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Editors

Urological Oncology

Second Edition

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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
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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.

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Contents

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

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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