

SIXTH EDITION

Cancer and its Management

Jeffrey Tobias and Daniel Hochhauser

A fluorescence microscopy image showing several cells with blue nuclei. Inside the nuclei, there are clusters of red and green fluorescent spots, likely representing specific genetic markers or proteins. The background is black.

 WILEY-BLACKWELL

Cancer and its management

This edition of *Cancer and its management* is dedicated to the memory of
Dr Gabriela Tobias (1950–2008)

Cancer and its management

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6th edition

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Foreword

Few medical textbooks that are entirely written by two people are alive and well almost 25 years after the first edition. They, and their authors, are usually submerged by changes in the subject and the difficulty and effort required in keeping up to date. This book, however, has the advantage of its primary purpose, which is to provide a balanced, readable, synthesis of the practice of cancer medicine: one that is accessible and of value to students and medical professionals, in all disciplines, who encounter cancer in daily practice but who are not themselves specialists in the field.

It is relatively straightforward to identify new treatments and principles that are in the process of becoming, or have become, part of everyday practice. It is more difficult to be sure of what is becoming redundant as a result of change and which should therefore be reduced in content or

excluded. Yet without these judgements the book would grow to become yet another indigestible tome that rests on the shelf and is seldom read.

Jeffrey Tobias and Daniel Hochhauser are among the relatively few oncologists capable of providing, over the entire field, the balance, authority and judgement necessary. To be publishing the sixth edition is a great achievement. In their hands the book will surely continue to prosper and will introduce new readers to the human and technical challenges that are at the heart of the care of patients who have cancer.

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London 2010*

Preface

Professor Robert Souhami and I began work on this book almost 30 years ago, and after a 5-year gestation the first edition appeared in 1986. Naturally we are delighted that it remains so popular. In the past, each time we settled down to start work on the new edition we always felt that this time, surely, the changes would be relatively minor. We were always wrong, and on this occasion, following Bob Souhami's retirement and joined for the first time by my close colleague Professor Daniel Hochhauser, I now discover that the necessary amendments, alterations and updates are greater than ever before.

It was a great pleasure working with Robert for so long, and from my own point of view, our book remains a lasting reminder of an exceptionally close working relationship over so many years. I am delighted that Daniel has agreed to join me in the challenging task of producing this sixth edition of *Cancer and its management*. As on all the previous occasions, we have been astonished by the scale of the innovations and changes in management that have rapidly become an essential part of the gold-standard care of cancer patients. Perhaps it is only by writing a book covering all aspects of malignant disease that these developments can be fully appreciated, though this is not an approach to what is now called continued professional development that we recommend to others!

Bidding a professional farewell to a highly respected close friend and colleague, and warmly welcoming a new one, set me to thinking about some of the changes that have occurred over the past 30 years, though they are far too numerous, of course, to list separately. Without question, the outlook has changed dramatically, and for the better. Patients now have access to a far more integrated and seamless service, with multidisciplinary teams regularly meeting to discuss all aspects of a patient's management, resulting in a more balanced and expert approach to decision-making. Patients are increasingly managed by well-informed specialists with particular experience and expertise in their field of practice. Communication between general practitioners, hospital specialists and community

services, including those for continuing and palliative care, have improved enormously.

New chemotherapeutic agents have appeared at a remarkably rapid rate. Most notable of all, even since the last (fifth) edition of this book appeared in 2005, we have seen the increasing and now routine use of biologically targeted therapies in a wide variety of malignant conditions, though it seems hard to believe that these agents, so ubiquitous today, have been available for only a decade or less. The very first of these, the monoclonal antibody rituximab, was approved in the USA by the Food and Drug Administration (FDA) for the treatment of relapsed low-grade CD20-positive non-Hodgkin's lymphoma as recently as the latter part of 1997. This relatively recent discovery has in turn led to the introduction of a huge spectrum of new targeted agents and monoclonal antibodies against the many cellular targets known to be involved in cancer cell growth. An even greater number are in development and we can further predict that microarray diagnostic techniques will lead to far more precise identification of patients who will gain the greatest benefit from the multitude of these newer treatments. It is an exciting time to be in cancer medicine, but it is profoundly important to remember that the human, pastoral and technical lessons of the past do not change. Our book is based largely on these. Virtually all other areas of cancer medicine have seen dramatic improvements as well, whether it be early detection and referral, improved diagnosis, surgical techniques or other major areas of clinical management.

