostate implantation using

transrectal ultrasound [9]. ^{125}I or ^{103}Pd seeds were implanted within the prostate using a transperineal approach with a perineal template, under transrectal ultrasound guidance – a technique later modified in Seattle by Blasko, Ragde and Grimm [10].

Clinical Evaluation of Patients

The clinical assessment establishes whether the patient is a suitable candidate for prostate brachytherapy and confirms their disease stage and risk group. Relevant features in the medical history include anticoagulant use, diuretic therapy, diabetes, inflammatory bowel disease, connective tissue disorders, previous diagnosis of pelvic cancer (especially bladder or rectum), prior pelvic radiotherapy and radiation sensitivity syndromes such as ataxia telangiectasia. Important urologic history would include prior transurethral or open resection of the prostate, urethral surgery, procedures for benign prostatic hyperplasia such as transurethral needle ablation or microwave therapy, medications for urinary symptoms and prior erectile dysfunction. Prior pelvic surgery or the presence of a total hip replacement would be relevant features of the surgical history. Information about the patient's baseline urinary, erectile and bowel function may be obtained from self-administered validated questionnaires such as the International Prostate Symptom Score (IPSS), the International Index of Erectile Function (IIEF) and the EORTC QLQ/PR-25 questionnaire [11–13]. During the outpatient consultation, the clinical T stage is evaluated by digital rectal examination. Uroflowmetry may be carried out in the outpatient clinic to assess the Q_{max} (maximum urinary flow rate) and voided volume. The post-void residual volume may be measured by transabdominal bladder ultrasound and should be less than 200 cm^3 for patients being considered for brachytherapy [14]. Transrectal ultrasound may be performed in the clinic to visualise the prostate gland. This can demonstrate median lobe hyperplasia, an existing TURP defect, eccentric BPH (which may displace the urethra from the midline) or the presence of intra-prostatic calcification (which creates artefact on the TRUS imaging used to guide seed implantation).

The authors consider undertaking cystoscopy and bladder neck resection in patients with small prostates (<40 cm^3) who have obstructive urinary symptoms or signs, together with median lobe hyperplasia, to attempt to reduce urinary obstruction in the long term. Figures 43.2 and 43.3 show the bladder neck at cystoscopy before and after resection.

The maximal cross-section of the prostate gland should be carefully compared to the anterior-posterior space between the pubic arch and the ultrasound probe to avoid the phenomenon of pubic arch interference during the eventual seed implant. This occurs when the pubic arch blocks the passage of the introducing needles into the anterior and antero-lateral prostate [15]. This tends to affect large prostates (>60 cm^3) but may also depend on pelvic anatomy, patient position and implant technique.

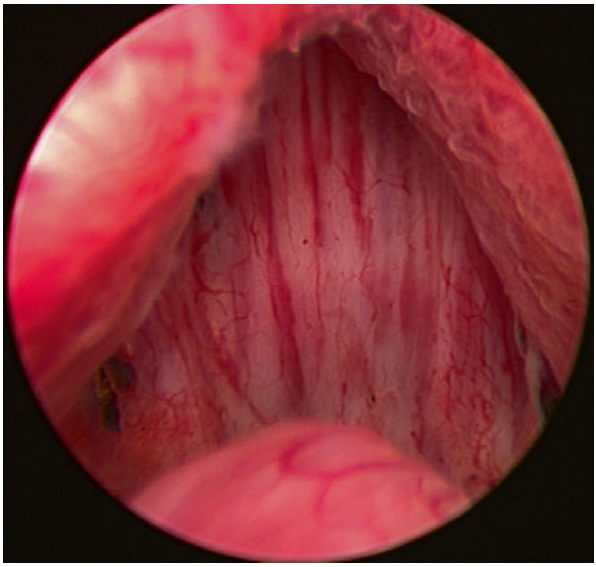

Fig. 43.2 View of the bladder neck and lateral lobes of prostate at cystoscopy

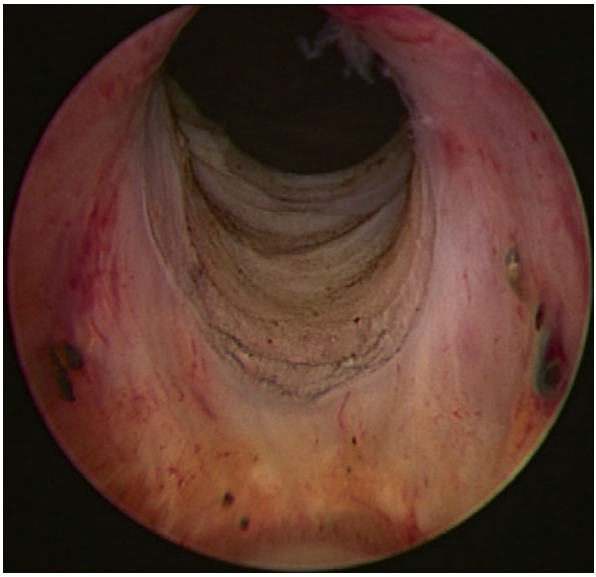

Fig. 43.3 View of resected bladder neck at cystoscopy

Selection of Patients for Prostate Brachytherapy

The diagnosis of prostate cancer has increased rapidly with the advent of widespread PSA screening of men in Western countries. The majority of these men are asymptomatic and have organ-confined disease which may be managed with active surveillance, radical prostatectomy, external beam radiotherapy or brachytherapy.

Several guidelines for the selection of patients for prostate brachytherapy are in use, but there is no universal consensus [16–18]. The selection criteria may be classified into general, functional, tumour biology and technical criteria.

Absolute Contraindications to TRUS-Guided Prostate LDR Brachytherapy

According to the updated American Brachytherapy Society (ABS) guidelines for TRUS-guided permanent prostate brachytherapy [14], absolute contraindications to brachytherapy include:

- Limited life expectancy (less than 10 years)
- Unacceptably poor performance status
- Unacceptable operative risks
- Distant metastases
- Absence of rectum such that TRUS-guidance is precluded
- Large TURP defects which preclude seed placement and acceptable dosimetry
- Ataxia telangiectasia

General Criteria

Co-morbid conditions that pose unacceptable surgical or anaesthetic risks should be considered. Active prostatitis and active inflammatory bowel disease may be considered relative contraindications [19], although there are small series of patients with a history of inflammatory bowel disease who have tolerated brachytherapy well [19–21]. Patients who have received prior pelvic radiotherapy need to be carefully assessed for symptoms and signs of late radiation toxicity to the pelvic organs, and may require evaluation with sigmoidoscopy and cystoscopy. The dose previously delivered to the prostate, rectum and bladder should be estimated from the details of their previous radiation therapy. Advanced age is not considered a contraindication to brachytherapy. Obesity may not be a contraindication provided the patient has an acceptable performance status and life expectancy, and can be supported by the operating theatre apparatus.

Functional Criteria

The presence of pre-treatment obstructive urinary symptoms is predictive of the development of acute urinary retention post-operatively [22]. This may be indicated by an International Prostate Symptom Score (IPSS) greater than 15 or a post-void

Table 43.2 NCCN risk group classification

Low risk	PSA < 10 ng/ml and T1c-T2a and Gleason score 6
Intermediate risk	PSA 10–20 ng/ml or T2b-T2c or Gleason score 7
High risk	PSA > 20 ng/ml or T3a or Gleason score 8–10

residual volume of greater than 200 cm^3. Patients with an IPSS of 8 or less have a low risk of developing acute retention and prolonged urethritis post-operatively [14]. Pre-implant IPSS correlates with the duration of post-implant obstructive symptoms but is not a predictor of long-term urinary quality of life [23, 24]. The pre-implant maximum urine flow rate, Q_{max}, and the presence of prostate median lobe hyperplasia are both predictive of post-implant acute urinary retention [12, 25, 26]. It is recommended that patients selected for brachytherapy should have Q_{max} greater than 15 ml/s [17].

Tumour Biology Criteria

The biological criteria of pre-treatment PSA, prostate biopsy Gleason score and clinical T stage are used to stratify patients with localised prostate adenocarcinoma into low-, intermediate- and high-risk groups. Several risk classifications exist, each based on the same three risk factors.

Patients presenting with high-risk disease or more than one intermediate-risk factors should be staged with an isotope bone scan and CT or MRI of the abdomen and pelvis [14]. The ABS favours the National Comprehensive Cancer Network (NCCN) classification (Table 43.2).

The risk of subclinical extracapsular extension (ECE) is reflected by the risk group classifications. Patients in the low risk group may be suitable for treatment with LDR seed implantation alone (monotherapy). Some practitioners select patients from the intermediate risk group for monotherapy and others use a combination of EBRT and brachytherapy. The ABS recommend combined EBRT and LDR implantation in patients with initial PSA >20 ng/ml or Gleason score 8–10 and T2b-T2c disease. The authors consider seminal vesicle invasion to be a contraindication to LDR brachytherapy. Such cases may be considered for neoadjuvant and adjuvant ADT with EBRT, with or without an HDR brachytherapy boost.

Technical Criteria

Prior TURP used to be considered a contraindication to LDR brachytherapy, due to rates of urinary incontinence as high as 17 % in early series in the 1990s, but this is no longer the case. With careful pre-operative assessment of the TUR defect, incontinence among selected patients treated with brachytherapy after TURP may be avoided. The seed implant should be delayed until 2–4 months after TURP to allow healing [14].

Pubic arch interference with large prostates (>60 cm^3 in volume) may be overcome by a period of 3–4 months of ADT, which may downsize the prostate volume by about 30 %. For more modest-sized glands, placing the patient in an exaggerated lithotomy position and re-aligning the TRUS probe in a horizontal rather than angled-down position may overcome pubic arch interference.

Selection of Patients for HDR Prostate Brachytherapy

The GEC/ESTRO-EAU selection criteria for patients for HDR brachytherapy are: T1b-T3b disease with any Gleason score and any initial PSA, with no evidence of distant metastases [18]. Their exclusion criteria include: a prostate volume greater than 60 cm^3, a TURP within the last 6 months, disease infiltrating the external sphincter of the bladder neck, significant urinary obstructive symptoms and a rectum-prostate distance less than 5 mm on TRUS. The ABS also consider offering HDR brachytherapy to selected patients with T4 disease.

LDR Brachytherapy: Monotherapy and in Combination with External Beam Radiotherapy and Hormone Therapy

Low-Risk Localised Prostate Cancer

Prostate LDR brachytherapy alone (monotherapy) is recommended for low-risk disease (see Table 43.2 for risk group definitions). Published series demonstrate that excellent long-term clinical outcomes can be obtained in this patient group provided adequate dosimetric parameters are achieved [14, 27–29]. ADT may be useful for downsizing the prostate gland [30–33]. The authors consider combining ADT with LDR brachytherapy in patients with a high burden of disease (i.e. all biopsies cores involved with Gleason 3 + 3 disease) due to the increased risk of occult extracapsular extension and metastasis.

Intermediate-Risk Localised Prostate Cancer

Patients in the intermediate-risk group are more likely to harbour adverse pathological features such as extracapsular extension, seminal vesicle invasion and lymph node metastasis than patients in the low-risk group. Pathological series have demonstrated that extracapsular extension of prostate cancer rarely extends beyond 5 mm in patients with clinically organ-confined disease [34, 35]. This region of potential extracapsular extension is covered by most good quality brachytherapy

implants due to the typical margin of 5 mm added around the prostate to generate the Planning Target Volume and the fact that the radiation dose distribution extending several millimetres beyond the prescription isodose is often adequate to treat microscopic disease [36–38].

Patients with low-volume disease, a predominant Gleason score 3 pattern and a single adverse factor for intermediate-risk disease may be treated with monotherapy [14, 39]. Among the remaining patients in the intermediate-risk group, the optimum therapeutic strategy is controversial. A pattern-of-care study among brachytherapists with a combined experience of more than 10,000 patients identified additional factors such as proportion of positive biopsy cores and the presence of perineural invasion which practitioners consider with T-stage, initial PSA and Gleason score when trying to decide whether to treat intermediate-risk cases with monotherapy or in combination with EBRT and ADT [39].

High-Risk Localised Prostate Cancer

Patients with high-risk disease have a substantial chance of subclinical ECE beyond the range of a permanent prostate brachytherapy implant. This was reflected in the poor results of monotherapy for this group in early brachytherapy series [29]. It has become standard practice to combine an LDR brachytherapy implant with EBRT for this reason. Retrospective series suggest that escalating radiation dose by combining EBRT and a LDR brachytherapy implant improves local control of prostate cancer and metastasis-free survival.

Large randomised prospective trials of EBRT dose escalation for high-risk locally advanced prostate cancer with 3-dimensional conformal radiotherapy (3D-CRT) and, more recently, intensity modulated radiotherapy (IMRT), have confirmed improvements in disease control [40–42]. Combining EBRT with LDR brachytherapy aims to deliver greater dose escalation to the prostate and any surrounding subclinical ECE.

The use of neoadjuvant and adjuvant ADT with primary EBRT is supported by randomised prospective evidence [43, 44]. Although the use of ADT with combined EBRT and LDR brachytherapy for high-risk disease is popular, the evidence that it produces improved clinical outcomes is limited [17]. Delivering a greater biologically effective dose in patients with Gleason score 8–10 disease was shown to improve overall and metastasis-free survival in a large multi-institutional series [45].

Permanent LDR Prostate Brachytherapy Technique

Permanent seed implantation may be performed as a daycase or with an overnight stay. The technique comprises of a volume study, treatment planning and the implant procedure itself. Written informed consent should be obtained at the time of the

implant and it should be documented whether prior pelvic EBRT has been given. The three main techniques for LDR prostate brachytherapy are: the two-stage Seattle technique (employing stranded seeds); the one-stage real-time technique using intra-operative dosimetry (as popularised by Stock and Stone: Proseed); and more recently, the 4D-Brachytherapy technique, which utilises stranded seeds in the prostate gland peripherally and loose seeds centrally, in a real-time technique with intra-operative dosimetry [46].

Volume Study

The volume study is a series of transverse TRUS images of the prostate which is used to plan the implant. Some centres perform this under anaesthetic; others in the outpatient setting with compliant patients who are able to remain still during the procedure. The rectum and sigmoid colon is emptied either by bowel preparation or an enema pre-operatively. The patient is placed in the dorsal lithotomy position and the perineum is infiltrated with local anaesthetic. Appropriate antibiotic cover for the implant procedure is recommended. A urinary catheter is inserted and then instilled with aerated gel to improve its visibility on the TRUS, so that it may be contoured on the treatment planning computer as a surrogate for the urethra. A biplanar TRUS probe is carefully positioned within the patient's rectum. Care must be taken to obtain ultrasound images of the best quality because they will form the basis of the treatment plan.

The TRUS is mounted securely on a stepper unit which allows the probe to be advanced and retracted along its cranio-caudal axis in precise increments, while the rotation of the probe along this axis is also monitored (Fig. 43.4).

This positional data is digitised, transferred to a treatment planning system and reconstructed in 3D. The TRUS probe is positioned so that the prostate is in the middle of the TRUS display. The urethra is usually in the central vertical row and the posterior prostate border along the lowest horizontal row of the template grid (Fig. 43.5). Axial images of the prostate gland are acquired at 5 mm intervals from the prostate base to the apex. The outline of the prostate on each axial image is contoured on the treatment planning system. The prostate is also visualised in the longitudinal plane to check the length and shape of the gland.

One-Stage and Two-Stage Techniques

The practitioner must implant a seed arrangement that meets accepted dose constraints for the prostate and adjacent normal organs to achieve good clinical results for each patient [47]. Techniques for LDR prostate brachytherapy implantation are broadly divided into two-stage and one-stage techniques, according to the number of attendances required for treatment planning and delivery.

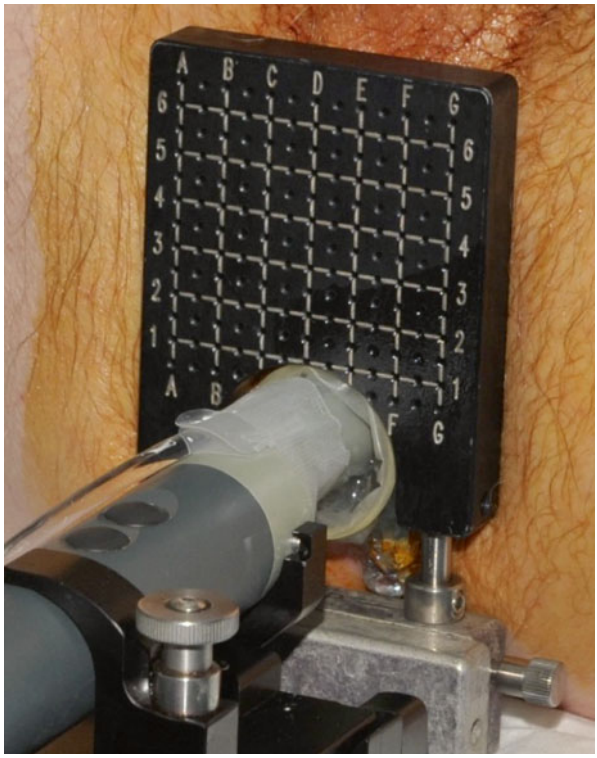

Fig. 43.4 Template and TRUS probe mounted on a stepper unit

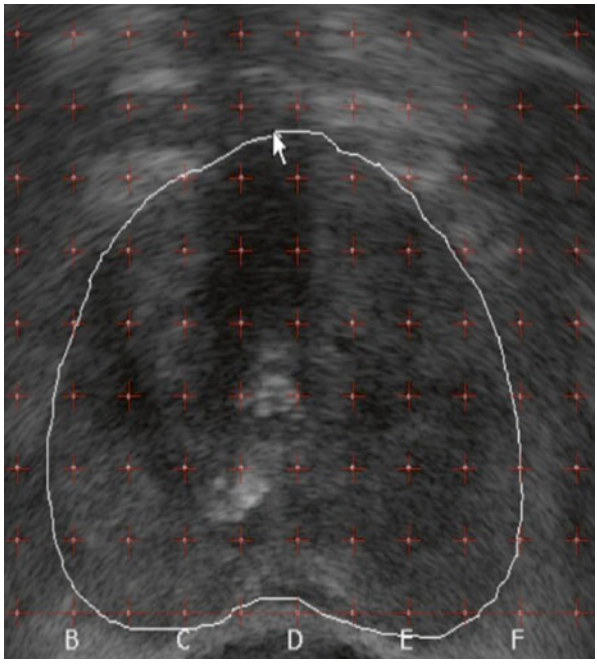

Fig. 43.5 Template grid superimposed upon axial TRUS image of prostate

Seattle Technique

At centres using a two-stage technique, the patient attends for the volume study and the seed implantation is performed on a later occasion [48]. The treatment planning is completed in the meantime and the required seeds are ordered. It can be difficult to accurately replicate the patient position from the volume study and internal pelvic organ motion may cause some variation.

Loose Seed Technique

Single-stage techniques, where dosimetry is calculated just before or during the implant procedure, are increasingly popular due to the flexibility of planning and need for just one anaesthetic. They were popularised by Stock and Stone [49]. The ABS subcategorises intraoperative planning techniques into: intraoperative preplanning, interactive planning and dynamic dose calculation.

Intraoperative preplanning involves performing a TRUS in the operating room and importing the 3-dimensional ultrasound data into the treatment planning system on a computer in the room. The target volume and organs at risk are contoured on the treatment planning system and the prostate is implanted according to plan generated.

Interactive planning involves real-time feedback of needle positions to the treatment planning system via image guidance so that the plan can be recalculated after each needle position is adjusted. Dynamic dose calculation uses feedback of 3-dimensional seed position to continuously recalculate the dose distribution throughout the procedure. Being able to re-plan the treatment intraoperatively gives a further opportunity to optimise the treatment plan compared to preplanned techniques.

Hybrid Techniques

Two of the authors have developed a versatile real-time one-stage technique ("4D-Brachytherapy") which avoids seed migration by using a combination of preloaded stranded seeds around the periphery of the prostate and loose seeds loaded with a Mick applicator [46]. An institutional nomogram has been developed from over 1,000 brachytherapy cases to enable the appropriate combination of stranded and loose seeds to be ordered based on the measurements of the prostate from a TRUS in the outpatient clinic. The technique has shortened the time taken for planning and implantation to around 40 min. Changing from the 2-stage Seattle technique to 4D-Brachytherapy has resulted in a significant improvement in prostate D_{90} and V_{100} doses [46]. Acute urinary morbidity and erectile function have also improved significantly (with potency rates 2 years post-implant improving from 61.7 to 83.3 % and use of phosphodiesterase-5 inhibitor medication falling from 53.3 to 31.7 %).

Table 43.3 Volume definitions based on ICRU Report 50 and the GEC ESTRO recommendations

Gross tumour volume (GTV)	Gross palpable, visible or radiological extent of tumour
	T1: there is no GTV
	T3: includes extracapsular extension or seminal vesicle disease
Clinical target volume (CTV)	GTV + margin including subclinical disease at a particular probability
	T1-2: Visible contour of prostate + 3 mm margin in all directions, constrained by the anterior rectal wall and the bladder neck
	T3: Visible contour of prostate and extracapsular extension + 3 mm margin, as above
Planning target volume (PTV)	CTV + margin for organ motion and daily setup error
	With real-time 3D dosimetry and TRUS image guidance, no further margin is required, so PTV = CTV

Target Volume Definitions in Prostate Brachytherapy

The concepts of Target volumes and Organs at risk were formalised by ICRU Report 50 [50], however brachytherapy practitioners had been using varying definitions of these volumes for prostate brachytherapy. The recommendations of the PROBATE group of GEC ESTRO sought to standardise the definitions, as shown in Table 43.3 [51].

The Gross Tumour Volume (GTV) is the gross palpable, visible or radiological extent of tumour growth. Usually prostate cancer is not visible on transrectal ultrasound and, by definition, T1c tumours are be impalpable. In these situations, there will not be a GTV to be visualised.

The clinical concept of the Clinical Target Volume (CTV) includes the GTV as well as adjacent tissue, which has a substantial chance of containing significant subclinical disease. The whole CTV must receive a tumoricidal dose to achieve eradication of local disease. Since prostate adenocarcinoma is often a multifocal disease, the CTV is considered to include the whole prostate gland. For organ-confined disease (T1-T2), the CTV will be the visible prostate capsule with an added margin of 3 mm in all directions, limited by the bladder neck superiorly and the anterior rectal wall posteriorly. For T3 disease, the CTV will contain the gross disease, including any visible extracapsular extension, with a margin of 3 mm in all directions.

The geometric concept of the Planning Target Volume (PTV) contains the CTV with a margin to account for uncertainties in the position of the CTV due internal organ motion and setup errors. Since implanted seeds or applicators are placed within the CTV under image guidance and move with the prostate gland these uncertainties and the margin from CTV to PTV are minimal in prostate brachytherapy.

Organs at risk can be outlined during the planning stage, to enable the treatment planning computer to estimate the dose they will receive and ensure that their dose constraints are met. The rectum surrounds the TRUS probe and its outer or inner wall may be delineated to estimate its dosimetry. The prostatic

urethra is very difficult to visualise, so the surface of the urinary catheter is delineated as a surrogate. Instilling aerated gel into the urethra or urinary catheter, if present, may facilitate visualising them on the transrectal ultrasound intraoperatively. Some centres have delineated the penile bulb and neurovascular bundles, seeking to minimise the dose they receive to try to improve erectile function. However, the dose received by the penile bulb may not correlate with postimplant erectile function [52].

Treatment Planning

The treatment planning system reconstructs the 3-dimensional arrangement of seeds within the prostate and calculates the dose distribution and the dose delivered to the target volume and adjacent organs at risk. TRUS is considered the standard imaging for the treatment plan and during the implant but planning may be performed on a CT or MRI dataset. Pre-planning with CT has been shown to produce consistently greater prostate target volumes than with TRUS and could theoretically lead to unnecessary implantation of the urogenital diaphragm and penile urethra [53].

The treatment plan combines the transverse images of the prostate with the numbered needle positions according to the template. The number of seeds in each needle and their activity are also denoted. The radiation distribution is represented visually by coloured isodose lines which run through points receiving equal dose levels, usually expressed as a percentage of the prescribed dose. In a brachytherapy treatment plan, the dosimetrist will aim to enclose the CTV so that at least 95 % of it receives the prescribed dose, while meeting volumetric dose constraints for the target and the adjacent organs at risk (such as the rectum and prostatic urethra). The GEC ESTRO recommendations for dosimetric criteria, which have been correlated with good dosimetry are shown in Table 43.4.

Table 43.4 GEC ESTRO recommendations for dosimetric parameters

Structure	Parameter	Constraint
CTV	V_{100} (percentage of CTV receiving the prescription dose)	≥95 %
	V_{150} (percentage of CTV receiving 150 % of the prescription dose)	≤50 %
	D_{90} (dose which covers 90 % of the volume of the CTV)	>145 Gy
Rectum	D_{2cc} (the minimum dose to the most exposed 2 cc of rectum, as a percentage of the prescription dose)	≤145 Gy
	$D_{0.1cc}$ (the minimum dose to the most exposed 0.1 cc of rectum, as a percentage of the prescription dose)	<200 Gy
Prostatic urethra	D_{10}	<150 %
	D_{30}	<130 %

Dose Prescription

The recommendations of GEC ESTRO and the American Association of Physicists in Medicine (AAPM) task group 137 are that the standard prescribed dose for ^{125}I monotherapy is 145 Gy and for ^{103}Pd, 125 Gy [51, 54]. For combination therapy, the ABS recommends 41.4–50.4 Gy EBRT in 1.8–2.0 Gy daily fractions and an LDR brachytherapy dose of 108–110 Gy with ^{125}I or 90–100 Gy with ^{103}Pd [14].

Implant Procedure

The seeds are implanted via the transperineal approach and template guidance with the patient in the lithotomy position. If a two-stage technique is employed, the patient should be matched closely to their position during the pre-planning volume study. The TRUS should have a high-resolution biplanar 5–12 Hz ultrasound probe and be equipped with software to generate an electronic grid, which is calibrated to coincide with that of the template (see Fig. 43.5).

The insertion of the implant needles into the prostate is guided by the template and determined by the pre-plan in the two-stage approach, or by interactive planning in the one-stage approach. Methods of seed implantation include using a Mick applicator to insert loose seeds individually [55], afterloading applicators and using preloaded needles [56].

Post-implant Dosimetry

The quality of the implant is assessed by dosimetric analysis post-implant. This is typically obtained from a CT scan performed 4–6 weeks post-implant, although some centres have experience using MRI image fusion. Some practitioners favour a post-implant CT on day 0 or 1, before the urinary catheter is removed, because it enables a more accurate estimation of the urethral dose (using the contour of the catheter as a surrogate for the urethral mucosa) [57]. This is more convenient for the patient but may underestimate dose delivered to the prostate due to postoperative oedema. The target volume, individual seeds and organs at risk are contoured on the postoperative CT scan and the dosimetry is re-calculated. The outer wall of the rectum is easily visualised for contouring on the CT, however the presence of a catheter or the instillation of aerated gel is required to visualise the prostatic urethra. The post-implant contour of the prostate capsule is delineated for the CTV and then a 3 mm margin is added [51].

Several studies have suggested that parameters based on the dosimetry calculated from this post-operative CT scan are related to clinical outcomes. A study of patients with localised prostate adenocarcinoma treated with ^{125}I implants found a

dose response of 4-year freedom from biochemical failure for the dose received by 90 % of the prostate, the D_{90}, at a level of 140 Gy [58]. In a study of over 700 patients treated with LDR implants, a cut-off of prostate D_{90} of 90 % of the prescribed dose was found to predict 4-year PSA-relapse free survival [59].

Radiation Protection

Patients are mildly radioactive after LDR brachytherapy implantation but the low energy of the photons emitted by ^{125}I and ^{103}Pd seeds mean that the dose rate at the skin surface does not pose a risk to the general public. The UK Royal College of Radiologists recommend that patients should be advised to avoid close contact with children and pregnant women in the first 2 months post-implant and that condoms should be used for the first five ejaculations. The brachytherapy centre should be contacted if pelvic surgery, post-mortem examination or cremation are required within 20 months of the implant. The centre provides each patient with a laminated card containing essential details about the implant that they must carry with them for the first 20 months post-implant [60].