As we pointed out in the preface to previous editions, a textbook limited to this size and designed to be widely comprehensible demands that only essential information be presented. We have had to synthesize and abbreviate a variety of differing, sometimes conflicting, opinions, and summarize interesting or unresolved controversies which, in a larger text, would have been the subject of more detailed discussion. Nonetheless, we hope the result is an accessible text that avoids being too didactic in tone or

synoptic in style. The aim of the book has not altered: it is to provide an introductory text for medical staff, nurses and other allied professionals, students and scientists interested in and challenged by the problems of cancer care.

Initially we wrote this book because we were aware that many busy physicians, surgeons and gynaecologists, who are not themselves cancer specialists, may find it difficult to keep abreast of areas of considerable importance to them. General surgeons, for example, spend a substantial portion of their time dealing with gastrointestinal and abdominal tumours, yet have little working knowledge of the non-surgical treatment of these conditions. Similarly, gynaecological surgeons need to know more about what the radiotherapist (nowadays more frequently termed 'clinical oncologist') and medical oncologist can offer.

In many medical schools, a student's knowledge of the basics and management of malignant disease is acquired from specialists whose main interest may not be related to cancer. Medical students should surely know more about the disease that in many countries is now the largest cause of mortality as well as being regularly recognized by the public at large as the most feared of all diseases. Needless to say, we hope that postgraduate trainees in medicine, surgery and gynaecology will find the book of value, and that it will also be of help to those beginning a career in clinical or medical oncology. Finally, we would like to think that general practitioners, all of whom look after cancer patients and who have such an important role in diagnosis, early referral of patients with suspicious symptoms, shared management, follow-up and terminal care, will find this book helpful. If specialists in cancer medicine feel it is a useful digest of current thought in cancer management, so much the better. However, this book is not intended primarily for them. There are several very large texts that give specialist advice. Although some of these details necessarily appear in our book, we do not regard it as a handbook of chemotherapy or radiotherapy. To some extent it is a personal view of cancer and its management today and, as such, it will differ in some details from the attitudes and approaches of our colleagues.

We have attempted to give a thorough working knowledge of the principles of diagnosis, staging and treatment of tumours and to do so at a level that brings the reader up to date. We have tried to indicate where the subject is

growing, where controversies lie, and from which direction future advances might come. In the first nine chapters we have attempted to outline the essential mechanisms of tumour development, cancer treatment and supportive care. In the remaining chapters we have given an account of the principles of management of the major cancers. For each tumour we have provided details of the pathology, mode of spread, clinical presentation, staging and treatment with radiotherapy and chemotherapy. The role of surgery is of course outlined, but details of surgical procedure are beyond the scope of this book. The references which we have included in the text or for further reading have been chosen because they are clear and authoritative reviews, historical landmarks or, perhaps most excitingly, represent the cutting edge of recent research.

For me personally, the gestation, writing and production of this new edition has been a wonderfully challenging task, enormously enhanced by the arrival of my co-author Professor Daniel Hochhauser, a medical oncologist as passionate and committed as his distinguished predecessor. We both hope that this edition of *Cancer and its management* will live up to the high standards that Robert Souhami always imposed, and that it will be of help to those of you struggling like ourselves to offer the highest standards of care for our cancer patients in a rapidly changing clinical world.