Complications and Toxicities of LDR Brachytherapy

Immediate side effects may include discomfort and bleeding at the perineal needle holes, haematuria and haematospermia.

Seed Migration

Cystoscopy may be required to remove misplaced seeds or blood clots from the bladder but is not performed routinely if bladder irrigation is clear and there is no radiological evidence of seeds within the bladder. Techniques employing loose seeds have a rate of seed migration as high as 15 %. Examples of seed migration to the chest, abdomen and pelvis have been documented, including a case of a non-smoker developing a limited stage small-cell lung cancer [61–64].

Urinary Toxicity

Irritative and obstructive urinary symptoms are the most common acute side effects of prostate LDR brachytherapy. Patients may be offered a 2–3 month course of an α-blocker post-implant, prophylactically. In many cases, exacerbation of urinary

symptoms resolves within 2–3 months of the implant. The authors published a study of 100 patients treated with LDR brachytherapy, which found that acute urinary symptoms peaked at 6 weeks post-implant and that a statistically significant decrease of IPSS score persisted until 9 months post-implant [12]. Seven patients in this study developed acute urinary retention, but the mean IPSS score 2 years post-implant was improved. In one study of 712 consecutive patients treated with LDR brachytherapy, resolution of IPSS (defined as the post-implant IPSS returning to within 2 points of the pre-implant score) occurred in 85.3 % of patients [65]. A questionnaire study of 174 patients with over 5 years follow up after LDR brachytherapy reported good or acceptable quality life due to urinary symptoms (an IPSS quality of life score of 0–4) among 98 % of respondents [66].

Acute urinary retention may occur shortly after the implant. A study of 216 patients treated with prostate LDR brachytherapy found that 9.3 % developed acute urinary retention postoperatively [67]. TURP should be avoided in patients after seed brachytherapy [17].

Urinary incontinence is rare after prostate brachytherapy. A study based on a survey of 112 patients who had received monotherapy, demonstrated that pre-implant IPSS and the urethral D_{10} on CT at around day 30 post-implant, were predictive of risk of urinary incontinence [68]. Selecting patients with pre-implant IPSS <15 and aiming for a urethral D_{10} as close to the prescribed dose as possible, were recommended.

Late strictures of the bulbomembranous urethra tend not to be long-lasting and can be remedied by dilatation. The incidence at 5 years is around 10 % [69].

Gastrointestinal Toxicity

Rectal soreness and minor bowel changes may be encountered. Proctitis is uncommon and may be managed conservatively. The development of rectal ulceration or recto-urethral fistulae is rare. Among 825 patients with a median follow-up of 48 months post-brachytherapy, four patients (0.5 %) were found to have rectal ulceration at colonoscopy 1 year post-implant [70]. In a series of 754 patients followed up after monotherapy or combined EBRT and brachytherapy, 7 (1 %) developed a prostatourethral-rectal fistula [71].

Erectile Dysfunction

LDR brachytherapy has the lowest risk of impotence of the standard treatment modalities for localised prostate cancer. Most men who are potent before brachytherapy will have intact erectile function after treatment. Many of those who develop erectile dysfunction after brachytherapy will respond to sildenafil [11].

Secondary Malignancy

Secondary malignancy following radiation therapy is a potential concern. A Dutch study comparing 1,187 patients treated with LDR monotherapy with 701 patients treated with radical prostatectomy found no difference in the 10-year cumulative incidence of second malignancy between these two cohorts [72]. A retrospective study of 140,767 men from the US SEER (Surveillance, Epidemiology and End Results) registry treated with local therapy after diagnosis of prostate cancer showed that men treated with EBRT had statistically significantly higher odds of developing a second malignancy more than 5 year after treatment, compared to men who received no radiation in their treatment [73]. In this study, men treated with brachytherapy implants, whether combined with EBRT or not, did not have significantly higher odds of a second malignancy occurring more than 5 years after treatment.

Quality of Life

Most studies of quality of life among patients treated with brachytherapy have been retrospective. A prospective study of 409 patients undergoing treatment for localised prostate cancer with radical prostatectomy, EBRT or brachytherapy, stratified participants according to their baseline sexual, urinary and bowel function [74]. They found that patients with normal baseline sexual function treated with brachytherapy tended to preserve function better than similar patients treated with surgery or EBRT, or patients with intermediate function who were treated with brachytherapy.

Another prospective study compared 785 patients treated with open radical prostatectomy, robot-assisted laparoscopic prostatectomy, brachytherapy or cryotherapy. All treatments adversely affected all health-related quality of life domains. Higher overall urinary function and bother scores were found among the patients treated with brachytherapy or cryotherapy [75]. Brachytherapy was associated with higher sexual function than the other treatment groups. Brachytherapy and cryotherapy had a three-fold greater rate of return to baseline urinary function compared to surgery.

A prospective trial randomised 200 patients with low-risk localised prostate cancer between radical retropubic prostatectomy and LDR brachytherapy, with evaluation of genitourinary and bowel function, and quality of life at baseline, 6 months, 1 year and 5 years follow-up [76]. Similar 5-year PSA disease-free survival were reported for the two groups: 91.0 % (prostatectomy group) and 91.7 % (brachytherapy group). At 6 months and 1 year, both groups suffered a significant decrease in quality of life measures, with the brachytherapy group developing a higher rate of urinary irritative disorders for a longer duration but with better erectile function than the prostatectomy group. At 5 years follow-up, there were no significant differences in functional outcomes between the two groups.

Health Economics

The Institute for Clinical and Economic Review's report on comparative effectiveness and value for management options for low-risk prostate cancer reviewed the international literature, competency standards and previous systematic reviews and technology assessments for active surveillance, radical prostatectomy, brachytherapy, IMRT and Proton Beam therapy [77]. Overall survival rates for the large brachytherapy series reviewed ranged between 60 and 95 % at 10 years. Comparative value between the treatment modalities was estimated based on measures of potential economic impact including cost per life year gained, cost per quality-adjusted life year (QALY) gained, cost of service use (e.g. tests and hospitalisations), cost per curative outcome and cost per hospitalisation averted. Brachytherapy was found to save nearly $3,000 compared to the lifetime costs of the reference treatment pathway, radical prostatectomy, with a similar total lifetime QALYs. The estimated cost per QALY with brachytherapy was less than that of radical prostatectomy.

Temporary HDR Prostate Brachytherapy

The ability to escalate EBRT dose is limited by the uncertainty of prostate position due to daily setup errors of the patient position, variations in relative organ motion between fractions, organ deformation and motion during each fraction, and the limited ability of the dose distributions produced to conform to the shape of the target while sparing adjacent normal tissue (i.e. conformality).

Prostate HDR brachytherapy was first introduced in the late 1980s where it was used to escalate the dose delivered to bulky prostate cancers with EBRT, while increasing the accuracy of treatment planning and dose delivery. ^{192}Ir was first used clinically as an HDR source in intracavitary brachytherapy for cervical cancer and is now the most widely used radioisotope in brachytherapy.

HDR brachytherapy delivered in one or a few fractions is less affected by inter- and intra-fraction organ motion and patient setup errors because the applicators are inserted under transrectal ultrasound guidance and interactive real-time treatment planning systems are able to recalculate dose distributions after changes in position of the source [78, 79]. Prostate HDR brachytherapy has been implemented mainly in combination with EBRT, but may also be used as monotherapy.

HDR Implant Technique

Typically, a single ^{192}Ir source welded to the end of a cable is driven by remote control along the connecting transfer tubes to dwell within the applicators inside the tumour. The computer of the remote afterloader unit precisely controls the motion

and position of the source and its treatment planning system produces an optimised sequence of dwell-times and dwell-positions to generate a conformal dose distribution that is adequate for treatment. The source is returned to its heavily shielded safe between treatments. Throughout the procedure, the patient and the afterloader unit are monitored by CCTV and intercom.

The improved radiation protection afforded by remote afterloading has led HDR brachytherapy to replace LDR for most of the clinical applications of brachytherapy in malignant disease – with the exception of prostate cancer. An HDR unit is able to treat multiple patients with a single source until it needs replacement 3–4 months later, whereas individual sources need to be ordered specifically for each LDR brachytherapy patient. Patients do not need to take radiation protection precautions after a prostate HDR implant, since they are no longer radioactive. By delivering treatment over a few minutes, HDR does not allow tumour cells to repopulate or repair sub-lethal genetic damage, and its dosimetry is not affected by early postoperative prostate oedema or late prostate shrinkage due to radiation fibrosis. Modern HDR treatment planning system aim to improve the conformality and homogeneity of dose delivered to the target while sparing organs at risk by precisely modulating source dwell times and dwell positions within applicators. Disadvantages of HDR brachytherapy include the prolonged duration of the procedure (3–4 h), the complexity of the treatment planning and the acute toxicity profile (see below).

In the rare event that the source becomes stuck outside the safe, in one of the applicators or transfer tubes, the staff must follow the emergency protocol to physically wind the source cable back into the safe using the emergency crank (while monitoring personal exposure under stopwatch) or if this fails, to remove the transfer tube and applicator to an emergency source safe.

The HDR implant procedure is similar to that of LDR brachytherapy. The patient receives general or spinal anaesthesia and is placed in the dorsal lithotomy position. A transrectal ultrasound probe is used to visualise the prostate gland. 10–15 guide needles are inserted into the gland through the perineum under ultrasound guidance.

Toxicity of HDR Monotherapy

Acute toxicity reported in a combined series with 248 HDR monotherapy patients from William Beaumont Hospital (WBH) and California Endocurietherapy (CET) was as follows: dysuria 39 %, urinary frequency or urgency 58 %, urinary retention 36 %, rectal pain 6.5 % and rectal bleeding 3 % [80]. Most toxicities were Grade 1 and median follow-up was 4.6 years. Late toxicity rates included urinary urgency or frequency 43 %, dysuria 15 % and urethral stricture requiring dilatation 3 %. The 5-year impotence rate was 20 %.

In a study of patients treated with three different HDR monotherapy dose-fractionations (20 Gy in 4 fractions, 18 Gy in 3 fractions and 19 Gy in 2 fractions), 45 patients developed at least one urethral stricture [81]. The overall risk of developing a urethral stricture at 2 years was 8.2 %. The 2-year risk of stricture formation

was 3.4 % for 18 Gy/3#, 2.3 % for 20 Gy/4# and 31.6 % for 19 Gy/2#. Half of the strictures affected the bulbomembranous urethra and one-third affected the external sphincter region. Most of the strictures were mild – only one required intervention. The dose schedule used was the only significant factor predicting increased risk of stricture formation on multivariate analysis, with the highest risk group being the patients who received 19 Gy in 2 fractions.

Follow Up

Patients should be seen 4–6 weeks postoperatively to assess their acute toxicity. In the first year, they should be seen 3-monthly, then 6-monthly up to 5 years and annually thereafter. Clinical assessment of late toxicity is assisted by using validated scoring systems for urinary, erectile and bowel function side effects. Digital rectal examination findings and serum PSA should be recorded.

Routine biopsies are not necessary, but may be indicated if a palpable nodule is detected on DRE or the PSA rises [14]. Biochemical failure may be denoted by three successive rises of PSA taken at least 3 months apart, however this may not be an indication for further treatment. The phenomenon of PSA bounce has been described in prostate EBRT and may produce a self-limiting rise in PSA a year or two after brachytherapy [82]. The ESTRO-EAU-EORTC guidelines recommend considering salvage treatment for biochemical failure if the PSA doubling time is less than 1 year and the PSA is greater than 10 ng/mL [17]. Patients with a longer PSA doubling time may be monitored with an annual isotope bone scan. Local salvage treatment options are accompanied by high risks of morbidity and include radical prostatectomy, further seed implantation and EBRT.

Results

LDR Monotherapy and Combination Therapy (EBRT and LDR Boost)

Most of the reports of clinical outcome with LDR brachytherapy come from large single and multi-institutional series and many of these contain a mixture of patients treated with LDR monotherapy and those who received a combination of EBRT and LDR boost. Several of these series use slightly different definitions of the three patient risk groups. There is no universal definition of biochemical failure.

The Memorial Sloan-Kettering group developed a risk classification based on EBRT dose-escalation studies in which the low risk group criteria were PSA $\leq$10 ng/mL and T1-T2 disease and Gleason score <7. Intermediate risk patients are defined by exceeding one of the low risk criteria, and high risk patients by exceeding two or

more criteria. Among their series of 248 patients treated with LDR monotherapy, 59 % were low risk, 34 % intermediate risk and 7 % were high risk [83]. With median follow-up of 4 years and adopting the ASTRO definition of PSA relapse, the overall 5-year biochemical relapse-free survival was 71 %. The 5-year PSA RFS for low-risk, intermediate-risk and high-risk were 88, 77 and 38 %, respectively.

The Mount Sinai group define their risk stratification as: low-risk (T2a or less, Gleason score less than 7 and PSA ≤10 ng/mL), intermediate-risk (T2b-T2c or Gleason score 7 or 10 < PSA ≤ 20) and high-risk (two or more intermediate risk factors or Gleason score 8–10 or PSA >20 ng/mL). They published a series of 243 patients treated with LDR monotherapy with a median follow-up of 6.3 months [84]. 60 % of patients received neoadjuvant ADT and 1-month CT post-implant dosimetry was available for all patients. Patients were retrospectively grouped into an optimal dose implant group (60 %) and a suboptimal dose implant group (40 %) according to whether their D90 reached the doses recommended by the AAPM Task Group 43: ≥140 Gy for ^{125}I and ≥100 Gy for ^{103}Pd [85]. They found that patients in the optimal dose implant group had a significantly better 8-year biochemical freedom from failure rate (bFFF) (using the Nadir + 2 criteria) of 82 % compared with 68 % among the suboptimal dose implant group. There was a superior 8-year bFFF for the low-risk patients within the optimal dose implant group (94 %) compared with low-risk patients in the suboptimal dose implant group (75 %).

The Mount Sinai group produced a study of disease-specific survival among 1,561 patients treated with LDR monotherapy (634 patients), brachytherapy and ADT (420 patients) and EBRT combined with brachytherpay (507 patients) [86]. The median follow-up was 3.8 years. At 10 years, disease-specific survival was 96 % and overall survival, 74 %. They found that Gleason score had a substantial impact upon 10-year disease-specific survival (98, 91 and 92 % for Gleason scores 6 or less, 7 and 8–10, respectively).

The Leeds group in the UK published their series of 1,298 patients treated with LDR monotherapy, stratified according to the Memorial Sloan-Kettering classification (low risk: PSA ≤10 ng/mL, Gleason score 2–6 and cT1-T2; intermediate risk: the presence of one of PSA >10 ng/mL, Gleason score < 6, or T3 disease; and high risk: the presence of two or three of the intermediate risk factors) [87]. The distribution of patients according to risk group was 44 % low risk, 33 % intermediate risk and 14 % in the high-risk group. Neoadjuvant hormone therapy with an LHRH analogue or an anti-androgen was used in 44 % of patients for cytoreduction for prostates larger than 50 mL and no EBRT was used. Two definitions of biochemical failure were used to aid comparison to previous series: the ASTRO definition (three consecutive PSA rises backdated to the mid-point of the nadir and the first rise) modified to account for PSA bounce, as well as the Phoenix definition (nadir PSA plus 2 ng/mL). The median follow-up was 4.9 years and the actuarial rates of biochemical relapse-free survival at 10 years of 79.9 and 72.1 % using the ASTRO and Nadir + 2 definitions, respectively. Higher presenting PSA or Gleason score and the use of neoadjuvant hormone therapy were found to be associated with a significantly increased risk of biochemical failure. CT-dosimetry 6–8 weeks post-implant was available in 53.0 % of patients and a dose–response relationship

with a significantly improved biochemical relapse-free survival for patients achieving $D_{90} \geq 140$ Gy.

In one of the largest series using modern brachytherapy techniques and day 0 post-implant dosimetry, 1,656 patients were stratified according to the Mount Sinai classification [88]. Thirty-five percent presented with low-risk disease, 37 % presented with intermediate-risk disease and 28 % were in the high-risk group. Neoadjuvant ADT was given to 37 % of patients. EBRT was given to 50 % of patients in combination with LDR brachytherapy. Biochemical progression-free survival (bPFS) was defined as a PSA of ≤0.40 ng/mL after nadir. Median follow-up was 7.0 years. At 12 years, bPFS was 95.6 % overall and was 98.6, 96.5 and 90.5 % for patients with low-, intermediate- and high-risk disease, respectively. The percentage of positive biopsy cores and risk group were found to be the strongest predictors of bPFS on multivariate analysis.

The Prostate Cancer Results Study Group reviewed the literature (mainly non-randomised series) during 2000–2010 of studies related to the treatment of localised prostate cancer, which reported PSA relapse-free survival with a follow-up of at least 5 years [89]. In their analysis, a higher average PSA progression-free survival was found for patients in the low-risk group treated with brachytherapy, compared to radical prostatectomy or EBRT. Among intermediate-risk patients, higher mean progression-free survival was reported with LDR and HDR brachytherapy, than for surgery or EBRT. For patients in the high-risk group, those treated with combined ADT, EBRT and brachytherapy had higher progression-free survival than radical prostatectomy, EBRT or brachytherapy alone.

Combination Therapy: EBRT and HDR Brachytherapy Boost

The addition of an HDR boost to EBRT has been shown to be superior to EBRT alone in two randomised trials. A Canadian study randomised 104 patients with T2-3 N0 M0 prostate cancer between 66 Gy in 33 fractions EBRT alone (a dose that would be considered suboptimal by contemporary standards) and HDR 35 Gy delivered over 48 h and 40 Gy in 20 fractions EBRT. The median follow-up was 8.2 years. The primary outcome was biochemical or clinical failure and this was significantly better in the HDR boost plus EBRT arm: 29 % versus 61 %. The 2-year post-treatment prostate biopsy positivity rate favoured the experimental arm: 24 % versus 51 % in the EBRT-only arm.

A UK phase III trial randomised 220 patients with non-metastatic prostate cancer and an initial PSA less than 50 ng/mL to receive either standard EBRT of 55 Gy in 20 fractions or 35.75 Gy in 13 fractions EBRT followed by an HDR boost of 17 Gy in two fractions over 24 h [90]. The median follow-up was 30 months. Actuarial biochemical relapse-free survival was significantly better in the combined HDR-EBRT arm ($p = 0.025$).

The results of a Canadian phase II/III study has led to the growing popularity of using a single HDR fraction as a boost with EBRT due to its tolerability. One

hundred and twenty one patients with cT1c-T2b disease and either a Gleason score of 6 with a PSA of 10–20 ng/ml, or a Gleason score of 7 and a PSA greater than 20 ng/ml, were given a single 15 Gy fraction of HDR followed by 37.5 Gy EBRT in 15 fractions over 3 weeks. Median follow-up was 1.14 years. Toxicities were assessed on the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) version 3. Within the first 3 months, 59 % experienced Grade 2 gastrointestinal toxicity and 6.5 %, Grade 1. Grade 3 acute genitourinary toxicity occurred in 1.6 % (2 patients required temporary catheterisation for urinary retention) and 62.8 % developed Grade 2 toxicity. Prostate biopsies planned at the 2-year point showed no evidence of malignancy in 16 of the 17 cases [91].

HDR Monotherapy

In one large HDR monotherapy series, 298 patients (the majority of whom were in the low-risk group) were treated with two biologically similar fractionations [92]. One hundred and fifty seven patients at California Endocurietherapy (CET) received 42 Gy in 6 fractions given using two implantations 1 week apart, and 141 patients at William Beaumont Hospital (WBH) received 38 Gy in 4 fractions with a single implantation. The median follow-up was 5.2 years. The 8-year biochemical control rate (using the Phoenix definition of sustained post-treatment PSA greater than the nadir PSA + 2 ng/mL) was 97 % and the 8-year distant metastasis-free survival was 99 %. Gastrointestinal toxicity was <1 % and genitourinary (toxicity scored with the National Cancer Institute Common Toxicity Criteria for Adverse Events version 3) was 10 % Grade 2 urinary frequency or urgency and 3 % Grade 3 urinary retention.

A UK HDR monotherapy dose escalation study treated 197 patients with four fractionations (34 Gy in 4 fractions, 36 Gy in 4 fractions, 31.5 Gy in 3 fractions and 26 Gy in 2 fractions) [93]. 52 % of patients were in the intermediate-risk group and 44 % had high-risk disease. 157 patient received ADT for a median duration of 6.3 months. At 3 years, 99 % of intermediate-risk patients were free of biochemical relapse, and 91 % among the high-risk group. The 3-year actuarial rate of urethral strictures requiring surgical intervention was 5 %.

Most of the reports of prostate HDR monotherapy are small series using a wide variety of dose fractionations, rather than large phase III studies. Prostate cancer is thought to be very sensitive to the size of dose per fraction. Thus HDR is expected to have a greater radiobiological effect on prostate cancer than EBRT or LDR brachytherapy.

Focal LDR Brachytherapy

Interest in treating low volume low- to intermediate-risk prostate cancer with local ablation techniques such as cryotherapy and high-intensity focused ultrasound (HIFU) has led to efforts to evaluate focal LDR brachytherapy in highly selected

patients [94, 95]. The aim of this experimental technique is to improve long-term quality of life by reducing genitourinary and rectal toxicity while maintaining local cancer control.

Conclusions

Modern brachytherapy delivers high radiation doses to a highly mobile prostate gland under image guidance. A selection of therapies including LDR monotherapy, neoadjuvant androgen deprivation therapy, external beam radiotherapy and HDR as a boost or monotherapy, can be used to manage low-, intermediate- and high-risk localised prostate cancer in suitable patients. The safe and accurate delivery of these treatments depends on rigorous quality assurance procedures, radiation protection measures, technical skill and carefully co-ordinated teamwork. Future technical innovations and large clinical studies offer the hope of further improvements in the quality of brachytherapy delivered and its eventual clinical outcomes.

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Chapter 44
Cryotherapy for Prostate Cancer

Eric Barret

Cryotherapy is a type of thermal therapy that ablates tissue by local induction of extremely cold temperatures. According to the American Urological association (AUA) Best Practice Statement [1], cryotherapy can be indicated as primary therapy or salvage therapy in prostate cancer (PCa).

Mechanism

The principles of cryotherapy include the mechanisms of cell injury and cell death. Cryotherapy induces cell damages due to direct cellular toxicity from disruption of the cellular membrane by ice crystals and vascular compromise from thrombosis and ischemia [2]. The first effect of cryotherapy is the extracellular ice formation which occurs at −7 °C. Ice crystals form between the cells and this dehydrates intercellular space which draws water from the cells causing the cells to dehydrate. The dehydration destroys or severely injures the intracellular mechanisms of the cell that keep it alive. The second effect is the intracellular ice formation: As the temperature drops to −15 °C, ice crystals form within the cells leading to the explosion of the cell membrane.

Finally, as this process continues, the blood that flows through the vessels within these tissues coagulates thereby cutting of the blood supply to these tissues eliminating oxygen supply and nutrition to the target cells. The end result is the coagulation necrosis in the target tissue [3]. Rapid freezing is preferred to slow freezing because of its destructive nature. In addition cancer cells can "adapt" to the process of slow freezing by losing water to the extracellular area, thereby reducing the probability of intracellular ice formation.

E. Barret, MD
Department of Urology, Institut Montsouris- Universite Paris Descartes, Paris, France
e-mail: eric.barret@imm.fr

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Procedure

Cryotherapy can be performed under either spinal or general anesthesia. The patient is placed in the dorsal lithotomy position. The ultrasound probe is placed in the rectum and is adjusted in such a way that whole gland can be properly visualized. Multiple cryoprobes (17G) are inserted into the prostate through the perineum, using a brachy-like template (Figs. 44.1 and 44.2).

Argon gas is used to cause the rapid freezing at the cryoprobe tip, based on the Joule-Thomson effect: when high pressure argon flows through the cryoprobe, it generates at the tip a very cold temperature, resulting in ice ball formation which damages the tissue. All the cryoprobes are inserted under ultrasound guidance. The number of cryoprobes used will depend on the target prostatic volume. Thermal sensor needles are also inserted into the prostate and the Denonvilliers' fascia for the temperature

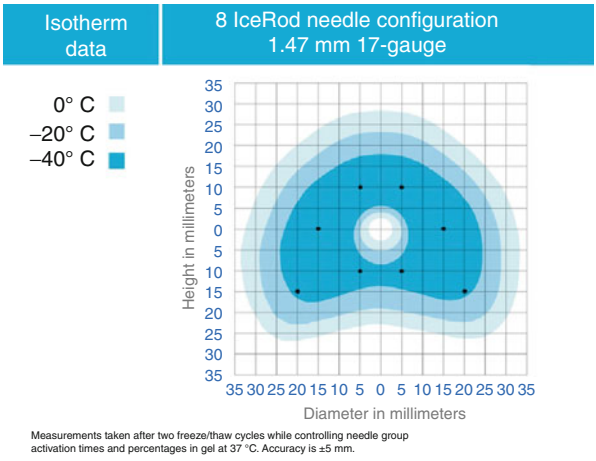

Fig. 44.1 Cryoprobe placement for whole-gland treatment (Courtesy of Galil Medical, Inc, USA with permission)

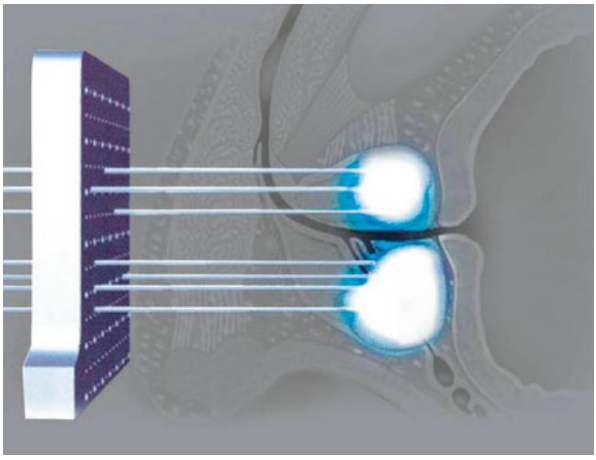

Fig. 44.2 Cryoprobe template insertion (Courtesy of Galil Medical, Inc, USA with permission)

monitoring. A warming catheter is placed in the urethra for its protection and also to prevent the freezing of sphincteric muscle. Thermal sensor needles and ultrasound allow a real-time monitoring and a good control of freezing during the procedure. The objective is to achieve a temperature of the target zone to −40 °C or lower while minimizing effects of freezing temperature on rectum and external sphincter which helps in avoiding collateral damage that can result in rectal and urinary symptoms. Once the targeted area is frozen for 10 min, the thawing is employed. This is called the freeze-thaw process. Two freeze-thaw cycles appear to achieve the best tissue ablation [4].

The exact position of the needle placement is verified using ultrasound during the procedure. To achieve a proper placement following precautions are observed.

Cryoprobes should not be placed farther than 1.8 cm apart, they should not be placed farther than 1.0 cm from the margin of the prostate and the distance between the urethra and any cryoprobe should not be less than 0.8 cm [5]. At the end of the procedure, cryoprobes, thermal sensor needles and warming catheter are removed. A urinary catheter is inserted and left in place for 2 or 3 days.

Assessment After Cryotherapy

The response to the treatment is assessed by serial serum prostate specific antigen (PSA) estimations as done after radical prostatectomy (RP) or radiation therapy (RT) (PSA). PSA levels are checked at 3 monthly intervals for the first year and thereafter once every 6 months [2]. After cryotherapy, PSA is still detectable because of the preservation of peri-uretral tissue, which could potentially produce residual PSA. The acceptable PSA levels following treatment are not well defined. However, getting the PSA nadir level within 3 months should provide early evidence of the treatment efficacy. We should consider that PSA nadir ≤0.5 ng/ml should be achieved to expect an increased chance of a stable PSA and negative control biopsy [6]. At the opposite, high PSA value should be associated with a high risk of residual disease [7].

Treatment failure should be determined by using the PSA-based definition of biochemical failure (BCF) and any positive biopsy. Various definitions of BCF are currently used in the literature including the American Society for Therapeutic Radiology and Oncology (ASTRO) definition (three consecutive rising PSA levels) and the Phoenix definition (PSA nadir plus 2). Then, in order to get a better evaluation of treatment results, control biopsies could be recommended between 6 months and 1 year after the treatment [8].

In the beginning, high morbidity rates were reported after cryotherapy. Patients were most concerned about the risks of incontinence and impotence. With improvements of technology, complication rates have fallen but a good evaluation remains mandatory as some of the complications can still be encountered: short term complications include urinary retention, penile or scrotal swelling, penile paraesthesia, sepsis while long term complications include urinary incontinence, fistula, urethral stricture, sloughing, perineal pain and erectile dysfunction [9].

Primary Cryotherapy

Primary cryotherapy represents a viable option for whole-gland treatment in patients with pathological evidence of localized PCa, who do not wish to undergo a RP or RT. Moreover, cryotherapy represents a valuable option in older population and patients with comorbidities.

Patient Selection

Suitable candidates for primary cryotherapy are men with clinically confined PCa (stage T1c or T2), with any Gleason grade, without metastatic disease (N0M0), and with a greater than 10-year life expectancy. Theoretically, cryotherapy can be considered for low, intermediate and high risk PCa. However, it is important to note that high risk patients may require multimodal therapy and also the role of cryotherapy for clinical T3 disease remains to be determined [2].

Other features like gland volume, prior transurethral resection of the prostate (TURP), number of positive cores, baseline PSA, and the risk of lymph node involvement are important to consider when selecting patients. In term of gland size, it may be difficult to achieve a uniformly cold temperature in a prostate larger than 50 cm^3. A short hormonal deprivation treatment could be used to downsize gland volume. A prior TURP is a relative contraindication for cryotherapy, due to the increasing risk of tissue sloughing. Larger number of positive cores and higher PSA (>20 ng/ml) represent a risk of lymph node involvement and therefore cryotherapy may not offer optimal local control [1] (Table 44.1).

To summarize, optimal candidates for primary cryotherapy generally include those with lower stage, lower-volume disease with PSA levels ≤10 ng/ml.

Treatment Outcomes

Oncological Outcomes

Long-term data after primary cryotherapy are now available. Several studies have been published on follow-up data ranging in duration from 5 to 10 years. Cohen et al. [10] reported a 10-year biochemical disease-free survival rate of 80.56, 74.16, and 45.54 % for low, intermediate, and high-risk groups respectively (D'Amico

Table 44.1 Indications to whole-gland primary cryotherapy

Indications to cryotherapy
cT1c- cT2
PSA < 20 ng/ml
Gleason score ≤ 7
Gland size ≤ 50 cm^3

criteria). The 10-year negative biopsy rate was 76.96 %. Five-year data from the Cryo-OnLine Database (COLD) Registry [11] demonstrated a biochemical free disease survival at 84.7, 73.4 and 75.3 % for % for the low, intermediate and high risk groups respectively, using the ASTRO definition and at 91.1, 78.5 and 62.2 % using the Phoenix definition. In this study, only 28.5 % of the patients underwent control biopsies. Positive biopsy rate was 38 % in the group of patients with suspicion of failure treatment due to abnormal or increasing PSA, and 14.5 % for patients who underwent biopsy without any cause. However, negative post-treatment biopsy will not be a proof of cancer eradication and a long term follow-up is necessary. Nevertheless, when comparing results with those of other non-extirpative technique (radiotherapy or brachytherapy), primary cryotherapy seems to offer equivalent outcomes in terms of efficacy [12, 13].

Complications

Clavien-Dindo' low grade (grade I) perioperative complications like urinary retention, penile or scrotal swelling and penile paresthesia can be seen in patients treated with cryotherapy [8]. These events can be easily managed with appropriate medical treatment. More serious complications such as perioperative sepsis are not frequent and they obviously require a more aggressive intervention. Below we will focus on the long-term adverse events of the procedure.

Recto-urtehral Fistula

Even though this complication is rarely reported after primary cryotherapy due to improved technique improvements, this is probably the most feared. The current risk of recto-urethral fistula ranges between 0 and 0.5 %, which appears similar to those following radical prostatectomy and radiation therapy [7].

Urinary Incontinence

Urinary Incontinence (UI) is a potential complication after cryotherapy. Use of a urethral warmer catheter should prevent such risk, but its possibility still exists. The causes are usually due to damage to the striated sphincter and detrusor instability [2]. The incidence of severe urinary incontinence reported in the range of 1–7.5 % [14].

Erectile Dysfunction

Erectile Dysfunction (ED) occurs frequently after primary cryotherapy primarily due to the freezing of neurovascular bundles. The rate of ED ranges from 49 to 93 % at 1 year [1]. The mechanism is significantly different from the damage that occurs

during surgery. As ED is caused by freezing of the neurovascular bundles, the nerves themselves remain intact during the treatment; so for this reason, a potential recovery is a possibility. In order to achieve a better penile rehabilitation, regular use of a vacuum erection device is recommended [5]. Nevertheless, because there is a high risk of post-treatment ED, whole-gland primary cryotherapy is not considered in patients who wish to preserve their sexual function.

It is important to note that these outcomes are not necessarily a reflection of the true efficacy of cryotherapy as currently practiced because some of the reported data have been collected from different generation systems. We could now expect decreasing rate of complications using modern cryotherapy.

Salvage Cryotherapy

Salvage cryosurgery can be considered as a treatment option with a curative intent in men who have failed radiation therapy. Salvage therapy is generally indicated for patients with rising PSA, positive prostatic biopsies and no metastatic disease. A pre-treatment nomogram based on serum PSA at diagnosis, biopsy Gleason grade and initial clinical stage was developed and might allow the selection of ideal candidates for salvage cryotherapy [15]. Williams et al. [16] recently reported that salvage cryotherapy led to an acceptable 10-year disease free survival with pre-salvage PSA and Gleason score as the best predictors of disease recurrence. A PSA nadir >1 ng/dl following cryotherapy was verified as a poor prognosis. Furthermore, Cheetham et al. [12] presented their long-term results of primary and salvage prostate cryotherapy and their series showed an 87 % overall 10-year prostate-cancer-specific survival, despite early cryotherapy technology and the majority of patients being D'Amico high risk.

In order to evaluate cancer control outcomes, one should keep in mind that undetectable measure of the marker (PSA) is not possible after salvage cryotherapy and therefore, a post-treatment biopsy is the ideal method to define treatment efficacy. Biochemical failure free rates vary from 59 to 74 % for whole gland salvage cryoablation. Partial cryoablation has been also explored and Eisenber and Shinohara achieved 3-year BCR free survival rates of 89 and 79 % at 3 years in accordance to ASTRO and Phoenix definitions, respectively [2, 17].

Concerning functional outcomes, there is still work to be done in terms of quality of life and urinary symptoms reporting after salvage cryotherapy. No baseline information is provided in the published reports and generally complications are reported in association with functional outcomes without the deployment of a validated instrument of evaluation. Overall over 70 % of patients report dribbling or leakage up to over a year post-procedure. Incontinence has been reported to around 36 % for patients undergoing savage cryotherapy [2, 17].

The evaluation of outcomes has been presented in terms of "bifecta" defined as achieving a post-cryotherapy nadir serum PSA level of $\leq$0.5 ng/ml with no urinary incontinence. Bifecta has been reported as achieved in 72 % of patients with a mean age of 71 years old and a baseline pre-salvage total serum PSA level of <10 ng/ml with a pre-treatment biopsy of a Gleason score <8 [2].

Regarding erectile function the baseline situation of patients with rising PSA is naturally poor and penile rehabilitation has not been prospectively evaluated in this population. Available literature shows that even with continuous administration of phosphodiesterase-5 inhibitors, the results are not beyond 15 % of patients capable to achieve erection good enough for penetrative sex. Complications are more likely to occur in patients undergoing salvage treatment vs. those who received primary therapy due to the altered tissue characteristics of the former group [2].

Focal Cryotherapy

Cryotherapy belongs to the group of minimally invasive therapy technologies that are suitable for focal therapy. Focal therapy in PCa is an individualized therapy that precisely ablates known disease while preserving functionality of the gland, attempting to minimize lifetime morbidity without compromising life expectancy [18].

Patient Selection

The selection of patients remains a controversial issue, where potential tumor multifocality and exact determination of index lesions remain the essential issues to assess. However, it is generally agreed that selection of patients with unilateral, low-volume/low-risk proven PCa may be suitable for focal therapy. The recommended inclusion criteria are: unilateral prostate cancer clinical stage cT1-cT2a, PSA <10 ng/mL, PSA density less than 0.15 ng/ml, PSA velocity less than 2 ng/ml yearly, no biopsy Gleason grade 4 or 5, no more than 33 % of cores containing cancer, <50 % of cancer in any core and no evidence of extraprostatic extension [19, 20].

Procedure

Cryoprobes are placed as previously described. By limiting the number of cryoprobes and adjusting their placement, it is possible to perform a focal treatment that ablates only a targeted portion of the gland. Mouraviev et al. [21] reported different options for focal prostate ablation: zonal ablation, hemi-ablation and sub-total ablation and he described the hemi-ablation as the optimal model for focal therapy.

Outcomes

Several publications demonstrated the role of focal cryotherapy as a successful treatment of localized PCa with limited morbidity. Nevertheless, post-treatment evaluation is difficult because current strategies reported for organ-preserving prostate cancer ablative therapy have varied in their eligibility criteria and the

Table 44.2 Oncological outcomes after focal cryotherapy

Authors	N	F. U.	bDFS	N Bx (%)	Ipsilat Pos. Bx	Controlat Pos Bx
Bahn et al. [22]	31	70	93 % (ASTRO)	25 (80 %)	0	1
Ellis et al. [5]	60	17	80 % (ASTRO)	35 (58 %)	1	13
Onik et al. [23]	48	54	94 % (ASTRO)	48 (100 %)	0	4
Truesdale et al. [24]	77	24	73 % (Phoenix)	22 (28 %)	3	7

Table 44.3 Morbidity outcomes after focal cryotherapy

Authors	N	Fistula (%)	Incontinence (%)	Potency rates (%)
Bahn et al. [22]	31	0	0	88.9
Ellis et al. [5]	60	0	3.6	70.6
Onik et al. [23]	48	0	0	90
Truesdale et al. [24]	77	0	0	95

amount of tissue targeted for destruction and/or preservation. Because the treatment is limited to one lobe with the contralateral lobe being intact producing PSA, the PSA interpretation is not easy. Furthermore, the authors did not use the same biochemical failure definition and control biopsies were not systematic in all the cases.

Despite the relative paucity of data, results are encouraging with biochemical disease free survival rates ranging from 73 to 94 %. Among patients who had control biopsies, very few of them proved to have residual cancer in the treated lobe [5, 22–24] (Table 44.2).

The reported potency preservation (with or without pharmaceutical assistance) was 70.6–95 % and the continence preservation was 96.4–100 %. No major complications (rectal injury, urethral stricture, urethral sloughing, abscess) were reported in any of the published series [5, 22–24] (Table 44.3).

Conclusion

Modern cryotherapy is a valid minimally invasive therapy option for PCa and should no longer be considered as an experimental treatment. Available long-term results support cryotherary as a safe and reliable treatment for both primary or salvage treatment.

The technique has evolved through experience and outcomes are expected to improve in the most recent experiences performed with the latest available technology. Cryotherapy evolution runs towards focal ablation of prostatic tumors, which is an interesting additional field in cryosurgery holding a great potential and currently under evaluation.

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Chapter 45
High Intensity Focused Ultrasound (Hifu) in Prostate Cancer

Gilles Pasticier

HIFU is an ablative technique which uses high frequency acoustic waves produced by a transducer and the waves deposit energy as they pass through the tissue in question. First described in the early fifties to destroy brain lesions [1], the ability of focused ultrasound on prostate in dogs and subsequently on human prostate cancer was reported by Gelet et al. in 1993 and 1999 [2, 3]. Gelet et al. published the results of their pilot study in 1996 and results of their first 50 patients in 1999 [3].

To date, around 30,000 patients have been treated worldwide. Two devices – Sonablate® (focus surgery Inc., Indianapolis, USA) and Ablatherm® (EDAP-Technomed, Vaulx-en-Velin, France) are currently available (Figs. 45.1 and 45.2).

Mechanisms of Action

In contrast to its use in ultrasound imaging techniques, the high acoustic energy leads to higher temperatures enough to cause a coagulation necrosis when focused on a precise tissue point [4]. In initial stages there is generation of microbubbles with the absorption of the energy and heat generation. The interaction between microbubbles and ultrasounds produces a cavitation effect resulting in cellular, and subsequent tissue destruction. Both thermal and cavitation effects are responsible of the tissue destruction by coagulative necrosis [5]. The sum of elementary lesions applied tight to each other allows a volume targeting compatible with prostate gland shape destruction.

G. Pasticier, MD
Department of Urology, Service d'urologie A-Hopital Pellegrin Place,
University Hospital Pellegrim, Bordeaux, France
e-mail: gilles.pasticier@chu-bordeaux.fr

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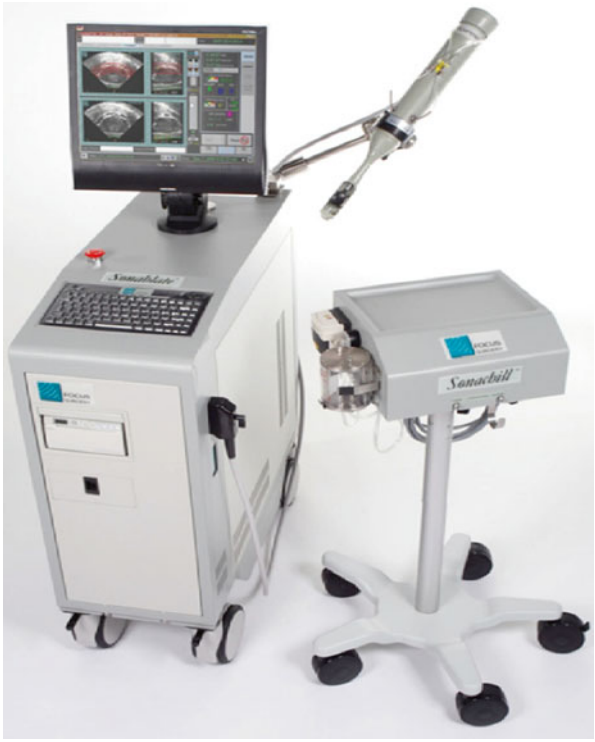

Fig. 45.1 Sonablate® device

Fig. 45.2 Ablatherm® device (Courtesy of EDAP)

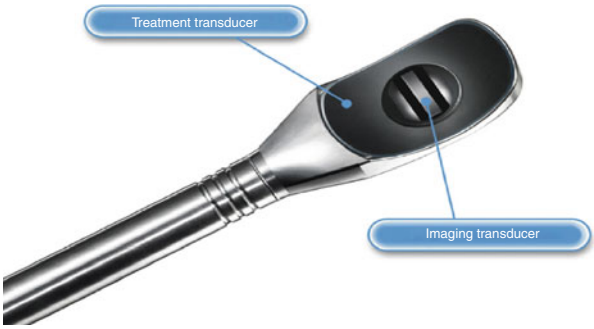

Fig. 45.3 Imaging and treatment transducer (Ablatherm® device) (Courtesy of EDAP)

The two available devices – Sonablate® (Focus Surgery Inc, Indianapolis, Ind, USA) and Ablatherm® (EDAP-TMS SA, Lyon, France) deliver focused ultrasound through a transrectal approach. The basic working principles are same apart from some technical differences. A transrectal high-frequency transducer in a balloon filled with water to prevent heating of the rectal wall (thereby minimizing the risk of recto-urethral fistula) is placed in the rectum. There is also a mechanism to monitor rectal temperatures.

Sonablate® offers transducers of different focal lengths (25–45 mm) with a fixed elementary lesion length of 10 mm × 2 mm in width while Ablatherm® includes a unique focal energy transducer (40 mm) and an imaging transducer in the same endorectal probe, thus allowing a real-time control of imaging the treatment (Fig. 45.3); elementary lesion length varies from 19 to 26 mm × 2 mm in width (Figs. 45.4, 45.5, and 45.6). Generally speaking for the two devices, the volume of the prostate at the time of delivery of HIFU has to be less than 35 cc. Therefore, a TURP or even a previous adenomyomectomy in high volume prostates may be beneficial to achieve an adequate volume at the time of HIFU. In fact there is evidence to show that a previous TURP before HIFU, reduces the chances of acute urinary retention and bladder outlet obstruction after HIFU treatment. This can potentially reduce the time of urethral catheterization (4 days vs. 15 days) [6–9].

Indications for HIFU

It is important to note that most of the available data has been retrospective and long term results and potential use of HIFU as a primary treatment similar to radical prostatectomy or EBRT need to be confirmed by randomised trials. There is also lack of consensus on various PSA thresholds and objective response criteria.

Various guidelines including European Association of Urology (EAU), the American Urologic Association (AUA), the UK National Health Service based National Institute for Health and Clinical Excellence (NICE) Prostate Cancer guidelines and the US Federal Drug Administration do not currently recommend HIFU as a standard treatment for the management of clinically localized prostate cancer [10–12].

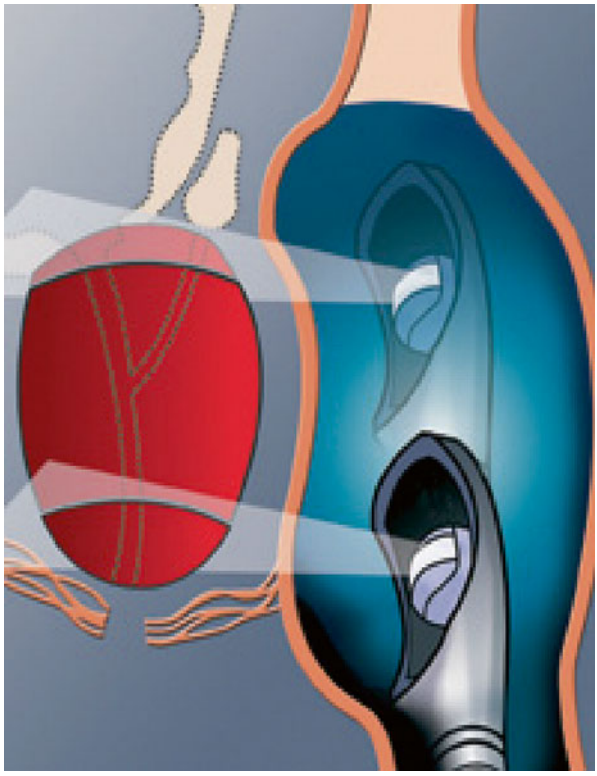

Fig. 45.4 Ultrasound probe used for imaging (Courtesy of EDAP)

However, the management of PCa by HIFU could be considered in three settings:

(a) As a primary treatment for localised prostate cancer (T1c-T2a, N0 M0)
(b) Salvage therapy after failure of EBRT or Brachytherapy
(c) Focal HIFU therapy

Contraindications for HIFU

There are some relative contraindications for HIFU but a rectal thickness >6 mm or rectal stenosis are the true real contra-indications of an HIFU treatment. In patients with of chronic inflammatory bowel disease the choice of treatment of PCa could be challenging and HIFU treatment is a feasible when employed cautiously [13]. As mentioned earlier gland volume is a relative contraindication. Any interference with ultrasound imaging such as prostatic stones can interfere with the procedure. This could be avoided by doing a TURP prior to the procedure.

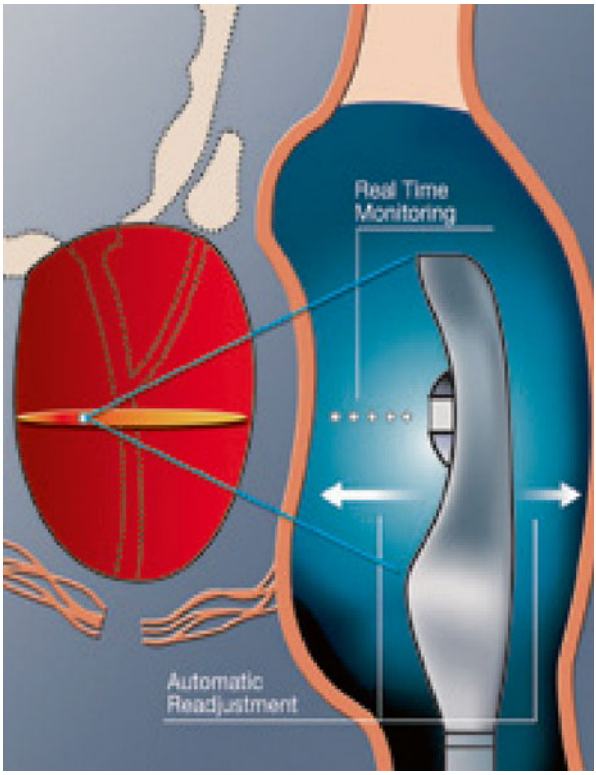

Fig. 45.5 delivering HIFU (Courtesy of EDAP)

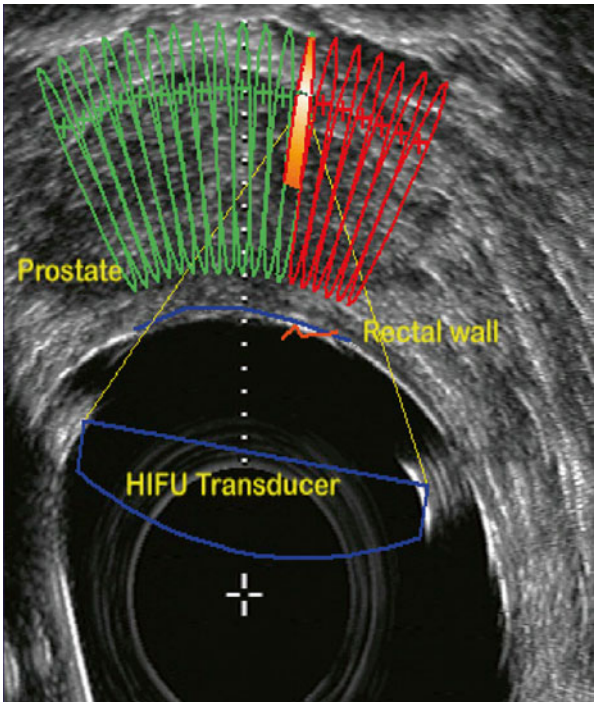

Fig. 45.6 Real time control imaging (Courtesy of EDAP)

Table 45.1 Criteria defined by French Urological Association

Age >70 years and >7 years of life expectancy
Clinical stage T1 or T2
PSA <15 ng/ml
Gleason ≤7
Prostate volume <50 cc

HIFU as a Primary Care Treatment

According to the French Urological Association, HIFU can be an option as a primary care treatment for the specific patients (Table 45.1)

HIFU can be repeated several times – It has been shown that a second HIFU session may improve oncological control [14–16]. However, there is no gain beyond two HIFU sessions and on the contrary there is a possibility of increase in morbidity [17, 18].

Salvage HIFU After EBRT Failure

Considering the high rate of positive biopsies after EBRT of 30–40 % [19] and the significant morbidity involved in salvage prostatectomy [20–23], the role of HIFU as a salvage option has been addressed since 1993 in specialized centres like Lyon University Hospital [24]. The key points in selecting these patients are, to confirm the local recurrence by prostate biopsies, exclude any detectable distant metastasis (with whole body CT scan, bone scintigraphy and eventually with [10] Choline PET/CT). An assessment is then made regarding the benefit of the treatment with a curative intent (considering the predictive factors of success) against the side effects of HIFU in this setting (see results section). In relation to brachytherapy failure, clinical trials are still ongoing with a very few published data at present [25].

Focal HIFU Treatment

The European Randomised Study of Prostate Cancer (ERSPC) has concluded that there is a reduction of mortality of prostate cancer thanks to screening of PCa but the screening has an underlying risk of overdiagnosis and therefore overtreatment [26]. Similarly, Cooperberg et al. have shown that selected men with intermediate risk features active surveillance may be appropriate as in these men the cancer is not likely to progress [27]. Although active surveillance is gaining a growing interest, it is worth noting that between 20 and 30 % of patients are misclassified and nearly 30 % of these patients will ultimately need a radical treatment. The negative impact of active surveillance in terms of progression of the cancer has still to be addressed [28, 29]. Nearly 20 % of PCa are located on one side only according to a series of radical prostatectomies [30]. In such patients, to prevent overtreatment

and undertreatment focal therapy may be the choice. The ideal conditions to for focal treatment are: that the treatment should be feasible (focal destruction proven), there has to be endpoints to address efficacy of treatment, treatment should be cost-effective, feasibility of another type of radical treatment in case of failure. All these criteria must be satisfied before undertaking the clinical trials. Although there are no major safety concerns about the treatment, evidence acquisition regarding mechanism of action and side effects is still lacking.

HIFU Outcomes

HIFU as a Primary Care Treatment

Oncological outcomes: Table 45.2 show results of HIFU as a primary treatment for the major series. As mentioned earlier, one of the limitations to address HIFU results properly is the relative heterogeneity of endpoints. Many series have used Phoenix definition to assess the biochemical failure. One of the main criticisms of usage of Phoenix definition is that it has been exclusively for radiation and not for other physical agents [34].

Usually PSA nadir is achieved around 3 months after HIFU. As the nadir value has a strong predictive value with a threshold of 0.2 and 0.5 ng/ml [35, 36], it is used as a criteria to evaluate the results. This can also be supplemented with systematic biopsies if it is deemed that nadir PSA values are insufficient. Early post HIFU evaluation with positive biopsies gives at least three options with a curative intent: treatment with a second HIFU session, salvage radiotherapy (as it has shown excellent oncological control after HIFU) and finally even radical prostatectomy after HIFU is a feasible option [18, 37–39]. All these endpoints taken together, the efficacy of HIFU can be evaluated through its biochemical results, or through an "adjuvant treatment free survival rate" since the decision of an additional treatment clearly represents a failure of HIFU treatment. Irrespective of the type of device used, HIFU achieves a biochemical control of prostate cancer in 58–83 % patients depending on the risk group and the adopted definition. Disease free survival rates range from 47 to 72 % according to high, intermediate, low-risk group disease at a median follow-up of 42 months [14, 31–33].

Functional Outcomes

Due to the effects of tissue destruction and high temperature effects in the prostate, patients can encounter voiding problems after HIFU, either due to outlet obstruction or urinary incontinence. Obstruction can be due to a urethral stenosis and/or a bladder outlet obstruction: these symptoms may be observed 3–12 months after the

Table 45.2 Results of primary HIFU treatment

Author	Institution (device S/A)	Year	No of patients	Median/mean follow-up (months)	Negative biopsy rate	Definition of success	5 year BFSR	5 year DFSR
Uchida et al. [31]	Tokyo (S)	2009	517	24 (median)	–	Phoenix	72 %	–
Ahmed et al. [32]	London (S)	2009	172	12 (mean)	–	PSA nadir ≤0.5	78 %	
						Psa nadir ≤0.2	58 %	
						NED[a]	92 %	
Blana et al. [33]	Regensburg/ Lyon (A)	2008	140	76 (mean)	86 %	Phoenix	77 %	66 %[b]
Thuroff et al. [15]	European multicentric (A)	2003	402	13 (mean)	87 %	–	–	–
Crouzet et al. [14]	French multicentric	2010	803	42 (mean)	85 %	Phoenix	83 % LR	72 % LR[c]
							72 % IR	56 % IR
							68 % HR	47 % HR

S/A device: Sonablate® or Ablatherm®, *BFSR* biochemical free survival rate, *DFSR* disease free survival rate, *NED* non evidence of disease, *LR/IR/HR* low-/intermediate- /high-risk disease

[a]PSAn ≤0.5 or negative biopsy

[b]PSA nadir <2 and negative biopsies

[c]PSA < nadir +2 and negative biopsies with no adjuvant treatment

procedure and are reported be seen in 3–15 % of cases. These symptoms require endoscopic intervention in 3–10 % of cases [8, 40]. The rate of urinary leakage is reported to be between 0.5 and 22.5 % [17, 41–43]. In most cases it resolves within 1 year. Generally speaking, in most series significant grade 3 urinary incontinence mentioned is ≤5 %. Potency after HIFU has been prospectively addressed in a quality of life survey on 326 patients, showing that 52–78 % of patients remained potent after HIFU with gradual improvement in a 24 months-period [44].