This edition is dedicated to the memory of my late wife Dr Gabriela Tobias (1950–2008), an outstanding general medical practitioner and champion of patient welfare, who died from metastatic cancer of the colon during the preparation of the manuscript. Gaby qualified from University College London and University College Hospital in 1973, and devoted virtually the whole of her professional life to the care of patients in the deprived East End of London. Words cannot sufficiently express my profound sense of gratitude to Professor Hochhauser and his team at University College Hospital, London, who supervised her care with such tireless devotion and expertise. The concept of 'patient-centred care', so widely discussed yet so often poorly understood, takes on profound significance from the other side of the consulting-room desk.

Jeffrey Tobias
London 2010

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Cover image: Fluorescent *in situ* hybridization image of cells recovered from a Her-2-positive breast cancer. Used with permission from Baylor College of Medicine, Lester & Sue Smith Breast Center's Pathology Core, Houston, TX.

Although every effort has been made to ensure the accuracy of the drug dosages and side-effects described in this book, the authors and publisher make no representation, expressed or implied, that they are correct. Readers are advised to refer to published information from the pharmaceutical companies and other reference works to check accuracy.

Abbreviations

5-FU	5-fluorouracil	CSF	cerebrospinal fluid
5-HIAA	5-hydroxyindoleacetic acid	CT	computed tomography
5-HT	5-hydroxytryptamine	CTV	clinical target volume
6-MP	6-mercaptopurine	DCIS	ductus carcinoma <i>in situ</i>
6-MPRP	6-mercaptopurine ribose phosphate	DHFR	dihydrofolate reductase
6-TG	6-thioguanine	DIC	disseminated intravascular coagulation
ACTH	adrenocorticotrophic hormone	DPD	dihydropyrimidine dehydrogenase
ADH	antidiuretic hormone	EBV	Epstein–Barr virus
AFP	α -fetoprotein	ECOG	Eastern Cooperative Oncology Group
AJCC	American Joint Committee on Cancer	EF	extended field
ALL	acute lymphoblastic leukaemia	EGF	epidermal growth factor
AML	acute myeloid leukaemia; acute myeloblastic leukaemia	EGFR	epidermal growth factor receptor
AMML	acute myelomonocytic leukaemia	EORTC	European Organization for Research and Treatment of Cancer
ANL	acute non-lymphocytic leukaemia	EpCAM	epithelial cell adhesion molecule
APL	acute promyelocytic leukaemia	EPO	erythropoietin
APUD	amine precursor uptake and decarboxylation	ER	estrogen receptor
ASCO	American Society for Clinical Oncology	ERCP	endoscopic retrograde cholangiopancreatography
ATRA	all- <i>trans</i> -retinoic acid	ESR	erythrocyte sedimentation rate
BCG	bacille Calmette–Guérin	FAP	familial adenomatous polyposis
BCNU	bis-chloroethyl nitrosourea	FDA	Food and Drug Administration
BMI	body mass index	FdUMP	5-fluoro-2-deoxyuridine monophosphate
BMT	bone-marrow transplantation	FIGO	International Federation of Gynecology and Obstetrics
BrdU	bromodeoxyuridine	FISH	fluorescence <i>in situ</i> hybridization
BTv	biological target volume	FIT	faecal immunochemical test
CALLA	common acute lymphoblastic leukaemia antigen	FOBT	faecal occult blood test
CCNU	<i>cis</i> -chloroethyl nitrosourea	FSH	follicle-stimulating hormone
CEA	carcinoembryonic antigen	G6PD	glucose 6-phosphate dehydrogenase
CGL	chronic granulocytic leukaemia	G-CSF	granulocyte colony-stimulating factor
CHART	continuous hyperfractionated accelerated radiotherapy	GFR	glomerular filtration rate
CI	confidence interval	GH	growth hormone
CIN	cervical intraepithelial neoplasia	GIST	gastrointestinal stromal tumour
CLL	chronic lymphocytic leukaemia	GM-CSF	granulocyte/macrophage colony-stimulating factor
CMF	cyclophosphamide, methotrexate and 5-fluorouracil	GSH	glutathione
CMI	cell-mediated immunity	GTV	gross tumour volume
CML	chronic myeloid leukaemia	HAART	highly active antiretroviral therapy
CNS	central nervous system	HBI	hemibody irradiation