Salvage HIFU After EBRT Failure

Oncological Outcomes

Table 45.3 summarizes the results of oncological outcomes in patients who were treated with HIFU after failure of radiotherapy treatment. With the Sonablate® device, Uchida et al. described a 52 % biochemical control rate while Zacharakis et al. reported no evidence of disease in 71 % of their patients in their series; also half of their patients achieved a PSA level of <0.2 ng/ml [25, 45].

Similar results were observed with the Ablatherm® device by Berge et al.; in a series of 46 patients, the median nadir PSA was 0.3 and the failure rate was 39.1 % in a median follow-up of 9 months [46]. In their series of 167 patients treated with 194 HIFU sessions, Murat et al. have reported mid-term results of salvage HIFU with a median follow up of 18 months. In this series the median nadir PSA was 0.19 ng/ml and the local control rate achieved was 73 % confirmed with negative biopsies. They further observed that the actuarial 3-year progression-free was significantly lower in the following circumstances: (a) worsening of the pre-EBRT stage with 53, 42 and 25 % for low-, intermediate- and high-risk groups patients respectively; (b) increase in the pre-HIFU PSA value and (c) the use of Androgen Deprivation associated with radiation therapy [18]. The threshold of 4 ng/ml for the pre-HIFU PSA value was further clearly identified as a reliable landmark to help decision making [47] (Fig. 45.7). The message is that to achieve satisfactory oncological outcomes, salvage HIFU has to be considered when PSA values are <4 ng/ml, so early referral of failed EBRT patients is of importance. Indeed another recognised factor in salvage HIFU therapy is to try to identify patients who have pure local recurrence and to exclude those who have metastasis.

Functional Outcomes

Some of the side effects of HIFU cannot be totally ignored and therefore it is important to balance potential side effects of HIFU salvage therapy in patients who had EBRT, against the oncological benefits. Urinary incontinence rates range between 7 and 52 % [18, 25, 45, 46]. Murat et al. [18] reported that urinary incontinence

Table 45.3 Results of salvage HIFU

Author	Institution (device S/A)	Year	No of patients	Median/mean follow-up (months)	Neg. biopsy rate	Median nadir PSA	5 year BFS	5 year DFSR
Uchida et al. [25]	Tokyo (S)	2011	22	24 (median)	91 %[a]		LR 100 %	–
							IR 86 %	
							HR 14 %	
Zacharakis et al. [45]	London (S)	2008	31	7 (mean)		–	71 % NED	
Murat et al. [18]	Lyon (A)	2009	167	18 (mean)	73 %[b]	0.19		LR 53 %
								IR 42 %
								LR 25 %
Berge et al. [46]	Oslo (A)	2010	46	9 (median)	–	0.3	–	

S/A device, *S* Sonablate®, *A* ablatherm®, *BFSR* biochemical free survival rate, *DFSR* disease free survival rate, *LR* low risk, *IR* intermediate risk, *HR* high risk, *NED* non evidence of disease

[a]Biopsies performed on 12 patients

[b]All patients underwent control biopsies

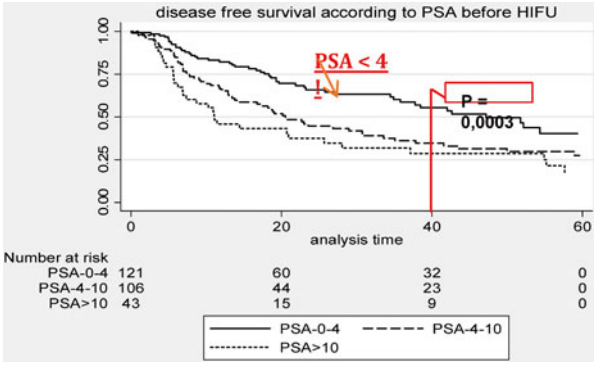

Fig. 45.7 Salvage HIFU & Disease free survival rat e according to pre-HIFU PSA (Based on data from Ref. [47])

accounted for nearly 50 % and artificial sphincter implantation was required in 11 % of their cases. Urethral stenosis or bladder neck strictures are observed between 16 and 36 % of cases, requiring sometimes an endoscopic intervention. Urethro-rectal fistula is a serious complication after salvage HIFU and was first described in 6 % of cases in the initial experience before 2000 [24]. After definition of specific post-radiation parameters, it dramatically decreased and no fistula has been observed in 111 consecutive patients with the use of these new parameters [18]. The risk of urethrorectal fistula is currently considered to be less than 1 % with the modern HIFU devices. Fistulae associated with the anterior part of the prostate, clinically manifest as osteitis pubis. Berge et al [46] described osteitis pubis in 2 of their cohort of 46 patients. Early diagnosis of anterior fistula is important as it can be effectively resolved with prolonged antimicrobial therapy; if the diagnosis or treatment is delayed, urinary diversion may be required to solve the problem. If these potential complications of salvage HIFU are carefully considered before the treatment decision is made and measures are taken to prevent them, they do not compare unfavourably with the other methods such as salvage prostatectomy or cryotherapy [20–23, 48]. It is therefore imperative that appropriate selection is made for HIFU treatment so that better results are obtained in patients who have recurrence after radiation therapy.

Focal HIFU Treatment

Muto et al. reported their first series of focal HIFU therapy in 2008 in patients who had unilateral disease [49]. In this retrospective study, patients presenting with unilateral low-risk or intermediate-risk disease were treated with a partial HIFU (total peripheral zone and half portion of transitional zone) and were compared to those treated with whole gland HIFU-ablation on the same period. The disease free survival rates at 2 years were similar in both the groups – 90.9 and 49.9 % versus 83.3 and 53.6 % in whole treatment and partial treatment groups respectively.

Emberton et al. conducted a small sized prospective phase I/II trial in the UK using the sonablate® device after receiving the approval of the UK National Cancer Research Network. The 20 enrolled patients had unilateral disease, Gleason ≤7 (4+3), PSA ≤15 ng/ml, and ≤cT2bN0m0 tumors. Their recruitment included an assessment by multiparametric MRI and template transperineal mapping biopsies. The outcomes of this small but very tightly followed cohort showed a preservation of erections sufficient for intercourse in 95 %, a total continence in 90 % and a negative biopsy rate of 89 % at 12 months. The trifecta (good erections, continence and no evidence of disease) was achieved in 89 % of patients [50]. This study appears to offer some promise for further evaluation of focal HIFU therapy/hemiablation albeit with some limitations that have to be acknowledged (small number of patients, lack of follow up, selection bias in patients cohort, residual foci of acini found in the treated area). One of the critical points to support this approach relies on the ability of predicting precisely where the cancer is present inside the gland and where it is not present. More advances in imaging diagnostic techniques will help to evolve focal therapy. Longer follow-up is also required to address the oncological outcomes. A French prospective national study using the Ablatherm® device is currently being conducted. Interim results have already been presented on 11 patients receiving a first treatment for localised prostate cancer: 78 % had negative control biopsies, no significant difference was noted before and after treatment on functional evaluation with international prostate symptom scoring (IPSS), international index of erectile function (IIEF), international continence society (ICS) and quality of life QLC-30 scores. The second part of the presentation reported on 21 patients with post-radiotherapy relapse receiving a salvage focal treatment. In this setting, the median PSA dropped from 3.06 to 0.34 ng/ml, with 85 % of patients remaining continent and all patients (with or without pharmacological aid) remained potent [51].

Future of HIFU

In the next two decades more attention would be given to focal therapy of prostate cancer because of the ongoing advances in the imagery of prostate. Radical therapy of prostate cancer has major side effects and HIFU in this regard is a well fitted technology for both focal and total therapy but needs randomised controlled trials and long term follow up of patients. This will give more information on oncological outcomes particularly when HIFU is the primary treatment. For the salvage HIFU option, a better knowledge of predictive factors of failure would help in a better patient selection. In addition, an adequate and specific definition of HIFU failure is also needed.

Combination of HIFU with others treatment modalities is possible: high risk cancers have been treated with a combination of HIFU and androgen deprivation therapy [52], A synergistic effect has been shown when using docetaxel in a neoadjuvant form just before HIFU in agressive tumors such as Dunning model [53].

A major challenge to achieve a complete and precise necrosis of the prostate targeted area and thus improve the oncological results while preserving the function

is to have a real-time temperature control during treatment as well as the ability to modify within a real time feedback model the thermal energy applied. The MRI when coupled with transurethral ultrasound transducers fulfils these features: prototypes have been described and successfully used on animals models [54, 55]. Following preclinical studies, a phase I clinical study has started in Toronto applying a transurethral ultrasound thermotherapy to 8 patients just before prostatectomy: the main objective of this study was to calculate the average radial distance between the targeted volume and the isothermal curve at 55 °C: the procedure was found to be feasible through a 15 min application of focused ultrasound. The average calculated distance was about 1 mm [56, 57].

Conclusions

High-intensity focused ultrasound treatment needs a thorough evaluation as to its efficacy in cancer outcomes and long-term quality of life. HIFU should be evaluated in a multicenter trial setting with uniform criteria right across all centre that use it. Otherwise it is not likely to be widely accepted as a primary treatment. From previous uncontrolled studies we know that HIFU has a role in the management of localized prostate cancer, as a salvage treatment in post-radiation therapy failure, or as a focal treatment. Another advantage is that HIFU can be repeated, Patients who were treated with HIFU as a primary treatment could undergo salvage radiation therapy or salvage radical prostatectomy after failure. This new and evolving technique is likely to find a place in the future armamentarium of treatment of prostate cancer.

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Chapter 46
Surgical Aspects of Prostate Cancer Management

Vinod H. Nargund

Introduction

Prostate cancer (PCa) is usually identified as a result of investigations or due to appearance of symptoms related to benign prostatic disease, which need intervention. PCa is generally the disease of the elderly but it is not uncommon to see it in younger men when its course is quite aggressive [1]. Like any other cancer management of PCa depends on the clinical stage of the disease. Clinical staging is used in decision-making about the management but this is not always clearly related to pathological staging. Surgical intervention is either directed at radical removal of the gland or to address the issues arising from the diseased gland itself. Although the main surgical procedure carried out for prostate cancer is radical prostatectomy (RP), there are however a number of surgical procedures and interventions that are necessary in the management of patients who receive various other forms of treatment for prostate cancer. This chapter summarizes principles and the indications for these procedures.

Following are the surgical procedures carried out in men with PCa:

1. Radical prostatectomy: retropubic, endoscopic (laparoscopic/robot-assisted laparoscopic) and perineal prostatectomy
2. Salvage prostatectomy
3. Salvage Lymph Node dissection (SLND)
4. Transurethral resection of prostate
5. Cystoscopy and Bilateral JJ stenting
6. Bilateral orchidectomy
7. Surgical techniques to treat metastatic spinal cord compression (MSCC)

V.H. Nargund, PhD, FRCSEd, FRCSUrol, FEBU
Department of Urology, Homerton University Hospital, London, UK
e-mail: vinodnargund@gmail.com

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Radical Prostatectomy (RP)

Prostate along with seminal vesicles is removed *en bloc* with or without pelvic lymphadenectomy. The goals of the operation are [2]:

(a) to obtain negative margins with complete excision
(b) to get favorable urinary and erectile function results
(c) to get favorable oncologic outcomes.
(d) to minimise postoperative complications

Men with clinical stage of ≤T2 with no evidence of metastasis are ideal patients for RP. The procedure is accomplished through retropubic, transperitoneal or perineal approaches (see below). In last decade or so endoscopic procedures (laparoscopic and robot-assisted laparoscopic) have become more popular. Currently robot-assisted radical prostatectomy is a popular mode of prostatectomy in spite of paucity of data on its comparison with open prostatectomy. The endoscopic procedures are discussed in detail in Chap. 12.

The main advantage of the RP is its ability to be curative treatment in appropriately selected men notwithstanding the fact that this could lead to overtreatment in some. The procedure is an established one and generally well-tolerated [3]. The potential risks include hospitalization for major surgical procedure, perioperative cardiovascular complications and rarely procedure-related death. Long-term urinary problems such as incontinence, urethral stricture, bladder neck contracture, bowel or erectile dysfunction could be expected [3]. Bill-Axelson et al. [4] reported benefits of RP compared to watchful waiting, which included reduced disease specific mortality, overall mortality and reduced risk of local progression and metastasis.

Most of the results of laparoscopic/robot-assisted procedures are from single centres reported by dedicated robotic surgery enthusiasts [5, 6]. There is a problem of recruiting patients for prospective randomised trials comparing various techniques [2, 7]. There is no doubt that robotic surgery offers many potential benefits for patients and its integration in the form of organizational and social aspects needs further evaluation [8]. It is also important to consider cost implications of buying and maintaining robot equipment. In a review article Bolenz et al. [9] observed the cost of minimally invasive RP ranged from US$ 5058 to US$ 11,806 while the cost of open radical prostatectomy ranged from US$4075 to US$2960.

Younger patients benefit more from RP than older patients. In one study the benefit of surgery with respect to death from prostate cancer was largest in men younger than 65 years of age (relative risk, 0.45) and in those with intermediate-risk prostate cancer (relative risk, 0.38) [10]. Extended follow-up confirms a substantial reduction in mortality after radical prostatectomy but its long-term benefits remain doubtful [10].

The radical surgical management of localized prostate cancer should be individualised by considering overall general health, comorbidities, life expectancy and on informed decision made by the patient.

Table 46.1 Patient factors for RPP

1. Patients with previous abdominal/pelvic surgery
2. High body mass index
3. Previous prostatic surgery
4. Kidney transplantation/mesh abdominal repair

Radical Perineal Prostatectomy (RPP)

Introduction of retropubic prostatectomy took over prostatectomy by perineal route in course of time. RPP can be done on any patient who is suitable for RRP. Table 46.1 outlines patients who are not suitable for RRP who could be considered for RPP. Patients who have large glands and with severe ankylosis of the hips or spine and those with unstable artificial hip replacements may not tolerate the exaggerated lithotomy position [11]. The pathological outcomes are same as RRP.

The proponents of RPP describe it as procedure that provides a small incision, perfect access to the prostate (especially the apex), urethra, and neurovascular bundles, avoids large muscles and vessels, and yields excellent cosmetic results. In addition the operative time is short and vesico-urethral anastomosis is "surgeon-friendly" – easy, very precise, fast, and watertight. RPP can be easily performed in a nerve-sparing manner also [12]. The technical details of removal of the prostate are well described in a review article by Comploj and Pycha [11]. Perioperative outcomes are similar to other approaches. However it is more economical than other approaches. Some centres are combining abdominal and pelvic approaches ('hybrid technique') [13].

Positive Surgical Margins After RP

Prostate gland has a narrow rim of periprostatic tissue usually less than 1 mm and is surrounded by important structures including rectum and urogenital diaphragm; so excision is likely to be extremely closer to the capsule. The international Society of Urological Pathology (ISUP) have issued recommendations on the handling, staging and reporting on RP specimens [14]. A positive surgical margin can be defined as tumor that extends to the surface of the prostate where the surgeon has excised across the tissue plane. Various studies have shown lack of correlation between margin distance and recurrence and residual cancer [15, 16]. Even when tumour has been 0.1 mm close to the resection margin there is mostly no evidence of tumour progression [15]. Several studies have shown that the extent of tumor however at the surgical margin correlates with postoperative disease recurrence [15, 17].

Salvage Radical Prostatectomy (SRP)

Removal of prostate for a localised and isolated recurrence with a curative potential may be considered in selected cases of recurrence after radiotherapy and brachytherapy [18], and less commonly after cryotherapy [19], high intensity focused ultrasound (HIFU) [20]. There are a number of options for patients with biochemical recurrence after radiotherapy. They include watchful waiting, androgen-deprivation therapy (ADT), or additional local therapy such as salvage radical prostatectomy (RP), salvage radical cystoprostatectomy, salvage cryotherapy, and salvage brachytherapy [21]. As there is no other definitive radical treatment for recurrence after radiotherapy, SRP remains the main treatment option. Oncologic outcomes in patients treated with salvage radical prostatectomy (SRP) are poorly defined and require further investigation. This is partly due to concerns regarding lack of efficacy and increased morbidity [22]. The published studies are often contain small sample; they are confined to single centres and the studies do not have end-points such as metastatic disease or cancer-specific survival or death.

Higher preoperative PSA levels are associated with disease progression and cancer-specific death after SRP. This means early detection of PSA doubling time followed by performing SRP early in the course of recurrent disease [23]. In a meta-analysis by Chade et al. [24], biochemical recurrence-free probability after SRP ranged from 47 to 82 % at 5 years and from 28 to 53 % at 10 year. Cancer-specific survival (CSS) and overall survival varied from 70 to 83 % and 54 to 89 % at 10 year follow up.

Salvage Lymph Node Dissection (SLND)

Some authors have described SLND as a treatment option for patients with prostate cancer relapse limited to the lymph nodes; however, more robust data derived from well-designed multicentre clinical trials are needed to validate the role of SLND in this selected patient population [25]. Imaging techniques, such as 11C-choline PET and diffusion-weighted magnetic resonance imaging, appear to enhance the accuracy in identifying LN relapse in patients with biochemical recurrence (BCR) and after RP.

Transurethral Resection of Prostate (TURP)

The tumour itself can cause obstruction to the urine flow in the prostatic urethra causing outflow symptoms. In such cases medical therapy with alpha-adrenergic blocking drugs may not be that helpful. The resection is usually limited to widening the urethral passage. In prostates that have tumours infiltrating the pelvic floor

musculature, TURP may lead to urinary incontinence. In patients with advanced CaP, palliative TURP can be performed safely with significant improvement in urinary symptoms. However, the rates of postoperative urinary retention and reoperation are higher than in patients undergoing TURP for BPH [26].

Cystoscopy and Bilateral JJ-Stenting

Uraemia as a result of malignant ureteric obstruction is a recognised event in men with advanced PCa, which, if left untreated, is quickly a terminal event or result in permanent renal damage [27]. Palliative decompression of the obstructed urinary system, either by percutaneous nephrostomy (PCN), ureteric stent or a combination of both is a recognised method of improving renal function, with presumed low morbidity. The obstruction may be in intramural part of ureter at the ureterovesical junction or extraluminal obstruction due to lymphadenopathy. The stenting probably is a permanent fixture in such cases. Endoscopic retrograde stenting had a success rate of 21 % whereas two-stage antegrade stenting was successful in 98 % of patients. The antegrade approach had minimal morbidity [28].

Bilateral Orchidectomy

Removal of testes (orchidectomy) or only testicular tissue leaving behind tunica albugenia (subcapsular orchidectomy) has been one of the widely practiced treatments for metastatic prostate cancer particularly before the introduction of antiandrogen therapy. Subcapsular orchiectomy is associated with significantly fewer postoperative complications than total orchiectomy [29]. The procedure can be done under local or general anesthesia. There is a decline in the number of bilateral subcapsular orchiectomies (BSOs) done due to a shift to earlier stages and younger ages at diagnosis, and the development of antiandrogens. It may be of value in a patient with metastatic prostate cancer with poor compliance and for economic reasons.

Surgery for Metastatic Spinal Cord Compression (MSCC)

Metastatic spinal cord compression (MSCC) is an oncologic emergency (see also Chap. 7) that needs early diagnosis and appropriate treatment. If not treated in time, it can lead to permanent neurologic impairment affecting the quality of life. MSCC should be ideally managed by multidisciplinary team. Nearly 30 % of cancer metastasis are found in the spine [30] and overall 5–10 % of cancer patients will develop metastatic spinal compression [31].

Spinal cord damage is characterised by vascular injury, haemorrhage, oedema of white mater, nerve damage including demylination and axonal damage [32, 33]. The main treatment modalities for the MSCC include steroids, radiotherapy and surgery. Various surgical options for MSCC are tumour cytoreduction, laminectomy and vertebrectomy [34]. Surgery followed by radiotherapy seems to be beneficial, especially for patients who are medically operable and have specific characteristics such as being symptomatic, having an expected survival of more than 3 months with good performance status, and having only one level of spinal cord compression [34].

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Chapter 47
Management of Locally Advanced Prostate Cancer

Elaine T. Lam and L. Michael Glodé

Introduction

Of the nearly 233,000 patients in the United States who will be diagnosed with prostate cancer in 2014, 10 % will have locally advanced disease [1]. Locally advanced prostate cancer is defined as clinically localized stage T3 (extracapsular extension or seminal vesicle invasion) or T4 (fixed tumor or invasion of adjacent structures) disease. Patients with localized T1 or T2 disease with high risk disease features (Gleason 8–10 or PSA >20 ng/mL) are treated similarly. In a study comparing outcomes of immediate vs. deferred treatment in patients with locally advanced prostate cancer, patients who deferred treatment had higher rates of progression to metastatic disease, development of metastatic pain, development of extra-skeletal metastases, cancer related complications (pathological fracture, spinal cord compression, urethral obstruction), and prostate cancer-specific mortality compared with patients who received immediate treatment [2]. Therefore, definitive therapy is recommended for these patients, unless it is not feasible due to age and/or comorbidities and life expectancy is less than 5 years.

A multi-modality approach is generally undertaken for patients with locally advanced prostate cancer [3]. The current treatment options for patients with locally advanced prostate cancer include (1) External beam radiation therapy (EBRT) using either a 3D conformal (3D-CRT) or an intensity modulated (IMRT) technique with image-guided radiation therapy (IGRT) and short-term/long-term androgen deprivation therapy (ADT), given neoadjuvantly, concomitantly and adjuvantly; (2) Shorter course EBRT using either a 3D-CRT or IMRT with IGRT plus a brachytherapy boost and short-term/long-term ADT, given neoadjuvantly, concomitantly and adju-

E.T. Lam, MD (✉) • L.M. Glodé, MD
Division of Medical Oncology, Department of Medicine,
University of Colorado, Aurora, CO, USA
e-mail: Elaine.lam@ucdenver.edu

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vantly; and (3) radical prostatectomy with pelvic lymph node dissection with or without adjuvant radiation therapy or ADT [4]. ADT monotherapy is indicated only if the patient is not a candidate for definitive therapy.

Specific techniques in prostate radiotherapy and brachytherapy have been previously discussed in Chaps. 42 and 43, respectively. This chapter discusses the role of ADT in the context of these combination approaches.

ADT Monotherapy

Androgen deprivation therapy alone is inferior to multi-modality approaches for locally advanced prostate cancer and is only recommended for patients in whom local curative therapies are not feasible due to comorbidities or other factors. In this setting, the optimum timing of ADT (immediate vs. delayed) remains controversial and has been evaluated in two large EORTC trials. The EORTC 30891 trial evaluated 985 patients with localized and locally advanced prostate cancer (T0-4, N0-2, M0) who were randomized to receive immediate or delayed (on symptomatic disease progression or occurrence of serious complications) ADT. The overall survival hazard ratio was 1.25 favoring immediate treatment (noninferiority $P > 0.1$); however, there was no difference demonstrated in prostate cancer-specific mortality or symptom-free survival [5]. In the EORTC 30486 study, 234 patients with pN1-3 disease who did not receive definitive local therapy were randomized to immediate vs. delayed ADT. There was no benefit seen for immediate ADT compared to delayed therapy with respect to overall survival, prostate cancer specific survival, or cancer-independent survival [6, 7]. One exception is that patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy do benefit from immediate ADT [8]. This is discussed in further detail below.

Survival Benefit of Adding Radiation Therapy to ADT

There have been two large trials evaluating the use of ADT or endocrine therapy with or without radiation therapy. The SPCG-7/ SFUO-3 trial randomized 875 patients with locally advanced prostate cancer to receive endocrine therapy (total androgen blockade for 3 months, followed by continuous anti-androgen therapy) alone or endocrine therapy plus radiotherapy. With a median follow up of 7.6 years, the 10-year prostate cancer specific mortality was 23.9 and 11.9 % for the endocrine therapy only group and endocrine plus radiotherapy group, respectively. The 10-year overall mortality was 39.4 and 29.6 %, for the endocrine therapy only group and endocrine plus radiotherapy group, respectively [9]. The NCIC Clinical Trials Group PR.3/Medical Research Council UK PR07 trial randomized 1,205 locally advanced prostate cancer patients to receive lifelong ADT versus lifelong ADT

plus radiotherapy. At a median follow up of 6 years, the overall survival at 7 years was 74 % for the ADT/RT group and 66 % for the ADT alone group (HR 0.77, p = 0.033). The prostate cancer specific survival at 7 years was 90 and 79 % for the ADT/RT and ADT alone groups, respectively [10].

Survival Benefit of Adding ADT to Radiation Therapy

The benefit of combining ADT to radiation therapy, compared with radiation therapy alone, has been demonstrated repeatedly in multiple trials [11–16]. However, the optimum duration of ADT in this setting is still controversial. The RTOG 8610 study randomized 456 patients with T2-T4, N0-1 prostate cancer to receive external beam radiation therapy (EBRT) alone or EBRT plus short-term (4 month) neoadjuvant and concurrent ADT. Ten year overall survival (43 % vs. 34 %, p = 0.12) and median overall survival (8.7 vs. 7.3 years) did not reach statistical significance. However, 10 year disease specific mortality (23 % vs. 36 %, p = 0.01), rate of distant metastasis (35 % vs. 47 %, p = 0.006), disease free survival (11 % vs. 3 %, p < 0.0001), and rate of biochemical failure (65 % vs. 80 %, p < 0.0001) favored the ADT plus EBRT arm, compared with EBRT alone arm [11, 12].

The RTOG 9202 study randomized 1,554 patients with T2c-T4, N0 prostate cancer to receive EBRT plus 4 months of neoadjuvant/concurrent ADT (short-term androgen deprivation, STAD) vs. EBRT plus 2 years of neoadjuvant/concurrent/adjuvant ADT (long-term androgen deprivation, LTAD). Ten-year overall survival was not statistically different for the intent-to-treat population (52 % vs. 54 %, p = 0.36), but was improved in a post-hoc subset analysis of patients with Gleason 8-10 cancer (32 % vs. 45 %, p = 0.0061). There were statistically significant improvements in 10 year disease free survival (13 % vs. 23 %, p < 0.0001), disease specific survival (84 % vs. 89 %, p = 0.0042), local progression (22 % vs. 12 %, p < 0.0001), distant metastasis (23 % vs. 15 %, p < 0.0001), and biochemical failure (68 % vs. 52 %, p < 0.0001) favoring the EBRT plus LTAD arm [13, 14].

The EORTC 22863 study comparing EBRT vs. EBRT plus 3 years of ADT in 415 patients with T1-2 high grade or T3-4 prostate cancer showed statistically significant improvements in 5 year overall survival (62 % vs. 78 %, p = 0.0002), disease free survival (40 % vs. 74 %, p = 0.0001), disease specific survival (79 % vs. 94 %, p = 0.0001), locoregional failures (16 % vs. 2 %, p < 0.0001) and distant metastasis (29 % vs. 10 %, p < 0.0001) all favoring the EBRT plus ADT arm [15].

From these studies, it appears that for cancer specific survival, at least 4 months of ADT is needed for benefit; and for overall survival, at least 3 years of ADT is needed for benefit. Prolonged duration of ADT needs to be balanced with adverse effects of ADT and study of prolonged intermittent ADT (known to provide improved quality of life compared to continuous therapy in advanced disease) has not been studied.

D'Amico and colleagues completed a study of EBRT vs. EBRT plus 6 months of ADT in 206 patients with T1-4, N0 prostate cancer patients with at least one

unfavorable prognostic feature (PSA >10 ng/mL, Gleason ≥7, T3a or T3b disease by MRI) and found an increased overall survival in the EBRT plus ADT arm among patients with no or minimal comorbidity (HR 4.2, $p<0.001$), but not among patients with moderate or severe comorbidity (HR 0.54, $p=0.08$) [16]. Further validation of this finding is needed.

Adverse Effects of ADT

The benefits of ADT are often weighed against the expected adverse effects. The most common adverse events include hot flashes, decreased muscle mass and bone mineral density, metabolic changes, and gynecomastia [17]. There is also a reduction of multiple quality of life measures associated with ADT, including fatigue, depression, cognitive changes, and decrease in sexual libido and function [18, 19].

Among patients receiving ADT, hot flashes may occur as frequently as 80 %, with severe hot flashes occurring up to 30 % of the time [20]. More than half of patients who suffer hot flashes report significant decreases in their quality of life and increase in their distress [21, 22]. The mechanism of hot flashes due to ADT in prostate cancer is incompletely understood; however, it is believed to be caused by negative feedback of plasma sexual hormones upon the hypothalamic secretion of norepinephrine and serotonin [23]. Current approaches to the treatment of hot flashes include hormonal (estrogens and progestins) and non-hormonal (clonidine, serotonin reuptake inhibitors, gabapentin) therapies which have variable activity and side effect profiles [20].

Loss of bone marrow density is seen early after initiation of ADT, with up to 3–4 % loss seen after 12 months of therapy [24]. The loss is ongoing and the risk of osteoporosis increases with the duration of therapy, with reported rates of osteoporosis of 35 % for hormone-naive men with prostate cancer, 49 % after 4 years of ADT and 81 % after 10 or more years of ADT [25]. In addition to vitamin D and calcium supplementation, current approaches to the treatment of ADT-induced osteoporosis include zolendronic acid and denosumab [26, 27].

The incidence of metabolic syndrome is higher in patients receiving ADT for their prostate cancer. Multiple studies have shown increases in weight, body fat, total and low-density lipoprotein cholesterol, as well as, increased rates of hypertriglyceridemia, abdominal obesity, and hyperglycemia [28, 29]. There is a substantial amount of data demonstrating that ADT adversely affects these traditional cardiovascular risk factors, and recent studies have reported a relationship between ADT and an increased risk of cardiovascular disease. However, different studies both have and have not reported an increased risk of cardiovascular death. The decision regarding whether or not to initiate ADT in patients with cardiac disease should consider the benefits of therapy against any possible risks. It is recommended that patients in whom ADT is initiated undergo periodic follow-evaluation of blood pressure, lipid profile, and glucose level. However, there is no need for specific cardiac evaluation in asymptomatic patients [30].

Surrogate Endpoints for Prostate-Cancer Specific Survival After RT Plus ADT

Given that the small survival benefit of LTAD compared with STAD is often associated with increased toxic effects from longer term ADT, there is much interest in the development of predictive biomarkers and surrogate endpoints for survival. D'Amico and colleagues reviewed the data from two randomized controlled trials (the Dana Farber Cancer Institute (DFCI) trial and the Trans-Tasman Radiation Oncology Group (TROG) trial) [16, 31] to try to identify men in whom radiotherapy and STAD was insufficient for cure. In this retrospective study of 734 men with localized and locally advanced prostate cancer who received radiotherapy and 6 months of ADT, they found that end of treatment PSA value >0.5 ng/mL and PSA nadir >0.5 ng/mL were both validated as potential surrogate markers for prostate cancer specific mortality. Men who do not achieve end of treatment or nadir PSA of ≤0.5 ng/mL was recommended to be considered for additional ADT therapy or participation in clinical trials [32].

Role of Radical Prostatectomy in Locally Advanced Prostate Cancer

Radical prostatectomy with extended lymph node dissection remains an option for select patients with locally advanced prostate cancer with no fixation to adjacent organs. The role of radical prostatectomy for high risk and locally advanced prostate cancer was evaluated by Lau and colleagues from the Mayo Clinic. Among 6,419 patients who underwent radical prostatectomy between 1987 and 1996, 407 patients had pathologic Gleason score ≥8. Among these patients, 26 % had localized disease and 27 % had lymph node positive disease. Notably, 45 % of these high-risk patients received some form of adjuvant therapy (ADT and/or radiotherapy). The 10-year overall survival was 67 %, progression-free survival was 36 % (53 % for those who received adjuvant therapy and 23 % for those who did not get adjuvant treatment), and disease specific survival was 85 % [33].

A nonrandomized, retrospective analysis comparing 1,318 patients treated with radical prostatectomy and 1,062 patients treated with EBRT with elective nodal irradiation at Baylor Medical College and Memorial Sloan Kettering Cancer Center showed an 8-year probability of freedom from metastatic progression was 97 % for radical prostatectomy patients and 93 % for EBRT patients. Surgery was associated with a lower risk of both distant metastasis (HR 0.35; $p < .001$) and prostate cancer–specific mortality (HR 0.32; $p = 0.015$). Differences in the rates of metastatic progression were more pronounced with higher risk disease (8 % in 8-year metastatic progression), compared with intermediate risk (3 %) or low risk (2 %) disease [34].

Role of Neoadjuvant ADT Prior to Radical Prostatectomy

Previous studies have evaluated the role of neoadjuvant hormonal therapy prior to radical prostatectomy. While none of these studies demonstrated improvements in overall survival, there were reductions in positive margin rates; and improvements in lymph node involvement, pathological staging, rate of organ-confined disease, and disease recurrence rates. However, most of these studies included patients with low-risk or intermediate risk disease [35–41].

In a Cochrane Database Systemic Review of these neoadjuvant androgen deprivation therapy trials for localized and locally advanced prostate cancer, neo-adjuvant hormonal therapy prior to prostatectomy did not improve overall survival (OR 1.11, $p=0.69$). However, there were significant improvements in the positive surgical margin rate (OR 0.34, $p<0.00001$) and other pathological variables such as lymph node involvement, pathological staging and organ confined rates. The use of longer duration of neo-adjuvant hormones, that is either 6 or 8 months prior to prostatectomy, was associated with a significant reduction in positive surgical margins (OR 0.56, $p=0.002$) [42].

More recent evidence evaluating the impact of neoadjuvant ADT prior to radical prostatectomy also showed no impact on the incidence of biochemical recurrence. A Korean study of 69 men randomized to receive or not to receive preoperative neoadjuvant hormone therapy showed no differences in positive margin rate or biochemical recurrence rate; however, the mean operative time was significantly higher in the group of men who received preoperative hormone therapy [43]. Thus there is no compelling evidence that neoadjuvant ADT should be used in patients with advanced localized prostate cancer.

Role of Adjuvant Therapy After Radical Prostatectomy

The need for adjuvant therapy after radical prostatectomy depends on pathological factors. Adjuvant radiation therapy may be indicated in patients with T3 disease (extracapsular extension or seminal vesicle involvement) or positive margins, and may be considered for patients with Gleason score ≥ 8, and/ or PSA that does not nadir to undetectable levels. The exact timing of post-prostatectomy radiation therapy (adjuvant vs. early salvage) is still being investigated [44]. Current NCCN guidelines recommend adjuvant radiotherapy for positive margins and adjuvant ADT for lymph node positive disease [4].

In the SWOG S9921 trial, 983 men with high risk prostate cancer (extraprostatic extension or high Gleason grade) received adjuvant therapy with ADT (goserelin and bicalutamide for 2 years) alone or in combination with mitoxantrone chemotherapy after prostatectomy. For the 481 men who received ADT only, the estimated 5-year biochemical failure-free survival was 92.5 % and 5-year overall survival was 95.9 %. This trial was closed to further accrual in January 2007, after three cases of acute myelogenous leukemia were reported in the mitoxantrone treatment arm. The final analysis of the primary endpoint of overall survival comparing the two arms for this trial has not been reported; however, the results seen for this ADT arm

makes a compelling argument to counsel patients with high risk prostate cancer about adjuvant ADT after prostatectomy [45].

Messing and colleagues reported on the results of a multi-institutional trial of 98 men who had undergone radical prostatectomy and had nodal metastases who were randomized to receive adjuvant ADT or to be followed until disease progression. Immediate treatment with ADT was associated with improved overall survival, prostate cancer specific survival, and recurrence rate, compared with observation and treatment at disease progression [8].

Wirth and colleagues evaluated adjuvant flutamide vs. no adjuvant treatment after radical prostatectomy in 309 patients with locally advanced, lymph node-negative prostate cancer. Recurrence-free survival was better in the flutamide group ($p=0.0041$); there was, however, no detectable difference in overall survival ($p=0.92$). Treatment with flutamide was also associated with significant toxicity [46].

The Casodex Early Prostate Cancer Trialists' Group evaluated the efficacy and tolerability of adjuvant high dose bicalutamide versus placebo for 8,113 patients with localized or locally advanced non-metastatic prostate cancer. In locally advanced disease, bicalutamide significantly improved PFS irrespective of standard care (surgery, radiotherapy, or watchful waiting). Adjuvant bicalutamide significantly improved overall survival in patients receiving radiotherapy but there was no survival difference in the prostatectomy subgroup [47].

Role of Chemotherapy in Locally Advanced Prostate Cancer

The role of chemotherapy in high-risk localized prostate cancer has been evaluated in multiple phase I-III clinical trials. It has been evaluated in the neoadjuvant, concurrent, and adjuvant setting in combination with radiation therapy and ADT where some trials revealed markedly increased incidence of severe toxicities, and other trials showing reasonable tolerability [48–54]. To date, there have been no trials demonstrating survival benefit of neoadjuvant or adjuvant chemotherapy; therefore, its use in this setting is still investigational. There is an ongoing trial investigating the role of neoadjuvant hormonal therapy in combination with docetaxel prior to radical prostatectomy (CALGB 90203).

Future Directions and Ongoing Clinical Trials in Patients with Locally Advanced Prostate Cancer

The development of newer agents may also offer a less toxic approach to neoadjuvant therapy [55]. Abiraterone, an inhibitor of extragonadal androgen synthesis approved for castrate resistant prostate cancer in the post-docetaxel setting, is being evaluated in the neoadjuvant setting in addition to LHRH agonist therapy (ClinicalTrials.gov identifier NCT01088529). Similarly, enzalutamide, a potent anti-androgen, is also under investigation in the neoadjuvant setting (ClinicalTrials.gov identifier NCT01547299). Other agents being tested in the neoadjuvant setting include

ipilimumab, an anti-CTLA4 antibody approved for melanoma (ClinicalTrials.gov identifier NCT01194271); OGX-011, a second-generation antisense molecule that blocks production of clusterin (ClinicalTrials.gov identifier NCT00138918); axitinib, a tyrosine kinase inhibitor (ClinicalTrials.gov identifier NCT01385059).

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Chapter 48
The Hormonal Management of Metastatic Prostate Cancer

Tanya Barauskas Dorff and Jacek Pinski

Introduction- What Is "Metastatic"?

While most men are diagnosed with prostate cancer that is localized, many will relapse after local therapy and 4 % still present with de-novo metastatic disease [1]. Serum PSA provides an early indicator of disease activity, such that men treated for cure who relapse most commonly relapse with PSA elevation many years before metastases are detected radiographically. This disease state has been labelled "biochemical recurrence", although it essentially represents a micro-metastatic state. The detection of metastases depends upon the use of radiographic surveillance in addition to clinical follow-up, and the availability of newer imaging modalities may alter the amount of time men spend in the biochemical state or the proportion of men who can be labelled as biochemically recurrent rather than frankly metastatic. Now that there is active research into treatments for men with biochemical recurrence, data are emerging which suggest that up to 40 % may be misclassified, since newer imaging techniques such as can identify radiographic evidence for metastases in cases where standard imaging has failed [2, 3]. An example is presented in Fig. 49.1. In particular, fluorine-18 fluorodeoxyglucose positron emission tomography (F18 PET) was shown to detect occult bone metastases in nearly 20 % of men with horone-naïve biochemical recurrence and whose standard technetium-99 bone scan was negative [4]. MRI of the axial skeleton may be more sensitive and definitive than nuclear medicine bone scans in detecting metastases; in high risk patients being staged prior to prostatectomy, MRI of the axial skeleton detected osseous metastases in 30 % of patients considered negative by bone scan and 47 % of those with equivocal findings [5].

T.B. Dorff, MD (✉) • J. Pinski, MD, PhD
Department of Medicine, USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA
e-mail: dorff@usc.edu

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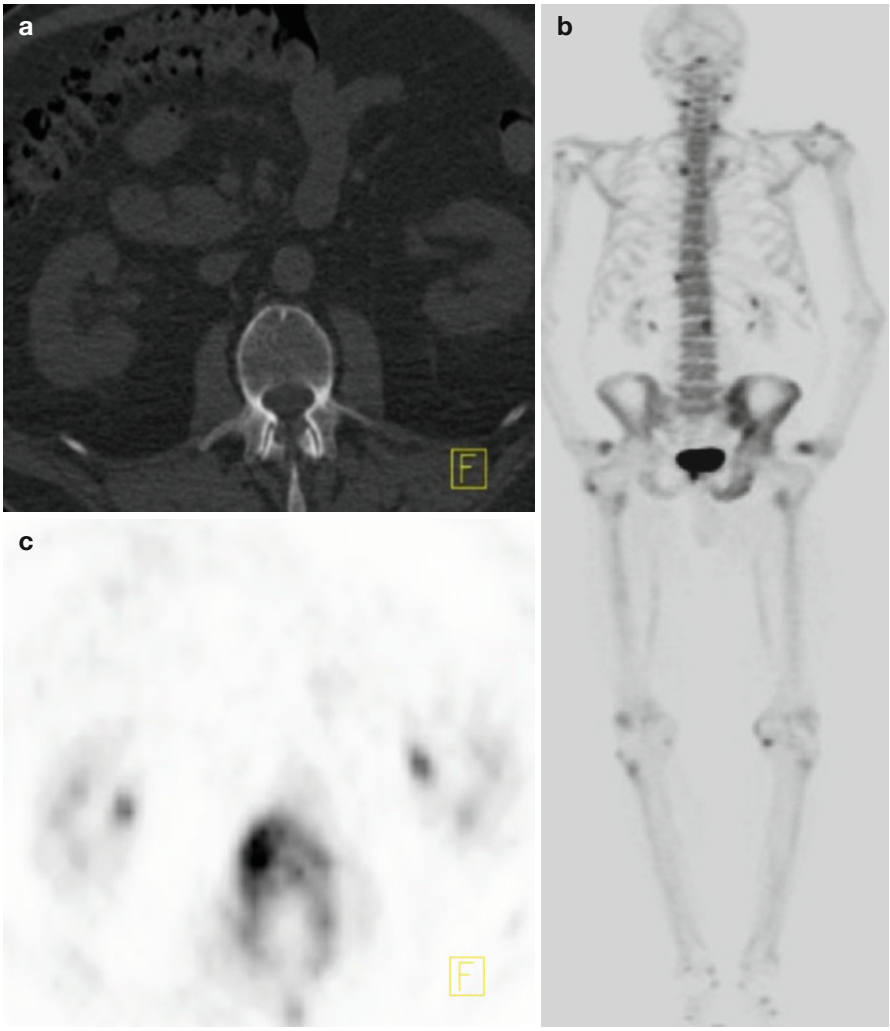
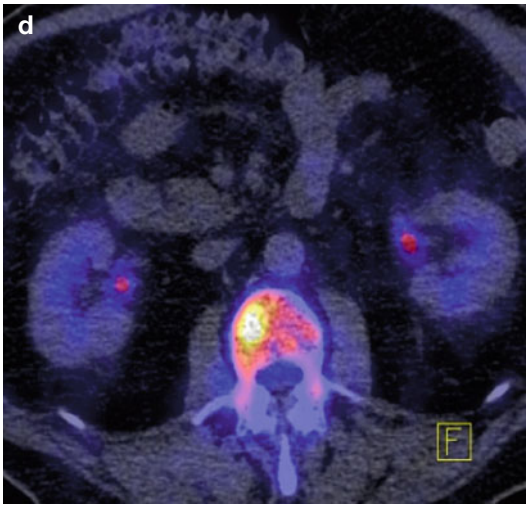


Fig. 48.1 F-18 NaF PET bone scan images of a 87 year old male treated with radical prostatectomy in 1997 for Gleason score 5 adenocarcinoma. He experienced biochemical recurrence, and continued to have rising PSA despite salvage radiation therapy in 1998. There is no evidence of recurrence or metastasis on standard imaging (CT abdomen and pelvis, panel **a** and MDP Tc 99 m bone scan, panel **b**). However, on the F-18 NaF PET bone scan, panels **c** and **d**, a right-sided L2 metastatic lesion is evident. Other non-neoplastic findings include T11 osteophytic activity, Paget's disease in the right hemipelvis, and degenerative changes in the knees, all manifested as uptake on the Tc99m bone scan (All images courtesy of H. Jadvar, Department of Radiology, Keck School of Medicine of USC; Support by NIH/NCI Grant R01-CA111613)

Fig. 48.1 (continued)



With more sensitive imaging and increasing treatment options, men will then potentially spend even longer in the metastatic state. This highlights the important dual goals of managing quality of life in addition to maximizing life span.

Once metastases are identified, whether by newer imaging modalities or traditional ones, men are treated with androgen deprivation therapy (ADT). Given the importance of quality of life, the traditional approach has been similar to that in hormone-receptor positive metastatic breast cancer, relying on hormone therapy initially, often several manipulations, followed by chemotherapy only at progression, in a sequential approach. This chapter will review the biology behind ADT and explore the evolution of the treatment to its current standards, discussing combined blockade versus monotherapy, intermittent versus continuous ADT, peripheral blockade, up-front chemohormonal therapy, and future directions such as combinations of ADT with biologic agents. Supportive care for men undergoing ADT is an important focus, given the increasingly recognized metabolic complications in addition to the many side effects, which impact quality of life. With its dominant proclivity for bony spread, interfering with the signaling between prostate cancer and bone marrow stroma is a high priority, and can have substantial impact by reducing fractures, bone pain, and spinal cord compression.

Androgen Deprivation Therapy (ADT): The Biology Behind the Cornerstone Treatment

Huggins and Hodges were awarded the Nobel prize in the 1940's for describing the clinical and pathologic responses in men with metastatic prostate cancer who were treated with surgical castration or estradiol [6]. Surgical castration remained a mainstay of treatment until further Nobel award-winning work by Andrew Schally discovered

the molecular structure of luteinizing hormone-releasing hormone (LHRH) and the importance of the hypothalamic-pituitary-gonadal axis [7]. This facilitated the subsequent development of synthetic LHRH agonists such as leuprolide and goserelin. Medical castration induced by LHRH agonists was then compared clinically against surgical castration or estrogen, and found to yield equivalent survival [8]. One downside of the agonist approach is an initial flare of testosterone induced by injection of the LHRH agonist, before the down-regulation of LHRH receptors occurs, which ultimately shuts down testicular production of testosterone. This flare can be clinically significant, inducing urinary retention in men with obstructive urinary symptoms or pain in men with bone metastases. A brief period of anti-androgen therapy with flutamide or bicalutamide before the first LHRH agonist injection and during the first few weeks after the injection protects against clinical progression during testosterone flare [9]. Alternatively, new agents, which are pure LHRH antagonists have been developed in order to avoid the flare; these include cetorolix and degarelix. Degarelix is reported to achieve superior testosterone suppression, compared to leuprolide [10], and is not associated with testosterone flare. The clinical significance in terms of cancer control, however, has not yet been established such that both agonists and antagonists are accepted as standard of care. Another pharmacologic alternative to avoid the flare is ketoconazole, an inhibitor of steroid hormone synthesis which blocks both testicular and adrenal production of androgens, and leads to a rapid decline in circulating testosterone levels [11]. The hypothalamic-pituitary-gonadal axis and role of antiandrogens is depicted in Fig. 48.2.

Responses to LHRH analogues occur in the vast majority of men; the majority of patients will have a PSA decline by 28 days into treatment [10] and 80 % of symptomatic patients will experience clinical benefit [12]. However, rising PSA

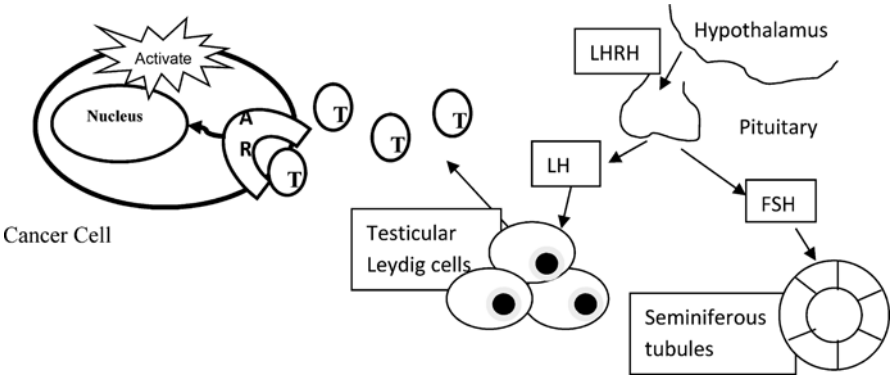


Fig. 48.2 Pituitary-Hypothalamic-Gonadal Axis, and the interaction of testosterone with the androgen receptor at the level of the cancer cell. Luteinizing hormone releasing hormone (*LHRH*) analogues act as either agonists, leading to cessation of testosterone production by testicular Leydig cells after an initial surge which downregulates LHRH receptors on the pituitary gland with subsequent absence of LHRH stimulation, or antagonists with immediate lack of LHRH stimulation, leading to cessation of testosterone production. Anti-androgens work at the level of the interaction between testosterone (*T*) and the androgen receptor *(AR)*

is inevitable, heralding the emergence of castration resistance and clinical disease progression. Multiple mechanisms of resistance have been described, including amplification of the androgen receptor (AR), mutation of the AR and splice variants, changes in AR coactivators, cross-talk or bypass via other growth factor signal pathways including epidermal growth factor receptor and insulin like growth factor, and extragonadal (even intratumoral) testosterone synthesis, reviewed by Attar and colleagues [13]. Interestingly, however, the striking differences among men in terms of time to castration-resistance have not yet been explained. The ability to identify men who will have a sub-optimal duration of disease control with LHRH analogues would facilitate more rapid testing of novel approaches to first-line therapy in metastatic prostate cancer.

Evolution of the Standard Approach to Androgen Deprivation for Advanced Prostate Cancer

Three major classes of drugs make up the androgen deprivation armamentarium: LHRH analogues, which turn off testicular androgen production, androgen receptor antagonists, and androgen biosynthesis inhibitors, which inhibit adrenal and intratumoral conversion of cholesterol into androgens. The last class has typically been utilized as salvage therapy, while the first two classes have been tested as monotherapy and in combination for first-line treatment. Although randomized clinical trial data regarding the following questions are available, the landscape is complicated by additional factors such as quality of life, cost-effectiveness, and metabolic consequences of ADT such that currently there is not one agreed-upon best practice, and both intermittent and continuous therapy, combined blockade and monotherapy are utilized.

Combined Blockade Versus Monotherapy

The rationale for combined androgen blockade began with the recognition that suppressing testicular production of androgens did not lead to the complete absence of androgens, and that all tumors ultimately gained the ability to grow in castrate conditions. In animal models, the addition of androgen receptor blockade to castration therapy enhanced antitumor efficacy. Early clinical trials seemed favorable, and two SWOG trials, 8494 and 8894, were completed to test combined blockade against medical or surgical castration monotherapy [14, 15]. The addition of flutamide to medical castration with leuprolide significantly prolonged survival, 35.6 months versus 28.3 months, two-sided $p=0.035$ [14]. However the addition of an antiandrogen to surgical castration did not significantly prolong survival (HR 0.91, 95 % confidence interval 0.81–1.01) [15]. A European (EORTC) trial mirroring the leuprolide trial also documented a survival advantage to combined blockade [16]. Several meta-analyses of combined blockade trials have been published; despite

methodological differences, there appears to be consensus that combined blockade is associated with a small but detectable improvement in 5-year overall survival, but questions remain about cost-benefit and quality of life trade-offs [17–19].

Intermittent Versus Continuous

Continuous testosterone deprivation was initially the standard, given that bilateral orchiectomy was the original means of reducing circulating testosterone, leading to permanent absence of testicular androgen production. After the development of LHRH analogues, the ability to reversibly suppress testosterone production fuelled interest in applying therapy intermittently. Using the Shionogi mouse model, Bruchovsky and colleagues [20] demonstrated that the number of castration-resistant prostate cancer stem cells was reduced by applying intermittent therapy, suggesting that cancer cells adapt to the hormone *milieu*, and suggesting that castration resistance could be delayed by intermittently re-introducing testosterone. Experiments in which prostate tumors were reduced via castration, then transplanted into non-castrate hosts, then re-transplanted into castrate hosts resulted in a fold-fold prolongation of time to castration resistance compared to tumors which remained in the castrate host [21]. In addition to the physiological rationale, there is a strong incentive to utilize intermittent therapy in order to improve quality of life and reduce adverse effects via testosterone recovery during the "off-treatment" period.

Multiple phase II and small randomized trials of intermittent androgen deprivation have documented the safety of the approach, reviewed by Boccon-Gibod and colleagues [22]. These studies document the intermittent experience across a wide range of induction durations, from as little as 3 months to as long as 48 months, and include studies using diethylstilbestrol, LHRH analogue monotherapy, and combined blockade with an antiandrogen. The triggers for resumption of ADT have been similarly variable, although essentially all have been PSA-based, ranging from any rise in PSA to a 50 % increase in nadir, an absolute PSA level >3 ng/mL to >20 ng/mL, and of course clinical progression being an absolute indication to reinitiate therapy regardless of PSA level. Importantly, nearly all patients respond to re-treatment and testosterone levels typically do recover, bringing with them restoration of sexual function for a majority of men. One small randomized trial suggested progression at 3 years was markedly lower for intermittent therapy [23], however larger studies have not borne this out.

Two large, randomized phase III trials comparing intermittent to continuous ADT have issued at least preliminary reports. The South European Uroncological Group (SEUG) treated 766 men with locally advanced or metastatic prostate cancer with cyproterone acetate plus monthly LHRH analogue for an induction period of 3 months [24]. The 626 men whose PSA declined to <4 ng/mL or to 80 % below the baseline value were randomized to intermittent or continuous therapy; those assigned to intermittent therapy stopped treatment at randomization. The re-treatment trigger was two-tiered; PSA >10 ng/mL for symptomatic patients and

20 ng/mL for asymptomatic patients and for patients whose PSA declined to below 80 % of the initial value, a PSA rise >20 % above the nadir triggered the next cycle of ADT. Survival was similar, with disease progression documented in 127 men from the intermittent arm and 107 men from the continuous arm; while there were more cancer-related deaths in the intermittent arm, there were more cardiovascular deaths in the continuous arm. Quality of life was not significantly different in the two arms, except that men on the intermittent arm had greater sexual function. A second multinational trial of intermittent therapy, JPR7, reported preliminary findings at the 2011 annual meeting of the American Society of Clinical Oncology [25]. One thousand three hundred and eighty-seven men with biochemical recurrence were treated with 8 months of LHRH analogue monotherapy. Those who achieved a PSA <4 ng/mL and did not show signs of castration resistance were randomized to intermittent or continuous therapy. Men on the intermittent arm resumed therapy when PSA reached 10 ng/mL and each treatment cycle was 8 months. For the primary endpoint of overall survival, there was no significant difference, and the p value was 0.009 for non-inferiority; as in the SEUG trial there were more prostate cancer deaths on the intermittent arm but more non-prostate cancer deaths on the continuous arm. Men on the intermittent arm spent only 27 % of their time on treatment, which would be expected to yield cost savings; quality of life data are not yet available. SWOG 9346 has a similar design, except that the treatment comparison is being made in metastatic prostate cancer patients; these data are anxiously awaited.

Peripheral Androgen Blockade

The ability to block AR activity without depleting the body of testosterone led to the question of whether this "peripheral" blockade could be therapeutic in the absence of castration therapy. The side effect profile may be favorable, however the available data suggest that it may yield inferior disease control compared to castration or combined blockade. A Swedish study which compared bicalutamide 50 mg to orchidectomy in metastatic prostate cancer found that survival was significantly better in the castration group, HR 1.76 (95 % confidence interval 1.27–2.44) [26]. An Italian study which compared bicalutamide 150 mg to goserelin plus flutamide in advanced prostate cancer found no difference in progression-free or overall survival, although combined blockade trended towards superior results in the subgroup of metastatic patients [27]. Some have argued that the addition of 5-alpha reductase inhibitors more completely deprives cancer cells of androgen fuel, and yields deeper PSA nadir than bicalutamide monotherapy, comparable to that achieved with castration [28]. On the other hand, the 150 mg dose of bicalutamide has been associated with some safety concerns, such as a higher death rate when added to active surveillance in the early prostate cancer trialists group study [29], which has led the United States and Canada to recommend against prescribing the 150 mg dose [30]. Overall, at present, most physicians would not include peripheral androgen blockade as a standard first-line treatment option.

Up-Front Chemohormonal Therapy

No randomized studies to date have proven that the incorporation of chemotherapy prior to the emergence of castration resistance is beneficial. However, *in vitro* experiments show synergism between taxanes and androgen deprivation, and in mouse models combination therapy was associated with a doubling of time to disease progression compared to androgen deprivation followed by chemotherapy [31]. A European trial tested combined androgen blockade alone or with epirubicin and found that progression-free survival was significantly prolonged 12 months versus 18 months, $p=0.02$, and overall survival showed a trend toward improvement 22 months versus 30 months, $p=0.1$; in the subgroup of men with >5 bone metastases the survival difference approached significance, 17 months versus 27 months, $p=0.06$ [32]. Phase II studies have shown promise for the addition of docetaxel to androgen deprivation therapy at biochemical recurrence [33], but the phase III studies which will definitively answer the question have not yet been reported.

Supportive Care for Men During Androgen Deprivation Therapy

Anticipating and minimizing the side effects of androgen deprivation as much as possible is a critical aspect of managing metastatic prostate cancer patients. In addition to ameliorating symptoms such as hot flashes, avoidance of serious metabolic and skeletal complications presents a significant challenge for urologists and medical oncologists. Side effects of androgen deprivation are summarized in Table 49.1 and depicted in Fig. 48.3.

Table 48.1 Summary of adverse consequences of androgen deprivation and potential interventions to offset side effects

Adverse consequence	Possible interventions	References
Bone mineral density loss	Exercise, vitamin D	Smith et al. [34]
	Toremifene	Oefelein, Michaelson, Smith [35–37]
	Bisphosphonates	
Hyperlipidemia	Standard lipid medications	Levine et al. [38]
	Toremifene	Smith et al. [34]
Gynecomastia/mastodynia	Prophylactic breast irradiation	Dicker [39]
	Tamoxifen	Boccardo [27]
Hot flashes	Venlafaxine, gabapentin, pregalbin, clonidine, paroxetine, and fluoxetine	Loprinzi, Loprinzi, Barton, Boekhut [40–43]
	Acupuncture	Deng et al. [44]

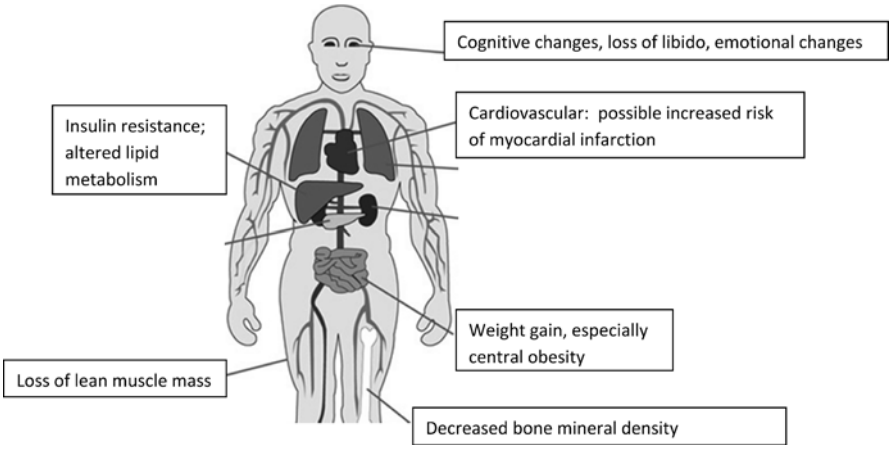


Fig. 48.3 An overview of some of the ways in which androgen deprivation affects organ function

Bone Mineral Density and Skeletal Related Events

One year of castration therapy is associated with the loss of 4 % of bone mineral density in the hip and 2 % in the spine [Diamond; 45] which corresponds to a fracture risk as high as 20 % at 10 years [35]. Bisphosphonates are effective in counteracting the bone mineral density loss; pamidronate administered every 12 weeks during a year of medical castration offset the bone mineral density loss induced by castration alone [46]. However quarterly administration, and even a single dose of zoledronic acid was subsequently shown to increase bone mineral density during a year of LHRH analogue therapy [36, 47]. Thus, bone mineral density should be evaluated at baseline and periodically during androgen deprivation so that appropriate patients requiring intervention can be identified. Calcium and vitamin D should be part of the approach to support bone mineral density, and weight-bearing exercise can also be recommended. The selective estrogen receptor modulator toremifene was also studied in this arena and was found to increase bone mineral density by 1.6 % in men receiving ADT compared to 0.7 % decrease in the placebo arm [47].

Bone metastases can cause significant morbidity, including pain, fracture, and spinal cord compression which are collectively labelled "skeletal related events". Unravelling the unique crosstalk between prostate cancer cells and bone marrow stroma have facilitated the development and study of bone-targeted therapies. In castration-resistant metastatic disease, zoledronic acid administered intravenously every 3–4 weeks was shown to reduce the risk of skeletal related events from 44 to 33 %, including fractures, which were reduced from 22 to 13 % [49]. In addition, zoledronic acid was associated with a significant delay in the time to the first skeletal event, from 321 days to 488 days, $p=0.009$ [50]. Denosumab, a monoclonal antibody against RANK ligand showed an even stronger reduction and delay in skeletal related events compared to zoledronic acid, with a median time to skeletal-related event of 17.1 months

for zoledronic acid compared to 20.7 months for denosumab [51]. The benefits of these agents in castration-sensitive disease have not yet been well described; a CTSU trial C90202 is currently enrolling men with bony metastatic disease and randomizing them to early bisphosphonate therapy versus bisphosphonates at the time of castration resistance with a primary endpoint of skeletal related events. This will inform clinicians of the relative risks and benefits of starting therapy earlier; significant adverse events related to bone-targeted therapies in general include osteonecrosis of the jaw and for bisphosphonates there is also the potential for renal toxicity.

Alterations in Lipids

Increases in serum total cholesterol and triglycerides occur during androgen deprivation, though the degree and pattern of changes varies somewhat according to the form of ADT (ex: monotherapy or combined blockade). For instance, LHRH analogue therapy for 1 year has been associated with a 9 % increase in total cholesterol and 26 % increase in triglycerides [37]. Although this has been difficult to correlate with clinical outcomes such as myocardial infarction or cerebrovascular accident, the changes are concerning. Selective modulation of the estrogen receptor, for instance with toremifene, appears to ameliorate these changes, leading to an increase in HDL, decrease in total cholesterol as well as LDL and triglycerides [48].

Insulin Resistance and the Metabolic Syndrome

Androgen deprivation is known to induce insulin resistance, which appears to be a direct consequence of hypogonadism and independent of body mass index changes during ADT [52]. Using Medicare data, investigators documented an increased risk of developing outright diabetes after orchiectomy or LHRH analogue use, with hazard ratios of 1.34 and 1.44, respectively [53]. In addition, abdominal obesity and the metabolic syndrome are more prevalent in men on long-term ADT than in matched prostate cancer and normal controls (55 % versus 22 % and 20 %, respectively) [54]. Clearly this is a serious problem which warrants attention. Lifestyle counseling should be part of the treatment plan when androgen deprivation is employed, though specific interventions have not yet been prospectively evaluated.

Cardiovascular Morbidity

Alarm was raised when Medicare database analysis and review of radiation oncology clinical trial data suggested a significant increase in cardiovascular morbidity, namely myocardial infarction and sudden cardiac death, when

men received androgen deprivation adjunctive to radiation [53, 55]. This is physiologically plausible, given the known propensity for androgen deprivation to cause weight gain, worsening lipids, and insulin resistance. However, other analyses have failed to find an association between ADT and cardiac mortality, or have found it limited to certain risk groups, such as those over 65 or with serious comorbidities [38]. As such there is no recommendation for routine involvement of cardiology in men undergoing ADT, but rather standard measures to control contributing risk factors such as lipids and blood pressure should apply. Undoubtedly this will continue to be an area of active research moving forward.

Hot Flashes

While most men will experience hot flashes during androgen deprivation, most will not require intervention. However, for those with severe vasomotor instability, multiple randomized controlled clinical trials in breast cancer patients have now demonstrated effectiveness of pharmacologic therapies to reduce hot flashes. Venlafaxine, gabapentin, pregalbin, clonidine, paroxetine, and fluoxetine have all been shown to reduce frequency and severity of hot flashes from 13 to 75 % [41–44]. In addition, non-pharmacalogic interventions have shown some promise. Acupuncture was shown to reduce the mean number of daily hot flashes in breast cancer patients compared to sham acupuncture [44] and hypnosis had a modest effect [56]. While the majority of data are in breast cancer, anecdotal data support the effectiveness of the same pharmacologic interventions for men with hot flashes related to ADT.

Breast Changes

Gynecomastia and mastodynia occur frequently in men treated with antiandrogens, up to 86 and 76 %, respectively. This can lead to treatment discontinuation and/or psychosocial distress. Prophylactic irradiation, typically a single dose of 8 Gy or up to 3 fractions of 3–5 Gy, has been shown to reduce the development of breast changes, reviewed by Dicker, with minimal risk of side effects [39]. Radiation is more successful when used prophylactically than when applied once gynecomastia is already present, although mastodynia may still be alleviated. Estrogen modulators have also been evaluated as preventive agents in conjunction with bicalutamide 150 mg monotherapy. Tamoxifen reduced the incidence of gynecomastia from 73 to 10 % and mastodynia from 39 to 6 % in a rigorous randomized prospective trial; anastrozole was not effective in the same study [27].

Tertiary Hormone Manipulations and New Androgen-Targeted Agents

Upon the development of castration-resistance, multiple therapeutic options now exist, which are reviewed in a subsequent chapter. We will review the mechanisms of action of tertiary hormone manipulations and summarize the available data for their efficacy, as well as describe the evolution of some third-generation hormone therapies such as Abiraterone and MDV3100.

Androgen Biosynthesis Inhibitors

Ketoconazole is antifungal agent which was noted to cause painful gynecomastia in some male patients, related suppression of testicular and adrenal androgen production. This suppression occurs due to ketoconazole's inhibition of cytochrome P450 14a-demethylase, which converts lanosterol to cholesterol, an early step in steroid hormone synthesis. Due to its ability to rapidly and effectively lower testosterone levels, some physicians have advocated a preference for ketoconazole over LHRH therapy in symptomatic metastatic disease, as a way to avoid testosterone flare. In the castration-resistant setting, PSA responses have been noted in 20–75 % of men with CRPC [55–60]. Side effects include adrenal insufficiency, which is offset by concurrent steroid replacement therapy with either hydrocortisone or prednisone, as well as fatigue, nausea, liver and renal toxicity. While ketoconazole was noted to significantly reduce DHEAS, androstenedione, and testosterone, the clinical trials have yielded conflicting results, though it appears that higher baseline DHEAS and/or androstenedione levels may be associated with response [59–62].

Abiraterone acetate is a new agent, rationally designed to inhibit androgen biosynthesis, without being broadly adrenolytic. It inhibits CYP17, a cytochrome P450 enzyme which is critical for conversion of cholesterol to androgen precursors, more potently and irreversibly than ketoconazole. Mineralocorticoid excess is a unique side effect of abiraterone, which is adequately palliated by the concurrent administration of prednisone, 10 mg per day [63]. Abiraterone has shown significant efficacy in castration-resistant disease, with a median survival advantage of 3.9 months compared to prednisone, in patients who had progressed after chemotherapy [63]. This efficacy led to its approval by the FDA in 2011 for chemotherapy-pretreated CRPC; results of the randomized, placebo-controlled phase III trial in the pre-docetaxel setting are anxiously awaited and additional ongoing trials are examining the role of adding abiraterone early, for instance at 7 months into first-line androgen deprivation for those who failure to achieve a PSA nadir <4 ng/dL (SWOG S1014, NCT01309672). Additional CYP17 inhibitors are under development, including TAK700.

Estrogens

In addition to its ability to suppress testicular testosterone production, estrogen may have a direct anti-neoplastic effect on prostate cancer cells, given that estrogen receptors are expressed and have been shown to have a role in malignant behavior [64, 65]. Diethylstilbesterol dosed at 1 mg daily, was associated with PSA responses in 43 % of men with castration-resistant disease [66], however concerns over thrombotic and cardiovascular complications [67], as well as the lack of availability of oral estrogen formulations, have limited the popularity of this approach. Transdermal preparations are safer, and have also shown robust activity. In a study using transdermal estradiol (6 patches weekly) as first-line therapy in metastatic prostate cancer patients, 20 of 20 patients achieved castrate levels of testosterone and PSA responses [68].

Anti-androgens

Bicalutamide is one of three non-steroidal anti-androgens which are commercially available for prostate cancer treatment. Their mechanism of action is to inhibit the binding of testosterone or dihydrotestosterone to the androgen receptor. The other two agents in this class, nilutamide and flutamide, have slightly different side effect profiles, most notably difficulty with vision accommodation ("night blindness") for nilutamide and diarrhea, hepatotoxicity for flutamide. Any of these three agents may be used in combined blockade or to block the LHRH-associated testosterone flare during first-line therapy of metastatic prostate cancer. The steroidal anti-androgen cyproterone acetate is used in Europe, but is not available in the United States. Interestingly, there is apparent incomplete cross-resistance between the three non-steroidal anti-androgens, as documented by a small series in which therapeutic responses to nilutamide were seen after failure of flutamide or bicalutamide [69]. Of 28 patients, 64 % had a PSA decline, and a 50 % reduction in PSA was achieved by 29 % of the study participants.

MDV3100 was designed to bind with higher affinity to the androgen receptor, and also prevents its translocation to the nucleus and interaction with DNA [70]. Early phase trials showed significant activity, and the randomized placebo-controlled phase III trial of MDV3100 in men with CRPC who have disease progression after docetaxel documented a significant survival advantage of 4.8 months [press release, Medivation, November 3, 2011]. Additional data from this trial as well as the similar trial in docetaxel-naïve CRPC are anxiously awaited.

Conclusions and Future Directions

Androgen deprivation therapy remains the mainstay of treatment for metastatic prostate cancer. It is highly effective, but resistance inevitably develops. Given the safety and potential quality of life and cost savings, intermittent therapy is considered

by many to be within the standard of care. Combined therapy and castration monotherapy are both used as there is no consensus on the superior management strategy. New approaches, including the addition of chemotherapy or targeted therapies, are being studied. At present, sequential therapy remains the standard of care. The large and growing body of literature describing side effects of androgen deprivation highlights the importance of managing symptoms to maximize quality of life in this group of men with relatively long life expectancy.

Ongoing and future clinical trials are focusing on the incorporation of novel therapies into early treatment of metastatic prostate cancer to delay or overcome castration resistance. For instance, SWOG S0925 is comparing combined androgen blockade alone or with cixutumumab, a monoclonal antibody targeting the insulin-like growth factor pathway. MD Anderson is evaluating the incorporation of immune therapy with ipilimumab, a CTLA-4 antibody, with androgen deprivation for newly diagnosed patients with metastatic prostate cancer.

Undoubtedly, trials to evaluate early incorporation of third-generation androgen-targeted agents such as abiraterone and MDV3100 will be developed. Perhaps the most significant emerging paradigm is that the androgen receptor continues to drive prostate cancer progression well beyond the emergence of castration resistance, and hormone therapies remain the most effective treatments for this disease.

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Chapter 49
Castrate Resistant Prostate Cancer: Systemic Chemotherapy and a System Problem

Derek Raghavan, Seungjean Chai, and John Mahoney

Introduction

The initial treatment of advanced, inoperable or metastatic prostate cancer is hormonal manipulation, as discussed in detail by Dorff and Pinski in Chap. 49. In many cases, responsiveness to androgen deprivation wanes after a period of months to years, and it may be necessary to provide further systemic treatment in this setting. Traditionally, after failure of hormonal manipulation, patients have been treated with cytotoxic agents, with variable effectiveness.

One of the important issues in the use of cytotoxic chemotherapy is the timing of treatment. When considering chemotherapy for "castrate resistant" prostate cancer, one must ensure that the cancer is really resistant to the impact of castration. Adrenal androgens contribute to the hormonal environment, so that some tumors that appear to be resistant or refractory to the testosterone-depleted setting, may actually be receiving stimulation from adrenal hormones, dehdroepiandrosterone (DHEA) and its sulphate (DHEAS), and will thus respond to second line adrenal blockers, such as aminoglutethimide, ketoconazole or the newer salvage agents, such as abiraterone and MDV-3100 (enzalutamide). These remissions may sometimes be sustained for months to years.

Thus important factors to consider before consideration of chemotherapy include:

- Adherence – i.e. is the patient taking the medications or are other medicines interfering with absorption or function of the treatment, thus interfering with the process of medical castration? In the case of surgical castration, was a sub-capsular orchidectomy performed, with traces of residual, functioning testicular tissue left in situ?

D. Raghavan, MD, PhD, FRACP, FACP, FASCO (✉)
S. Chai, MD • J. Mahoney, MD
Levine Cancer Institute, Carolinas HealthCare System,
Charlotte, NC, USA
e-mail: derek.raghavan@carolinashealthcare.org

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- Is there a late agonist effect from peripheral androgen blockers, such as flutamide, nilutamide or bicalutimide?
- Is there a significant component of adrenal or other androgenic function that is still stimulating growth of prostate cancer tissues?
- Is this truly adenocarcinoma, or is there a neuro-endocrine or urothelial cancer outgrowth?
- Is this a second malignancy?

These issues can be assessed via careful history and physical examination, and appropriate tests, such as measurement of gonadotrophins, testosterone, and adrenal androgens. In some cases, where there is no evidence of rapid, symptomatic tumor progression, a therapeutic trial of second-line hormone therapy with an adrenal blocker may yield another remission, and this should be considered before the initiation of chemotherapy. However, the pace of the disease is a crucial consideration, as second-line hormonal therapy may require a time lag of 6 weeks or more before showing an effect. Dorff and Pinski (Chap. 49), have discussed the new generation of novel second-line therapies, including abiraterone and enzalutamide, which have demonstrated clear anti-cancer efficacy in this clinical setting, and provide additional options for patients with apparently "castration-resistant" disease.

An additional domain of emerging systemic therapy is the group of immunotherapies and vaccines, which is beyond the scope of this chapter. In addition, we have viewed the bone-stabilizing agents as falling within the category of supportive therapy rather than representing active anti-cancer options.

Widening the Goal Posts in Assessment of Success

The utility of chemotherapy for patients with advanced, castrate-resistant prostate cancer has been the subject of controversy [1, 2]. However, it has become clear that there is a defined role for cytotoxics in advanced, symptomatic, hormone refractory or castrate-resistant disease, leading to reduced tumor-related symptoms and/or improved quality of life and a survival benefit [3, 4]. Analogous to the management of breast cancer, it seems that chemotherapy may eventually be introduced earlier into clinical practice, perhaps as neo-adjuvant or adjuvant therapy, and will then realize its most useful impact.

In the early days of chemotherapy in the 1980s, attempts were made to define criteria for the assessment of response, culminating in efforts to identify patient benefit within the broad category of disease stabilization [5]. The National Prostatic Cancer Project documented the variability in response patterns and identified that stable disease (SD) correlates frequently with prolonged survival, leading to its inclusion in their criteria of response. As the category of stable disease included both patients with very indolent or "stable" disease prior to treatment, as well as those with a genuine slowing of tumor growth rate by treatment, the NPCP system was heavily criticized [1] and fell into disrepute. This was unfortunate as the basic

system was predicated on sound reasoning, focused on the concept that the slowing of the rate of tumor growth would be beneficial in treating prostate cancer. This problem was compounded by the absence of a reliable biomarker that might have been used to measure the changing amount of tumor.

Surrogate Markers of Response

In recent times, many surrogate markers of response have been studied for the assessment of chemotherapy for prostate cancer, in an attempt to address the heterogeneity of outcome within the category of stable disease. With the introduction of serial measurement of PSA, it was hoped that clinical benefit could be more easily defined. A reduction in circulating PSA of 50 % or more has been used to identify patients who have shown an improvement after chemotherapy [6, 7]. This group includes those with stable clinical disease.

Some years ago, the National Cancer Institute convened an expert panel to attempt to achieve consensus on the use of PSA measurements as a surrogate for tumor response in phase II trials [8]. This panel identified four groups of patients that they believed would be suitable for entry into phase II clinical trials: progressive measurable disease, progressive bone metastases, stable bony disease with rising PSA, and rising PSA-only disease [8]. They also required proof of effective castration (via measurement of serum testosterone) at the time of progression to constitute "hormone refractory" disease.

The inclusion of patients with a minimum PSA level of only 5 ng/ml weakened their approach. This lower limit allowed the presence in these trials of patients with lower volume disease and also of those with predominant neuroendocrine or small cell anaplastic differentiation (which is characterized by lower PSA levels and the presence of other markers). Furthermore, it is difficult to conceive that a treatment that reduces a PSA from 5 to 2.5 ng/ml can really be having the same biological impact as one that causes a 50 % reduction from 5,000 ng/ml.

There have been a series of meetings convened by the Food and Drug Administration and the National Cancer Institute to rationalize and update the use of surrogate markers, but these have failed to identify a reliable or optimal surrogate marker; thus there has been no resulting peer-reviewed publication.

Reporting a study from the Southwest Oncology Group, we demonstrated that maintenance at 3 months of PSA remission may be one of the more powerful surrogate markers for patients with advanced hormone-refractory disease, treated by mitoxantrone- or docetaxel- based regimens [9]. Furthermore, in this study we questioned the utility of the specific criterion of a 50 % PSA reduction as a useful surrogate marker.

Other unvalidated PSA endpoints have included PSA velocity, PSA density, and PSA release phenomena. In fact, the acute release of PSA into the circulation, in response to tumor death induced by treatment, can potentially confound the assessment of rates of circulating tumor marker level declines if not measured and calculated in the algorithm.

Circulating Tumor Cells

An important domain of research has focused on the measurement of circulating tumor cells (CTC) as predictive and prognostic markers of treatment of advanced prostate cancer [10–12]. It has been shown that prostate cancer cells are shed into the circulation by primary tumors, although they are not necessarily predictive of a poor prognosis for all prostate cancers [10].

However, in patients with castrate resistant prostate cancer, we have demonstrated in a non-comparative trial that absolute numbers of circulating tumor cells prior to systemic therapy predict outcome, and that reduction in numbers of these cells after treatment also correlates with response and survival [11, 12]. Although many phase II trials in recent times have recorded CTC levels as if they were validated surrogates of survival, this technology still requires validation in the randomized trial setting.

In addition to biomarkers, investigators have studied quality of life indicators in the hope of reflecting the efficacy of systemic therapy.

Quality of Life Assessments: Adding to Confusion

The tools for the measurement of the quality of life (QOL) of patients with prostate cancer have improved somewhat, but are still imperfect. Some systems confuse symptoms of castration or advanced age with those of the cancer or its treatment; others focus on indirect measures that may be inaccurate (e.g. weight gain that is interpreted to suggest improvement, when it may reflect fluid retention). Yet QOL is being incorporated more often into the assessment of new treatments, despite the current flaws in methodology. In inexperienced hands, this may constitute a much less robust surrogate endpoint, leading to artificially high response rates. It is important that validated purpose-designed instruments be employed for prostate chemotherapy trials [13].

It should not be forgotten that many patients who receive chemotherapy for prostate cancer have already been castrated, have intercurrent diseases and are elderly. Symptoms associated with these states may easily confound the assessment of the side effects of chemotherapy or of tumor-related quality of life. For example, castration per se can cause fatigue, depression, lassitude, and even occasional nausea. Symptoms of arthritis in the elderly patient may be mistaken for bone pain associated with progressive tumor.

Nonetheless, with the broader acceptance of structured QOL assessment tools in the field of oncology, the Food and Drug Administration approved the use of mitoxantrone for the indication of advanced prostate cancer, based largely on QOL comparisons in a large Canadian randomized trial [14]. In this study, mitoxantrone plus prednisone was compared to prednisone alone [14]. The primary index of clinical benefit was improved QOL, based on a validated model [13].

This trial represented an important paradigm shift, but there are still substantial problems in the methodology of QOL assessment [15]. We believe that the primary index for the assessment of novel compounds in the management of advanced, hormone refractory prostate cancer should still be objective tumor regression or survival.

Stage Migration: Less Tumor Burden at the Outset

Stage migration is a phenomenon in clinical trials where the amount of tumor in patients presenting for treatment changes over time because of improved staging technology or changes in treatment patterns. In the past 10–15 years, stage migration has contributed prostate cancer study populations with less tumor burden and thus a better inherent prognosis (Table 49.1). This has confounded interpretation of these studies over prolonged time periods, and in particular has confused the assessment of the impact of novel treatments on median survival.

For example, the availability of PSA monitoring after primary therapy or hormonal manipulation has now led to the identification of harbingers of clinical

Table 49.1 Comparable series with stage migration

Parameter	Raghavan et al. [16]	Tannock et al. [14]	Kantoff et al. [17]	Ernst et al. [18]	Berry et al. [19]	Raghavan et al. [20]
Age						
Median	64	69	72	71	70	73
Interquartile range	50–77[a]	63–75	67–75	64–75	49–87	
ECOG P.S.						
0	}48 %	6 %	}85 %	13 %	75 %[b]	4 %
1	52 %	57 %	15 %	62 %	23 %[b]	79 %
≥2		37 %		25 %	2 %[b]	18 %
Metastases:						
Bone	90 %	98 %	91 %	Not stated	86 %	93 %
Lung	10 %	}4 %	21 %		2 %	10 %
Liver	6 %		9 %		4 %	17 %
Nodes	16 %	22 %	9 %		18 %	28 %
PSA (ng/ml)						
Median	Not stated	209	150	150	57	210
Interquartile range		66–678	52–362	45–361	4–2,375[a]	77–430
Alkaline p'ase						
Median	Not stated	2.0 (S.I. units)	167	229	Not stated	355
Range		1.0–5.3	105–317	150–495		44–3,018
% with Pain	Not defined	99 %	Not defined	100 %	0 %	100 %
% with Narcotic analgesics	Not defined		Not defined	22 %	0 %	100 %
2 year actuarial survival		~15 %	~20 %	~15–17 %	~15 %	21 %[b]

[a]Total (not interquartile) range

[b]Actual, not actuarial survival; patients treated with mitoxantrone plus tesmilifene, a biochemical modulator

relapse much earlier, often many months before the onset of clinical symptoms. By contrast, in the 1980s, prior to the routine use of PSA or high resolution CAT scan or bone scan monitoring, the first evidence of clinical relapse or metastasis was often pain, a pathological fracture, a palpable mass, or some other indication of more advanced cancer.

This change has resulted in the inclusion of patients with lower pre-treatment tumor mass in the current era than in the chemotherapy studies conducted three decades ago. This, in turn, has led to a potential artifact of interpretation where new drugs appear to yield better outcomes than old drugs. For example, the median survival of patients treated with mitoxantrone/prednisone for hormone refractory prostate cancer has increased 50 % in the past 30 years, potentially due to stage migration and better supportive care [9, 16–20]. Therefore we believe that randomized trials are still required to show definitively that a survival benefit can be achieved by the use of a novel systemic therapy, and that historical comparisons are likely to be flawed for such analyses [1, 2].

Importance of Randomized Clinical Trials in Assessment of Chemotherapy

In view of all these variables in the assessment of new treatments, one must ensure that there is rigor and structure in the assessment of progress in this field, which is best done through the use of randomized trials. Non-comparative phase I-II trials have been essential in identifying the potential role of the conventional and novel cytotoxic agents and combination regimens for advanced prostate cancer [1, 2, 21–26]. The following conventional drugs have been shown to have anti-cancer effect against bone-dominant, hormone refractory prostate adenocarcinoma when used as single agents: doxorubicin, cyclophosphamide, cisplatin, carboplatin, mitoxantrone, paclitaxel, docetaxel and mitomycin C [1, 2, 21]. Each produces objective response rates of about 15–20 %, sometimes with reduction of tumor-related symptoms and/or improvement in measured quality of life.

The problem is that the newer endpoints of assessment could easily lead to misinterpretation of the benefit from novel agents, as compared to the utility of some of the older drugs studied in the trials of the 1980s and 1990s. Softer end points (PSA response, reduction in circulating tumor cell numbers, application of waterfall plots, and a new emphasis on progression-free survival) or changes in the population of patients treated may have led us into the trap of making it too easy to attribute "patient benefit" to novel agents. There is a relatively new fashion of expressing tumor reduction through the vehicle of "waterfall plots". In a waterfall plot, reductions of tumor mass are graphically expressed as a bar below the baseline, and reductions as small as 5 % can be interpreted to indicate treatment benefit, a much lower bar than the 50 % mass reductions required in earlier classification systems. We may thus have begun to over-emphasize the utility of some novel agents [27].

Ultimately the most reliable way to prove that novel agents are achieving more than older compounds is through randomized clinical trials. Through this vehicle, direct

comparison has shown that mitoxantrone improves QOL compared to non-cytotoxic treatment [13, 14], and that docetaxel is more active against prostate cancer than is mitoxantrone (at the expense of more toxicity) [3, 4]. This paradigm will continue to be essential to the accurate evaluation of novel agents for prostate cancer.

Evolving Role of Cytotoxic Chemotherapy

Although single agent chemotherapy has been shown to improve QOL and yield a modest survival benefit, randomized trials have not yet proven the superiority of combination chemotherapy over single agents. Some promising combination regimens were reported in non-randomized trials in the past decade, suggesting that combination chemotherapy may increase patient benefit, despite the problems of stage migration and altered endpoints. However, few confirmatory randomized trials have proven this benefit.

The combination of paclitaxel or docetaxel plus estramustine has been reported to produce subjective response in approximately 50–60 % and PSA response in 40–75 %. Objective tumor responses occurred in up to 30 %, depending on whether patients with soft tissue disease dominated the population of patients [22–24]. Others have reported that the addition of carboplatin to the paclitaxel-estramustine doublet adds to clinical activity, claiming higher objective and PSA response rates [25, 26]. A meta-analysis of randomized trials comparing chemotherapy versus chemotherapy plus estramustine concluded that there was a survival benefit from the addition of estramustine [28]. However, once again, a decade after initial reporting of estramustine-based combinations, these data seem to remain controversial. There are significant concerns regarding the thrombo-embolic effects of this combined therapy, and many believe that the gold standard remains single-agent chemotherapy for castrate-resistant prostate cancer.

More recently, cabazitaxel, formerly known as XRP6258, a new generation semi-synthetic taxane with low affinity for multidrug resistance protein, was demonstrated in a phase I trial to show efficacy against docetaxel-treated castrate-resistant prostate cancer [29]. In an international randomized trial, known as "TROPIC", 755 patients were allocated to treatment with mitoxantrone or cabazitaxel after prior failure of docetaxel [30]. A statistically significant median survival benefit of 3.4 months was noted with cabazitaxel. In several eastern European centers, toxic deaths were experienced in patients treated with this novel agent, emphasizing the hazards of myelosuppression in an elderly population with potential renal dysfunction and bone marrow compromise. These outcomes highlight the importance of subspecialty experience when applying novel therapies to an at-risk population [30]. Nonetheless, this agent was approved by the Food and Drug Administration for use in North America for castration-resistant prostate cancer.

Studies are being implemented to test cabazitaxel versus docetaxel in front line therapy for castrate-resistant disease and to assess utility and safety of novel combination regimens that employ this new agent.

Future Directions: Targeted Therapies, New Agents, Need for Precision

Novel compounds that have some functional similarity to the taxanes, the epothilone B analogues, have been tested against prostate cancer. One of these agents, ixabepilone, has recently been shown to induce objective response in up to 30 % of cases, and a 50 % PSA reduction in 48 % of patients [31]. Similar patterns of response have been recorded with a structural analogue, patupilone [32]. This concept will require further testing, with a focus on randomized clinical trials, to compare activity with that of the taxanes, and to evaluate utility in combination regimens. To our knowledge, this class of compounds has not been approved for use in North America by the Food and Drug Administration, and they thus remain investigational.

Novel therapeutic approaches focused on vitamin D metabolism (e.g. Calcitriol), oncogene and growth factor receptor targets, and immunological manipulation have shown promising results in phase II studies. However, some of these findings have been questioned based on the reduced stringency of assessment of outcome, further supported by failures in randomized clinical trials.

The FDA recently licensed sipuleucel-T, an immunological manipulation focused on enhancing targeted T-cells, based on a statistically significant improvement in survival in a randomized trial [33]. This trial focused on the use of sipuleucel-T for patients with minimal-extent, metastatic prostate cancer. However, a more recent, provocative analysis has questioned the utility of such treatment, and proposed that the leukopheresis implicit in the process caused a deficit in outcome in the control population due to the reduction in circulating immunologically active cells [34]. The argument in this analysis focused on the impaired outcome among the elderly in the control population, and the apparently improved outcome in younger patients who did not receive sipuleucel-T [34]. This controversy serves only to emphasize the importance of design and structure in future studies. It was subsequently suggested that the principal author of this latter study had a significant conflict of interest, adding to the controversy.

Another approach has involved the use of targeted therapies. For example, cabozantinib, also known as XL-184, an oral tyrosine kinase inhibitor directed against the c-MET gene and VEGFR, which may also impede tumor invasion, has been shown to be active against medullary carcinoma of the thryoid [35]. Consequent upon the demonstration of c-MET and VEGFR functionality in prostate cancer, surprising anticancer efficacy was demonstrated in a randomized, discontinuation placebo-controlled phase II trial that assessed outcomes in 171 patients [36]. Patients showed regression in soft tissue disease and improvement in bone scans, although the majority of responses were in the stable disease category [36], and it is important to note that the study was discontinued early because of the obvious superiority to the placebo arm. Further trials are in progress to define the true role for this targeted therapy.

In view of the clear evidence of anticancer efficacy of cytotoxics in hormone refractory disease, chemotherapy is now being assessed earlier, analogous to the progression of studies in breast cancer 30 years ago. For example, Waxman and

his team have suggested that adjuvant mitoxantrone chemotherapy adds to the impact of castration [37]. While the published data were provocative, case selection bias may have influenced the results. This led to formal testing of the concept in a randomized trial by the Southwest Oncology Group (SWOG). SWOG 9921 compared castration versus castration plus mitoxantrone and prednisone in patients who had undergone radical prostatectomy for locally extensive disease. Despite the promising non-randomized data from the United Kingdom, SWOG 9921 was terminated early on the recommendation of the Data Safety Monitoring Committee. There was an apparent excess of cases of iatrogenic leukemia in the chemotherapy arm [38].

Predicated on the results of SWOG 9916, comparing docetaxel and mitoxantrone [3, 4], studies assessing the utility of adjuvant docetaxel have been started, although these may be hard to implement, given the toxicity of docetaxel and the relatively modest potential difference in outcome. For example, NCT00283062, testing this hypothesis, was opened, accrued poorly, and closed without yielding meaningful results. In contrast to some of the studies in adjuvant therapy of breast cancer in women, men have been more reluctant to participate in such studies with only modest gains and significant toxicity (or perhaps their physicians have been more reluctant to involve them).

Another variant of this approach, neoadjuvant chemotherapy, has been to test novel cytotoxics in patients with untreated, locally extensive disease who are about to undergo radical prostatectomy [39]. In preliminary studies of neoadjuvant docetaxel, reductions of PSA have been documented, although major tumor cell kill has not been identified [39], and more extensive phase II-III trials will be required to validate this approach. One such study NCT00430183 is currently accruing patients.

In a variant of this approach, Shepard et al. [40] assessed a nano-engineered taxane, with purportedly improved tumor uptake characteristics, in the neoadjuvant setting prior to radical prostatectomy. Although we demonstrated minor histological changes in the resected prostate specimens, there was no evidence of objective tumor regression, and further studies were not implemented. However, this design may represent a paradigm for assessment of other novel therapeutic compounds.

Promising new data will require validation in carefully structured comparative clinical trials to ensure that real progress is being made in the use of chemotherapy for prostate cancer, and that improved results are not just a reflection of improved supportive care, earlier diagnosis and stage migration, or altered clinical trial endpoints or surrogates of outcome [27]. For example, our initial clinical experience with enzastaurin appeared to suggest clinical benefit in castrate-resistant disease, but formal testing in a double-blind, placebo-controlled fashion, failed to confirm this observation [41]. Rigor in clinical testing will be essential, especially as several new concepts are being tested in early phase trials, including biochemical modulation, application of nano-technology, and the use of targeted therapies that are directed to the determinants of cellular turnover.

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Chapter 50
Cancer Penis and Scrotum

Simon Horenblas

Epidemiology and Etiology

Incidence Cancer of the penis is a rare malignancy with incidence rates of 0.3–1/100,000. High-incidence areas are found in South-America with a highest incidence in Brazil 8/100,000. Extremely low incidence rates can be found in countries where circumcision at birth or at a very young age is practiced (Israel, Middle-East) [1–4].

Etiology

Phimosis A non retractable foreskin predisposes to penis cancer, most probably because of chronic infection and inflammation of the glans penis and the prepuce (chronic balanoposthitis) [3, 5].

Human Papilloma Virus (HPV) HPV is a sexually transmittable agent. Persistent infection with high risk HPV plays an important role in the etiology of cervical cancer [6]. In approximately 30 % of cases HPV-DNA can be found in cancer of the penis [7, 8]. HPV accounts for mutations in the retinoblastoma gene and the p53 gene through activity of E6 and E7 viral transcripts [9]. The prevalence of high-risk HPV is different in various parts of the world [10]. This could explain partially the differences in incidence.

S. Horenblas, MD, PhD, FEBU
Department of Urology, Netherlands Cancer Institute, Amsterdam, The Netherlands
e-mail: s.horenblas@nki.nl

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Other Chronic Inflammatory Conditions Lichen sclerosis et atrophicus (LSA), in the male also called Balanitis Xerotica Obliterans (BXO), is a chronic inflammatory skin disease of unknown etiology. In contrast 5–10 % of women with vulval LSA develop squamous cell carcinoma [5].

Cigarette Smoking In well controlled studies, the association of smoking with genital squamous cell carcinoma has been established. The mechanism for this association is not known, but accumulation of nitrosamines in genital secretions has been suggested as a possible mechanism [5, 11, 12].

Premalignant Lesions and Natural History

Premalignant Lesions

Penile Intraepithelial Neoplasia (PIN) Like most epithelial malignancies the intraepithelial component is considered as a premalignant lesion, especially of cancers of the penis associated with HPV. Nearly all PIN-lesions have evidence of HPV-DNA in the tumor. Nevertheless, only a small proportion of cases of PIN will develop into invasive cancer (estimated rate 5–15 %) [13, 14].

Lichen Sclerosis et Atrophicus (Balanitis Xerotica Obliterans-BXO) This has already been mentioned above. This chronic condition leads to malignancy in a minority of patients (5–10 %). LSA is presumably the precursor of penis cancer in those cases not associated with HPV-infection [5, 15].

Natural History From the little information that is available it looks like a prolonged process and following picture emerges. It usually takes 10–15 years from the development of a PIN lesion to an infiltrating tumor. The majority of tumors develop in the sulcus of the glans and the prepuce. After locally infiltrative growth strictly lymphogenic metastasis develop in the regional lymph nodes in the groin. Lymphatic spread follows a sequential pathway from inguinal lymph nodes to pelvic lymph nodes. Skip metastasis are hardly found. Only very late in the natural history does hematogenic spread occur [3, 16, 17].

Pathology and Staging and Prognostic Factors

Pathology

Squamous cell carcinoma accounts for 95 % of the malignant tumors of the penis. The other 5 % of malignant tumours such as melanoma and basal cell carcinoma originate in the skin, and occasionally soft tissue tumors arise from the cavernous elements. Rarely metastases may be found in the penis or lympho-reticular malignancies [4, 18, 19] also manifest in penis.

Table 50.1 TNM classification: penis cancer

T – Primary tumor
TX Primary tumor cannot be assessed
TO No evidence of primary tumor
Tis Carcinoma in situ
Ta Noninvasive verrucous carcinoma
TI Tumor invades subepithelial connective tissue
T1a Tumour invades subepithelial connective tissue without lymphovascular invasion and is not poorly differentiated or undifferentiated (T1G1-2)
T1b Tumour invades subepithelial connective tissue without with lymphovascular invasion or is poorly differentiated or undifferentiated (T1G3-4)
T2 Tumor invades corpus spongiosum or cavernosum
T3 Tumor invades urethra or prostate
T4 Tumor invades other adjacent structures
N – Regional lymph nodes
NX Regional lymph nodes cannot be assessed
NO No regional lymph-node metastasis
NI Metastasis in a single superficial inguinal lymph node
N2 Metastasis in multiple or bilateral superficial inguinal lymph nodes
N3 Metastasis in deep inguinal or pelvic lymph node(s), unilateral or bilateral
M – Distant metastasis
MX Distant metastasis cannot be assessed
MO No distant metastasis
MI Distant metastasis

Stage grouping
Stage O Tis NO MO/Ta NO MO
Stage I TI NO MO
Stage II TI NI MO/T2 NO, NI MO
Stage III TI N2 MO/T2 N2 MO/T3 NO, NI, N2 MO
Stage IV T4 Any N MO/Any T N3 MO/Any T Any N MI

Staging

The staging is based on TNM classification (Table 50.1) [20] Grading is mostly based on Broders' principles [21].

Prognostic Factors

Factors predisposing to local recurrence after treatment are increasing T-stage and increased grade of differentiation [22]. The most important prognostic factor for survival is presence or absence of lymph node metastasis [23–25].

Clinical Features

The most prominent clinical feature is the presence of the primary tumor. Regional metastasis may present as occult metastases or overt lymph node involvement [3, 16, 17, 23].

Primary Tumor Present lesion commonly originates in the sulcus of the corona glandis. The lesion is clearly visible and palpable after retracting the foreskin. The lesion can be papillary, solid or ulcerating. Depending on the stage at diagnosis, the lesion is superficial or infiltrating into all the tissue layers of the penis. Patients with non-retractile foreskin (phimosis) often present with a foul-smelling discharge as a first sign. The tumor can usually be palpated under the foreskin [3, 16, 17].

Features Regional Metastases Enlarged inguinal lymph nodes are the main clinical feature. Lymph node metastases could be unilateral or bilateral. Signs of inflammation may dominate the clinical picture (hyperemia, pain, edema). Further spread is only manifested by secondary symptoms like lymphedema, because of proximal lymphatic obstruction, flank pain because of ureteric obstruction, bone pain, because of bone metastases or the signs of hypercalciemia [3, 16].

Diagnosis and Staging

Biopsy and Imaging

Biopsy Primary Tumor A biopsy (incisional or excisional) is strongly recommended to establish a correct tissue diagnosis. The biopsy should be taken on the border of normal and abnormal tissue and should encompass the full thickness of the tumor enabling the pathologist to give an impression of the depth of infiltration [3, 16, 17, 26].

Biopsy Regional Metastasis Presence of lymph node metastasis can be proven by fine needle aspiration (FNA) biopsy, preferably under ultrasound guidance. Removal of a single lymph node is not recommended, unless proof of lymph node involvement cannot be obtained in suspicious cases by repeated fine needle aspiration biopsies [27].

Staging

Primary Tumor Physical examination is usually sufficient. Details of the lesion including exact location, diameter and involvement of the skin, subcutaneous tissue, cavernous tissue, urethra and neighboring tissues are recorded. In case of doubt about the proximal extent ultrasound and MRI can be helpful [28–30].

Staging of the Regional Lymph Nodes Occult metastases cannot be found by palpation. Ultrasound combined with fine needle aspiration biopsy may be of helpful [31]. In a small series of 7 patients, promising results have been published on the use of lymphotropic nanoparticle (ferumoxtran- dextran-coated iron oxide) enhanced

MRI [32]. More invasive is the use of so called dynamic sentinel node biopsy (see later). In patients with overt metastases one should record the size, number and fixation to the skin or underlying structures like femoral artery/ vein or femoral nerve.

Management Primary Tumor and Management Regional Lymph Nodes

Management Primary Tumor

Surgical Management Primary Tumor Penis preserving therapies can be attempted if removal with a minimal margin of 2–3 mm normal tissue can be achieved. This can be done by simple excisional surgery or in combination with the use of the laser [22, 33]. Involvement of the epithelium of the glans can be managed by partial or total removal of the epithelium with split skin grafting [34]. If penis preservation is not possible, a partial amputation or total amputation is required. It is possible to void in standing position after partial penile amputation. After total amputation the urethral opening is positioned in the perineum, behind the scrotum (perineal urethral stoma, perineo-urethrostomy).

Non Surgical Management Primary Tumor Penile preservation can also be achieved by external beam radiation therapy or brachytherapy. These modalities can be chosen as an alternative to partial amputation [22, 35, 36].

Management R+egional Lymph Nodes

Management Clinically Node Negative Patients This is a controversial issue with two groups of proponents. One group advocates inguinal lymph node dissection in all but the smallest tumors and the other group advocates a wait and see policy in all patients except in those with unfavorable prognostic characteristics. There is uniform consensus that patients presenting with stage Tcis and well differentiated T1-tumors could be treated expectantly [23, 37, 38]. Based on biopsy protocols of melanoma and breast cancers the so called dynamic sentinel node biopsy was developed for all other categories [39]. A lymph node dissection is done only in sentinel node positive patients. Results show acceptable false negative rates and excellent survival figures compared to a cohort of patients managed conservatively [17, 40].

Management of Clinically Node Positive Patients Treatment usually consists of a straightforward inguinal lymph node dissection. This should be preceded by FNA in order to prove metastatic involvement of the lymph node. Depending on the number of tumor positive nodes, extracapsular growth and the location of tumor positive nodes, a complementary iliac lymph node dissection is mandatory. Patients with fixed nodes and or presenting with retroperitoneal nodes should undergo preoperative treatment with combination chemotherapy or radiation therapy. After response evaluation subsequent surgery should be scheduled in patients with clinical response. Because of the rarity of this disease this should be done preferably within the framework of a clinical study [27, 41, 42].

Treatment Results

Results of Primary Tumor Treatment Penis preserving treatment is safe, but meticulous follow up or self-examination is of utmost importance as the local recurrence rate varies from 19 to 37 % irrespective of type of treatment. As a local recurrence can be the source of further spread this should be treated at the earliest possible moment. Local recurrences after partial or total amputation is rare. The most common complication is stenosis of the neo-urethra (5–10 %) [22, 43].

Standing urination and normal erection are maintained in penis preserving treatments and often after partial amputation, dependent on the size of the stump. After total amputation standing voiding is impossible. Of note is the fact that patients can have a normal ejaculation after total penile amputation [44, 45].

Patients with a single metastasis in the regional lymph nodes have a 5 year disease specific survival of 70 %, in contrast to 50 % with bilateral lymph node invasion. This decreases further to 29 % in patients with microscopic pelvic lymph node invasion. Patients presenting with fixed inguinal masses or large pelvic lymph nodes do poorly, with hardly any long term survivors [41, 46, 47].

Tumours of the Scrotum

Epidemiology and Aetiology

Incidence Scrotal tumors are exceedingly rare with an age adjusted incidence of 0.2–0.3/100,000 population [48].

Etiology From a medical history point of view scrotal cancer is interesting as an occupational cancer. The disease was initially described by Pott in the eighteenth century as a disease common in chimney sweepers [49]. This association led to the discovery of the carcinogenic role of industrial oils, like alkaline ether, and coal tar. Occupation related and induced tumors are rare now. The role of Human Papilloma Virus is unclear [48].

Pathology and Staging and Prognostic Factors

Pathology

The commonest tumor is squamous cell carcinoma. Other tumors include basal cell carcinoma and melanoma [48].

Staging

There is no official TNM classification for scrotal cancer. The spread of th tumour is to the inguinal lymph nodes. Another staging system was based on the probability of surgical treatment (Table 50.2).

Table 50.2 Staging system for scrotal carcinoma

Stage A1	Localized to scrotal wall
Stage A2	Locally extensive tumor invading adjacent structures (testis, spermatic cord, penis, pubis, perineum
Stage B	Metastatic disease involving inguinal lymph nodes only
Stage C	Metastatic disease involving pelvic lymph nodes without evidence of distant spread
Stage D	Metastatic disease beyond the pelvic nodes involving distant organs

Prognostic Factors

Just like squamous cell carcinoma of the penis invasion of regional lymph nodes is the most important prognostic factor for survival [48].

Clinical Features

Clinical Features Primary Tumor

Clinical presentation is most often a solitary tumor in the scrotal skin [50]. Various benign diseases should be distinguished from cancer like: sebaceous cysts, dermoid cyst and cutaeous nevus [48].

Clinical Features of Regional Metastasis

Patients may present with palpable masses in the inguinal region, especially if the primary tumor remains undetected for a long time [51].

Management

Management Primary Tumor

Treatment consist mainly in straightforward surgical removal of the affected part of the scrotum [50]. In extensive cases a complete scrotectomy is mandatory. The scrotum can be reconstructed using free skin graft on the tunica vaginalis of the testes [48].

Management Regional Metastasis

Patients presenting with clinically node positive disease should undergo a lymph node dissection in cases with proven cancer invasion of the lymph nodes, usually after fine needle aspiration biopsy. Clinically node negative patients could benefit from a dynamic lymph node biopsy in analogy to squamous cell carcinoma of the penis [17].

Treatment Results

Treatment Results Primary Tumor

Local recurrence rates of 21–40 % have been reported. However all reports include very small number of patients [48, 52–54].

Treatment Results Regional Metastasis

Five year survival figures can hardly been given based on the scanty published information. However, patients with a minimal amount of metastatic load, do survive after a lymph node dissection. By contrast there are hardly any survivors in patients presenting with involved pelvic lymph nodes [48].

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Chapter 51
Non-Urological Cancers Affecting the Urinary Tract

Melanie Powell

The genito-urinary tract is not infrequently affected by malignancy arising from non genitourinary organs. This is most frequently by direct spread, either from the primary tumour itself or lymph node metastasis. But it may, occasionally be by a metastasis arising within the genitourinary tract. This chapter will outline the urological manifestations of pelvic malignancy, which may require urological assessment and intervention.

The tumours that most commonly affect the urinary tract are gynaecological cancers, in particular cancers of the cervix and body of uterus, colorectal cancer and non-Hodgkin's lymphoma. The management is multidisciplinary and an understanding of basic anatomy, pathology and clinical details of pelvic malignancies is valuable to understanding how they may give rise to urinary tract problems. For example, ureters in women are closely related to the cervix, uterine vessels and vaginal vault, which makes them vulnerable during surgery and in the course of the disease or as a result of treatment. Ureters also run in close proximity to the rectum and sigmoid colon. The relationship between prostate, its neurovascular bundles and rectum has been described in chapter on prostate.

Carcinoma of the Cervix

Incidence and Aetiology

Cervix cancer, although decreasing, in developed countries where screening programs are in place is the third commonest cancer in women worldwide and the seventh overall, with an estimated 530,000 new cases and 275,000 deaths in 2008. More

M. Powell, MB, BS, MD, FRCP, FRCR
Department of Clinical Oncology, Barts Health NHS Trust,
St. Bartholomew's Hospital, London, UK
e-mail: melanie.powell@bartshealth.nhs.uk

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than 85 % of the global burden occurs in developing countries, where it accounts for 135 of all female cancers [1]. The most significant risk factor for the development of cervical cancer is human papilloma virus infection and in particular types 16 and 18. Other risk factors include immuno-suppression, high parity and smoking.

Spread

Local

Tumour may extend laterally into the parametrium and then to the pelvic sidewall where it may encroach onto the ureter leading to hydronephrosis. More advanced tumours invade the urethra, bladder or rectum.

Lymphatic

Pelvic nodal disease is frequent and related to size and stage of the tumour, its differentiation and lymphovascular space invasion. In the presence of positive pelvic lymph nodes the incidence of para-aortic disease is over 50 %. Supraclavicular lymphadenopathy are a sign of disseminated cancer and confer a poor prognosis.

Haematogenous

Once a rare mode of spread, improved local control has led to an increase in frequency of metastases to lung, bone, liver and brain.

Pathology

More than 80 % of cervical tumours are **squamous cell carcinoma**. About 15 % are adenocarcinoma. Both of these are related to HPV infection. Other tumours are rare and include small cell, neuroendocrine, sarcoma, lymphoma, melanoma and metastases from other primary cancers.

Clinical Presentation

Gynaecological

Presentation is usually to a gynaecologist with abnormal vaginal bleeding, either post menopausal or, in younger women, intermenstrual or post coital. Other symptoms include persistent vaginal discharge and pelvic or back pain.

Urological

Urological symptoms such as urinary frequency, difficulty voiding, dysuria, haematuria and incontinence may be a presenting feature. These are due to extrinsic pressure on the bladder or urethra or direct infiltration of the bladder. Incontinence may be due to a vesico-vaginal fistula and suggests advanced disease.

Ureteric obstruction may occur by direct tumour extension to the pelvic sidewall or pelvic lymphadenopathy. It is often bilateral and untreated leads to acute renal failure. Obstructive nephropathy may also be due to tumour infiltrating the trigone of bladder, neck of the bladder or proximal urethra.

Investigations

Blood

Full blood count, blood biochemistry and liver function analysis. Testing for human immunodeficiency virus (HIV) should be considered in any patient from a high risk group.

Imaging

Pelvic and abdominal imaging using either magnetic resonance (MR) or computed tomography (CT) scanning is recommended. This enables assessment of both extent of the primary disease and also lymph node involvement. Chest x-ray or CT is also advised.

Clinical

Staging of cervical cancer remains clinical and examination under anaesthetic (EUA) is an essential investigation and should include bimanual examination of the cervix and uterus, cystoscopy and sigmoidoscopy.

Staging

The clinically based International Federation of Gynaecology and Obstetrics (FIGO) staging system is the most widely used (Table 51.1) [2].

Prognosis

Prognostic factors include tumour size and stage, lymphovascular invasion, lymph node involvement and parametrial invasion [3].

Table 51.1 FIGO staging of cervix cancer

Cervix (%risk nodal metastases)	Cervix (%risk nodal metastases)
IA	Microscopic disease confined to the cervix
IA1	1 – ≤3 mm deep, ≤7 mm wide (<2 %)
IA2	2 – 3–5 mm deep, ≤7 mm wide (<4 %)
IB	Clinically visible lesion confined to cervix
IB1	1 – ≤4 cm (15 %)
IB2	2 – >4 cm (30 %)
II	Beyond cervix (not to pelvic wall or lower 1/3 vagina)
IIA1	No parametrial spread max dimensions ≤4 cm (20 %)
IIA2	No parametrial spread >4 cm
IIB	Parametrial spread present (30 %)
III	Beyond uterus but not outside of pelvis
IIIA	Lower 1/3 of vagina (30 %)
IIIB	Pelvic side wall/hydronephrosis/ non-functioning kidney (50 %)
IV	Extension into bladder or bowel or beyond the pelvis
IVa	Bladder or bowel mucosa spread
IVb	Distant metastases

Management of Cervical Cancer

These patients are managed in a specialist cancer centre by a multi-professional team. The guiding principle of management is that it should be tailored to avoid the need for both surgery and radiotherapy as the toxicity of combined treatment is considerable.

Surgical options include cold knife cone biopsy for the very smallest stage Ia_1 tumours. For stage Ia_2 and early Ib_1 tumours Large Loop Excision of Transitional Zone (LLETZ) or fertility sparing trachelectomy (cervical amputation) are considered. Wertheim's radical hysterectomy is used for larger Ib_1 tumours and IIa disease. Wertheim's hysterectomy involves resection of uterus, fallopian tubes, ovaries, upper vagina, parametrium and pelvic lymph nodes.

Chemoradiation

Although radiotherapy and surgery offer equivalent disease control for early disease (stage Ia, Ib_1 and IIa) [4], for more advanced disease (i.e. stage Ib_2 and above) chemoradiotherapy is the treatment of choice. Chemoradiation involves the use of a cisplatin chemotherapy given concurrently with external beam treatment. A Meta-analysis of thirteen chemoradiotherapy studies has shown a 6 % improvement in 5 year survival compared to radiation alone [5].

Cisplatin is nephrotoxic, and good renal function is a prerequisite as it is mainly excreted through kidneys. It is essential that renal function is optimised promptly and prior to treatment commencing. Hydronephrosis should be relieved by nephrostomy and/or stent placement before chemoradiotherapy starts. Radiation fields encompass the uterus, cervix upper vagina and pelvic nodes up to the aortic bifurcation. The para-aortic nodal region is only included if clinically indicated. Daily treatment over 5–6 weeks is given followed by intracavity brachytherapy using a radioactive source, allowing a total dose of at least 75–80 Gray (Gy) to be delivered to the cervical tumour. If the patient is frail shorter radiotherapy schedules may be used without the addition of chemotherapy. Palliative care input may be useful in addressing symptom control (particularly pelvic pain) and psychological support.

Recurrent or Metastatic Disease

Metastatic disease is incurable and management is aimed at symptom control. Radiotherapy, chemotherapy or surgery may all be useful at this time.

Surgery or Radiotherapy (Salvage)

Following radiotherapy local recurrence may be treated with surgery and vice versa. In surgical salvage anterior pelvic or total pelvic exenteration may be necessary which would include urinary diversion.

Chemotherapy usually uses platinum containing regimens. Its primary aim is symptom control and it offers no significant improvement in survival.

Renal Failure secondary to outflow tract obstruction is not uncommon in advanced pelvic malignancy and nephrostomy or JJ-stenting may be necessary. This may offer a slight increase in life expectancy and by improving the general condition of the patient provide an opportunity for palliative chemotherapy.

Carcinoma of the Uterus

Incidence and Aetiology

Cancer of the uterine body predominantly affects post-menopausal women and is the commonest gynaecological cancer with an age-adjusted incidence of 24.7 per 100,000 population [6]. It is increasing in incidence in developed countries, which is almost certainly related to the rising problem of obesity. In developing countries it remains a relatively uncommon malignancy. Risk factors are shown include obesity, unopposed oestrogen exposure (related to hormone replacement therapy, anovulatory cycles, polycystic ovary syndrome), nulliparity, hypertension, diabetes, tamoxifen, genetic predisposition e.g. HNPCC

Spread

The risk of spread of the disease depends on certain histopathological risk factors. These include grade of tumour, depth of extension into the myometrium, presence of lymphovascular space invasion and cell type such as serous or clear cell.

Local infiltration beyond the body of the uterus occurs into the cervical stroma, the parametrial and para vaginal tissues, the vagina, adnexa (fallopian tubes and ovaries). More advanced tumours may invade into the bladder or rectum.

Lymphatic

As mentioned above tumour grade, depth of myometrial invasion and the presence of lymphovascular space invasion and also cervical involvement may all increase the risk of spread particularly to lymph nodes. Pelvic node metastases will be present in 30 % of cases with deep myometrial invasion. Positive para-aortic nodes are unusual in the absence of pelvic nodes and confer a poor prognosis [7].

Haematogenous spread to lungs and liver occurs late and is associated with a poor prognosis. Distant bone metastases are less common but direct invasion may be seen into the lower spine, sacrum or pelvis. In sarcoma haematogenous spread to lung is common even at presentation.

Pathology

Adenocarcinomas constitute more than 90 % of uterine cancers. Most are endometrioid (papillary, secretory, ciliated cell). The remainder are adenosquamous, mucinous, serous, clear cell or squamous cell. Clear cell and serous cell types behave more aggressively and have a poorer prognosis. Other tumours are include leiomyosarcoma, carcinosarcoma (mixed mesodermal tumours) endometrial stromal sarcoma and rarely lymphoma.

Clinical Presentation

Gynaecological

Uterine cancer tends to affect post menopausal women and over 75 % present with early stage 1 disease. This is because vaginal bleeding is a common symptom. In younger women presentation may be with intermenstrual bleeding. Late symptoms include back pain, urological or rectal symptoms. Other symptoms include persistent vaginal discharge and pelvic or back pain.

Urological

Urological symptoms such as urinary frequency, difficulty voiding and incontinence may be a presenting feature. These may be due to an enlarged uterus causing

extrinsic pressure on the bladder or urethra. Direct infiltration of the bladder is a sign of advanced disease and may also give rise to haematuria and ureteric obstruction. Incontinence may also be due to a vesico-vaginal fistula and again suggests advanced disease.

Ureteric obstruction is unusual and is a sign of advanced disease. It may occur by direct tumour extension to the pelvic sidewall or pelvic lymphadenopathy. As with cervical cancer it should be relieved by nephrostomy and stent insertion prior to any treatment.

Investigations

Blood

Full blood count, blood biochemistry and liver function analysis.

Imaging

Trans vaginal ultrasound to assess the endometrial lining is useful in diagnosing endometrial cancer (pipelle biopsy may be done synchronously). Pelvic imaging using either magnetic resonance (MR) or computed tomography (CT) scanning is recommended. The abdomen and chest should be also be included in locally advanced or high risk tumours.

Histopathology

Diagnosis is made by pipelle biopsy or endometrial curettage for uterine.

Staging

The clinically based International Federation of Gynaecology and Obstetrics (FIGO) staging system is the most widely used (Table 51.2) [2].

Prognosis

Prognostic factors include grade, depth of invasion, lymphovascular space invasion, positive nodes, tumour volume and cervical involvement [7, 8].

Management of Uterine Cancer

Surgery is the preferred treatment of uterine cancer. This involves hysterectomy and bilateral salpingo-oophorectomy with or without pelvic lymphadenectomy. This may be done either laparascopically or as an open laparotomy.

Table 51.2 FIGO (2009) staging of endometrial cancer

Endometrium (%risk nodal metastases)	
I	Confined to uterus
IA	No or <½ myometrial invasion (5–20 %)
IB	>½ myometrial invasion (30 %)
II	Cervix involved
	Cervical stromal invasion (30 %)
III	Beyond uterus (within true pelvis)
IIIA	Extends through serosal and or adnexa
IIIB	Vaginal and or parametrial involvement
IIIC1	Pelvic
IIIC2	Para-aortic nodes
IV	Spread to pelvic organs or distant metastases
IVA	Bladder or bowel mucosal spread
IVB	Other distant metastases

For early disease (stage 1 and 2) the need for adjuvant radiotherapy is determined by an assessment of risk factors that include tumour grade, depth of myometrial invasion, presence of lymphovascular space invasion and clear cell or serous cell type.

Well-differentiated tumours with minimal muscle invasion are deemed low risk for recurrence and no further treatment is indicated. Where there is deep muscle invasion but the tumour is either well or moderately differentiated and there is no lymphovascular space invasion the risk of recurrence is considered to be in the range of 5–10 % and brachytherapy to the vaginal vault may be offered [9]. Where there is deep muscle invasion, poorly differentiated tumours and clear cell or serous pathology external beam radiotherapy to the pelvis has been shown to reduce the risk of loco-regional relapse [10].

The use of adjuvant chemotherapy in the post-operative setting remains uncertain. There does appear to be a disease free survival benefit, which has yet to be proven to offer an overall survival advantage [11]. Ongoing studies are addressing this [4, 10].

Where patients are unsuitable for a surgical approach, radiotherapy may be considered for primary treatment.

Recurrent or Metastatic Disease

Locally recurrent disease may be successfully treated with surgery or, where it has not previously been used, radiotherapy. Systemic treatment may be of palliative value in recurrent or metastatic disease. In tumours with estrogen and progesterone receptors hormonal manipulation carries a 15–30 % response rate. Similar findings are seen with chemotherapy.

Colorectal Cancer

Incidence and Aetiology

Colorectal cancer is the third commonest cancer in both men and women in the USA. Between 1998 and 2002 the US incidence was 52/100,000 population. Mortality from colorectal cancers has declined mainly because of increased screening and polyp removal [12]. Cancer of the colon and rectum remains, however, one of the leading causes of cancer-related morbidity and mortality in most parts of the developed world [13]. The incidence of colo-rectal cancer increases with age, rising sharply after the age of 60. There is a large geographical variation in incidence with Africa and Asia having a much lower incidence than Western Countries. The majority are found in the rectum (almost 40 %) and sigmoid colon (20 %).

Aetiology

Polyps

Including Familial Polyposis.

Genetic Links

Around 80 % of colorectal cancers are sporadic. Of the rest, 5 % are linked to hereditary non-polyposis colorectal cancer (HNPCC) and 1 % to familial adenomatous polyposis (FAP).

Inflammatory bowel disease confers an increased lifetime risk of colorectal cancer with Crohn's disease having a relative risk of 1.5–2 and ulcerative colitis giving a 10 % incidence of malignant change at 25 years.

Environmental Factors

There are thought to be several environmental factors particularly dietary with the Western diet high in fat, low in fibre increasing risk.

Spread

Most colorectal cancers develop by malignant transformation of adenomatous polyps. The progression is from mucosal hyperplasia through adenoma and then via growth and dysplasia to malignancy. Advanced disease may present with rectal bleeding and change in bowel habit.

Spread is initially by local invasion. Lymph node involvement increases with greater depth of invasion and is seen in 40–70 % of patients at presentation. Haematogenous spread is to the lungs (more common in rectal tumours), liver (more common in colonic cancers), bone, skin and brain (rare).

Pathology

Macroscopically tumours may be sessile or pedunculated. They may ulcerate and bleed or produce stenotic lesions and hence obstruction. Microscopically over 95 % are adenocarcinomas. Other histological types are carcinoid, sarcoma and lymphoma.

Clinical Presentation

Colorectal

Up to one fifth present as an emergency with either obstruction or peritonitis due to perforation. The majority, however, present with one or more of; rectal bleeding, passage of mucus, change in bowel habit, iron deficiency anaemia, tenesmus, anorexia, weight loss or abdominal swelling.

Urological

Urinary symptoms can occur with locally advanced colorectal cancers. Direct extension into the bladder can cause cystitis-like symptoms, recurrent infection or haematuria. Infiltration into the prostate may cause prostatic symptoms. Obstructive uropathy is rare and likely to be due to tumour surrounding the ureter.

Investigation

Examination and Endoscopy

Digital examination may reveal rectal tumours but endoscopic evaluation with biopsy is needed. Assessment of the entire lower gastrointestinal tract is mandatory since about 3 % of tumours are associated with synchronous bowel lesions.

Blood Tests

Full blood count, renal function, liver blood tests and carcino-embryonic antigen (CEA) are routine. CEA is a tumour marker that can aid diagnosis and be useful in serial monitoring following treatment.

Imaging

Colon

For early colon cancers chest X-ray and liver ultrasound are sufficient to exclude metastases but in more advanced lesions CT imaging of the chest, abdomen and pelvis is required. Laparoscopy and MRI of the liver may be useful in determining resectability of hepatic metastases.

Rectal cancers are best assessed for operability with a pelvic MRI and endorectal ultrasound; these determine depth of mural invasion and presence of nodal enlargement. Metastases should be excluded with a CT of the chest and abdomen.

Histopathology

Diagnosis is made from endoscopic biopsy or, in the case of acute presentation, the surgical specimen.

Staging and Prognosis

Staging

There are several staging systems in use for colorectal cancer classification, TNM classification being the most preferred [14] (Tables 51.3 and 51.4).

Prognosis

Advanced stage, high tumour grade, site of tumour, emergency presentation and the loss of chromosome 18q are predictors of poor prognosis.

Table 51.3 Staging systems of colorectal cancer

Stage			
TNM	Dukes	UICC	Astler-Coller
T1, N0	A	1	A
T2, N0	A	1	B1
T3, N0	B	2a	B2
T4, N0	B	2b	B3
T1-2, N1	C	3a	C1
T3-4, N1	C	3b	C2
Any T, N2	C	3c	C3
Any T/N, M1	D	4	D

Table 51.4 TNM definition of colorectal cancer

TNM	Definition
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ or invasion into lamina propria
T1	Invades submucosa
T2	Invades muscularis propria
T3	Invades into subserosa, or into non-peritonealised pericolic or perirectal tissues
T4	Invades other organs/structures and/or perforates visceral peritoneum
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node involvement
N1	1–3 regional lymph nodes positive
N2	4 or more regional lymph nodes positive
Mx	Distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases present

Management of Colonic Carcinoma

Early Disease

Surgery is the mainstay of treatment. Tumour within a segment of normal bowel and the attached mesentery including the draining lymph nodes are resected. In early stage disease (stage I - Dukes A or Astler-Coller A and B1) no additional treatment is indicated.

Adjuvant chemotherapy improves outcome in node positive tumours. Trials have shown a 40 % reduction in risk of recurrence and a 10 % absolute survival benefit [14, 15]. It is considered for those at high risk of recurrence based on pathological findings [15, 16]. The gold standard combination is 5-Fluorouracil (5-FU) and leucovorin (folinic acid) and oxaliplatin (FOLFOX) [17]. Radiotherapy is not routine. However, it may be used to reduce the risk of local recurrence in T4 tumours with dense adhesions or positive margins.

Late Disease

Curative

Even with hepatic metastases some patients may still be suitable for curative treatment. Neo-adjuvant combination chemotherapy in patients with liver metastases may also increase resectability and improve outcome.

Palliative treatment may use both surgery and chemotherapy. Surgical interventions include stent placement, palliative resection, bypass operations or stoma formation. Chemotherapy may improve overall survival by 3–6 months without detriment to quality of life if given early. The most active drugs are 5-FU,

oxaliplatin, irinotecan and capecitabine [18]. Newer targeted antibodies such as bevacizumab which is an antibody against vascular endothelial growth factor receptor A (VEGF-A) and cetuximab which is a monoclonal antibody against epidermal growth factor receptor (EGFR) antibiological agents have also been shown to prolong overall survival when used in combination with standard chemotherapy agents.

Management of Rectal Carcinoma

A combination of surgery, chemoradiation and chemotherapy are used.

Local excision is possible only in very early tumours. The main surgical procedures used are anterior resection and abdomino-perineal resection both of which should include excision of the entire contents of the mesorectum. In good prognosis tumours surgery alone may be sufficient however in intermediate or poor prognosis tumours radiotherapy is also used either pre-or post –operatively.

Pre-operative irradiation given as a short 1 week course immediately prior to surgery is used where the mesorectal excision margin appears intact on staging MRI. It can reduce the risk of a positive margin and halve local recurrence [19, 20]. Where complete excision is unlikely, a standard 'long' course, 5-week treatment is given with concurrent chemotherapy. Surgery is carried out 6 weeks later.

Post-operative radiotherapy is used to reduce the risk of local recurrence where pathology shows poor prognosis features [21, 22]. Adjuvant and palliative treatment is given as for colon cancers. Palliative radiotherapy may palliate pain, bleeding and tenesmus.

Lymphomas

Incidence and Aetiology

The classification of lymphoproliferative malignancies is complex. In broad terms they can be divided into Hodgkin's disease (HD) and Non-Hodgkin's lymphoma (NHL). Between 1998 and 2002 the US incidence was, respectively, 2.7 and 19.1/100,000 population [1].

Hodgkin's disease has a bimodal age distribution (20–30 and 60–70 year) and is more common in males. The incidence of Non-Hodgkin's lymphoma increases with age and is seen equally in male and females.

Majority of urological symptoms are manifested in advanced lymphomas. The rate of involvement of urinary tract is low [23]. Urological intervention is necessary in patients who have renal failure and on occasions to obtain tissue for histological diagnosis.

Aetiology

Hodgkin's disease: The aetiology of Hodgkin's lymphoma (HL) is unclear although it has been postulated to have infective pathology. Epstein-Barr virus (EBV) antigens can be detected in up to 40 % of all HL cases [24]. RS cells also express EBV latent membrane antigen protein (LMP-1).

Non-Hodgkin's Lymphoma (NHL) may have an infective aetiology and is also seen following radiation exposure. Immunocompromised states such as post transplant or HIV infection also increase risk of lymphoma particularly in the later stages of the disease in HIV infection [24].

Spread

Lymphoma may affect any nodal group. Spread is usually contiguous in Hodgkin's Disease but in NHL often skips nodal groups. Extra-nodal sites are more commonly involved in NHL and may affect any site in the genito-urinary tract. Most often affected are the kidney, bladder, testes and prostate.

Pathology

NHL is classified according to the Revised European-American Lymphoma (REAL) 1998 classification that uses the principles of morphology, immunology, genetics and clinical behaviour [25]. The main division is between B and T cell neoplasms. B cell Neoplasms include entities such as mantle cell, hairy cell, follicular, diffuse large B cell and Burkitt's lymphoma. T cell Neoplasms are less common and include Mycosis Fungoides, Sezary syndrome and natural killer cell lymphoma.

Hodgkin's Disease

The diagnosis of HD is dependent on the presence of Reed-Sternberg cells (giant, atypical, binucleate cells which are CD 15 and 30 positive) in an appropriate pathological background which varies according to subtype. Pathologists currently use the World Health Organisation classification which is as follows [26]:

- Nodular lymphocyte predominant Hodgkin's lymphoma
- Classical Hodgkin's lymphoma
  - Nodular sclerosing Hodgkin's lymphoma
  - Lymphocyte rich classical Hodgkin's lymphoma
  - Mixed cellularity Hodgkin's lymphoma
  - Lymphocyte depleted Hodgkin's lymphoma

Presentation

Nodal Enlargement

Enlarged nodes may be palpable or cause symptoms from compression. Abdominal nodes may cause non-specific gastrointestinal symptoms, jaundice or an obstructive uropathy. Pelvic nodes may cause lower limb or genital oedema, urinary tract obstruction or pain.

Systemic 'B' symptoms are defined as pyrexia of unknown origin over 38 °C, drenching night sweats and weight loss of more than 10 % body weight in the last 6 months.

Urological

Renal impairment may be seen with obstruction of the urinary tract and less commonly with direct involvement of the kidney, ureters or bladder. It also occurs with urate nephropathy or secondary to hypercalcaemia. Hyperuricaemia can be seen spontaneously in lymphomas and results in deposition of urate crystals in the distal renal tubules. Nephrotic syndrome may be seen in lymphomas, particularly HD where minimal change glomerulonephritis is the most common pathology. This is best resolved by treating the underlying malignancy. Testicular masses may occur with lymphomatous infiltration (particularly in older men). Lymphoma of the bladder or kidney may present with haematuria.

Investigations

Blood

Full blood count, urea and electrolytes, liver blood tests, erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), β_2 microglobulin and albumin. HIV serology should be considered in at risk patients.

Imaging

A CT scan of the neck, chest, abdomen and pelvis is needed for accurate staging. PET–CT is useful in the diagnosis and follow-up of both NHL and Hodgkin's Disease.

Histology

Histology requires a biopsy rather than a fine needle aspirate as architecture is important in correct pathological diagnosis. Testicular masses should be removed at orchidectomy via inguinal incision if malignancy is suspected.

In NHL bone marrow aspirate and trephine (BMAT) is done in all patients except those with stage IA disease. In HD it is only done in advanced disease.

Lumbar Puncture

Central nervous system involvement is more common with testicular, gastrointestinal or head and neck involvement. These cases and those with HIV, Burkitts lymphoma or neurological symptoms should all have CSF examined.

Staging and Prognosis

Staging

Both types of lymphoma are staged according to the Ann Arbor system (Table 51.5).

Prognosis

Prognostic determination depends on histology and stage.

NHL

The international prognosis index for NHL consists of five factors, including age, stage, performance status and LDH, each giving a score of one [27]. Low risk patients with a score of 0–1 have an overall 5 year survival of 73 % whereas high risk groups with a score of 4–5 have an overall five year survival of 25 %.

Table 51.5 Ann Arbor staging of lymphoma

I – single lymph node region involved OR localised involvement of a single extra-lymphatic site (IE)
II – 2 or more lymph node regions on the same side of the diaphragm OR a single extralymphatic site and its regional lymph nodes ± lymph nodes on the same side of the diaphragm (IIE)
III – lymph node regions on both sides of the diaphragm ± localised involvement of extralymphatic site +/or spleen (IIIE + S)
IV – multifocal involvement of 1 or more extralymphatic organs ± associated lymph nodes OR isolated extralymphatic organ involvement with distant lymph nodes
A – no B symptoms
B – presence of B symptoms
E – extranodal site

S spleen, *O* bone, *P* pleura, *H* liver, *M* bone marrow, *L* lung, *D* skin, *X* bulk disease; includes mediastinal mass >1/3 chest diameter at the level of T5/6, or lymph node mass >10 cm

Follicular lymphoma uses the FLIPI (Follicular Lymphoma International Prognostic Index) classification of five points (including haemoglobin, age, stage and LDH). A score of 0–1 gives a 10 year survival of 70 % and 3 or more gives a 10 year survival of 35 %.

Early Hodgkins Disease can be assessed with EORTC (European Organisation for the Research and Treatment of Cancer) risk factors [28] placing patients into favourable and unfavourable groups. The presence of any of the following place a patient into the unfavourable group – four or more nodal areas, age over 50, ESR over 50 if asymptomatic or over 30 with B symptoms.

Advanced Hodgkin's disease uses the Hasencleaver index with nine factors each giving a score of one [29]. A score of four or more puts patients into a poor prognosis group and if all are negative then overall survival is estimated at 84 %.

Management of NHL

High Grade

Early localised (stage IA and non-bulky IIA) disease is treated with three to four cycles of combination chemotherapy together with the monoclonal antibody anti-CD20 antibody, (if the tumour is CD20 positive) rituximab followed by radiotherapy treating the pre-chemotherapy nodal volume [30]. Prior to chemotherapy male patients should be offered sperm storage.

Other stages, including primary bladder or testicular lymphoma, are treated with six to eight cycles of combination chemotherapy with the addition of rituximab [31]. This addition increases the complete response rate and prolongs event free and overall survival. Residual or recurrent disease may be treated with second line chemotherapy followed by a peripheral blood stem cell autologous transplant if the patient is considered fit enough. Local radiotherapy may also be considered.

Low Grade

Localised radiotherapy may be used for stage I disease as curative treatment [32].

'**Watch and wait**' can be used in stage II and above providing there is a normal full blood count, no B symptoms, compression symptoms or any nodal mass over 7 cm. Studies have shown this approach to give comparable overall survival as giving chemotherapy at diagnosis [33].

Chemotherapy

If immediate treatment is deemed necessary there are many agents that have been shown to be effective. The most commonly used drug is oral chlorambucil with response rates of up to 75 %. Combination chemotherapy regimes may be

preferable if rapid response is necessary for severe symptoms. Radiotherapy may be useful in sites of disease not responding to chemotherapy or where there is localised relapse.

Management of HL

Early Disease

This has a high cure rate of over 90 %. Usually a combination of chemotherapy and involved field radiotherapy is used, however in young women upper body radiotherapy is avoided as it may significantly increase the risk of breast cancer.

Radiotherapy Alone

Non-bulky stage Ia lymphocyte predominant HD can be treated with involved field radiotherapy alone. Otherwise because of higher relapse rates combined chemotherapy and radiotherapy is preferred [34].

Combination Chemotherapy and Radiotherapy

Classical HD stages Ia Ib and IIa and are generally treated with four cycles of combination chemotherapy (doxorubicin, bleomycin, vinblastine and dacarbazine – ABVD) followed by involved field radiotherapy [34].

Advanced Disease

Advanced disease is treated with six to eight cycles of chemotherapy. Radiotherapy is usually given to sites of bulk disease [35, 36]. High dose chemotherapy with stem cell rescue may be given if there is progressive disease during initial chemotherapy, if the first relapse is within 1 year or at second relapse.

Urological Complications Relating to Treatment of Pelvic Malignancy

Surgical

Pelvic surgery may be complicated by damage to the urethra, ureters or bladder. This can result in haematuria, frequency, urge or stress incontinence, urinary fistula or obstructive renal failure. The general complications include septicemia, pulmonary embolism, myocardial infarction, stroke and anaemia.

Chemotherapy

Renal Failure

Many drugs can lead to both acute and chronic renal failure. Cisplatin is nephrotoxic drug can cause direct damage of the renal parenchyma, via acute tubular necrosis or tubular interstitial fibrosis (irreversible). These problems can be limited by close monitoring of renal function during treatment and ensuring good hydration and diuresis during chemotherapy administration.

Where high dose methotrexate is used renal failure can occur secondary to precipitation in the tubules and collecting ducts. Adequate pre-hydration is essential and alkalinisation of urine with intravenous sodium bicarbonate (to maintain urinary pH above eight) may reduce the incidence. Methotrexate renal impairment usually reverses once the drug is stopped although this may take some weeks.

Electrolyte Imbalance

Cisplatin may cause electrolyte imbalances. The most common is hypomagnesaemia and extended oral magnesium replacement may be needed hyponatraemia and orthostatic hypotension is also seen. Both cyclophosphamide and vincristine may be associated with a clinical picture similar to the syndrome of inappropriate anti-diuretic hormone (SIADH). Treatment is with drug withdrawal and occasionally fluid restriction is necessary though this is best avoided as it can precipitate haemorrhagic cystitis.

Haemorrhagic Cystitis

Chemotherapy with the commonly used drug cyclophosphamide can cause haemorrhagic cystitis. This is unusual with the doses used in treating lymphoma and can be prevented with aggressive hydration and frequent voiding. This is discussed in detail in Chap. 7.

Tumour Lysis Syndrome

This may occur in patients with lymphoma whose disease responds so dramatically and rapidly to chemotherapy that the extensive rapid tumour lysis. This causes metabolic disturbance as intracellular constituents leach into the blood. It is characterised by hyperkalaemia, hyperuricaemia, hyperphosphataemia and hypocalcaemia. This can result in cardiac arrhythmias, renal failure (from intratubular obstruction causing acute tubular necrosis) and, rarely, sudden death. To prevent this patients are aggressively hydrated and given allopurinol prior to chemotherapy.

Treatment of uric acid nephropathy (either spontaneous or secondary to tumour lysis) is with hydration (to maintain urine output of >100 mL/h), urinary alkalinisation and allopurinol. In the event of oliguria (where obstruction has been excluded) diuretics are used. Rarely temporary haemofiltration or haemodialysis is necessary.

Radiotherapy

Early effects of radiation toxicity begin about 2–3 weeks into a standard course of treatment and are usually mild but may last about 6–8 weeks following completion of treatment. Problems include cystitis and urethritis, which are managed symptomatically although acute infection must be excluded. Rarely, it may be severe enough to interrupt treatment.

Late radiation damage of some degree occurs in at least a third of patients; fortunately less than 5 % develop severe problems. It usually manifests 6–12 months after treatment and is often progressive. Although it is rarely life threatening it often has a detrimental affect on a patient's quality of life and needs to be managed pro-actively. The risk of developing radiation toxicity increases with diabetes, vascular and inflammatory bowel disease. Other risk factors include previous surgery, irradiating large areas of tissue, using large doses per treatment, and concurrent chemotherapy.

Bladder Manifestations

Mild damage to the bladder manifests by pale colour of the mucosa, other changes may be prominent blood vessels (telangiectasia) on the mucosal surface which can sometimes cause bleeding. More severe toxicity includes mucosal ulceration, haemorrhagic cystitis, fibrosis and loss of bladder volume and fistula. Clinical symptoms include urgency, frequency, incontinence, nocturia, haematuria. Cystectomy or urinary diversion is occasionally necessary.

Ureteric stenosis may require permanent stenting and urethral stenosis may need urethral dilatation or intermittent self-catheterisation.

Radiation Nephritis

If the radiotherapy dose to the kidney is not limited (no more than 50 % of each kidney should receive more than 20 Gy) then post radiation nephritis may ensue 6–12 months later. This is characterised by hypertension, proteinuria and microscopic haematuria. Prevention is achieved by careful radiotherapy planning.

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