UNION FOR INTERNATIONAL CANCER CONTROL

Manual of CLINICAL ONCOLOGY

NINTH EDITION

BRIAN O'SULLIVAN (EDITOR IN CHIEF), **JAMES D. BRIERLEY, ANIL K. D'CRUZ, MARTIN F. FEY, RAPHAEL POLLOCK, JAN B. VERMORKEN,** AND **SHAO HUI HUANG**

WILEY Blackwell

International Union Against Cancer

Manual of Clinical Oncology

UICC Manual of Clinical Oncology

NINTH EDITION

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This edition first published 2015 © 2015 by UICC. Published 2015 by John Wiley & Sons, Ltd

This Work is a co-publication between the UICC and John Wiley & Sons, Ltd.

Registered office: John Wiley & Sons, Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial offices: 9600 Garsington Road, Oxford, OX4 2DQ, UK
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Library of Congress Cataloging-in-Publication Data

UICC manual of clinical oncology / editors, Brian O'Sullivan, editor in chief; James Brierley [and five others]. — Ninth edition.
p. ; cm.
Manual of clinical oncology
Preceded by UICC manual of clinical oncology / editor, Raphael E. Pollock. 8th ed. 2004.
Includes bibliographical references and index.
ISBN 978-1-4443-3244-5 (cloth)
I. O'Sullivan, Brian, 1952– , editor. II. Brierley, James, editor. III. International Union against Cancer, issuing body. IV. Title: Manual of clinical oncology.
[DNLM: 1. Neoplasms—Handbooks. QZ 39]

RC262.5
616.99'4—dc23

2015021962

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Cover image: Photo of banner © UICC.

Set in 9pt/12pt Frutiger Light by Aptara Inc., New Delhi, India

1 2015

Dedication

This *Manual* is dedicated to Leslie H. Sobin MD, an internationally renowned pathologist and previous long-term Chair of the UICC TNM Prognostic Factor Committee. Les, as he is known to colleagues all over the world, has devoted most of his career to promoting multidisciplinary cancer control in a truly global manner.

Contents

Foreword

UICC unites the cancer community to reduce the global cancer burden, to promote greater equity and to integrate cancer control into the world health and development agenda with the goal of delivering on the World Cancer Declaration. One of the nine targets of the Declaration that shape the overarching goal of improving cancer survival is the education and training of healthcare professionals. The *UICC Manual of Clinical Oncology* has for many years been part of UICC's educational platform. I have always kept the latest edition of this book as an essential oncology guide in my library since my early years in oncology. By bringing together for the 9th edition a multidisciplinary authorship from across the globe with the purpose of generating an accessible and realistic guide for cancer management in all resource settings, Dr O'Sullivan and the editorial team of the *UICC Manual of Clinical Oncology* have further strengthened UICC's commitment to improve cancer services and patient outcomes.

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Preface

It is with great pride that I introduce the 9th edition of the *UICC Manual of Clinical Oncology*, representing the work of a remarkably diverse international group of colleagues. The *Manual* continues to emphasize a devotion to multidisciplinary assessment and care. Disease-site chapters have been co-authored wherever appropriate by representatives of medical, radiation and surgical oncology in addressing the different fields of cancer management. As well, an international panel of authors has been assembled that strives to emphasize, where relevant, needs in jurisdictions where a disease may be most prevalent. For example, many head and neck cancer chapters are authored from India which sustains an unfair burden of tobacco-related mucosal cancers, but the nasopharyngeal and oropharyngeal chapters are authored by specialists from South East-Asia and the Western World, respectively, in recognition of the unique disease incidence and profile in these locations.

As in previous editions, the target readership comprises oncologists-in-training and the many subspecialty disciplines and allied health practitioners involved with multimodality cancer treatment programmes, as well as practising physicians and others throughout the world who care for cancer patients. Wherever feasible, a succinct style is used and characterized by bullet point displays and tabular depictions instead of the traditional dense text that characterizes many textbooks. In large part this convention is concentrated in the disease-site chapters which form the backbone of the manual and where the hallmark is immediate access to information for readers. The philosophy is particularly mindful of the needs of jurisdictions where information is less available and practitioners may be unusually busy and working in smaller units. For all chapters, references are provided as recommended reading without encumbering the direct narratives of specialists with knowledge and experience of the domain under discussion.

This edition has been completely revised and all chapters rewritten. New chapters address information needs and approaches that highlight areas of contemporary oncology, including, among others, practical understanding and application of evidence-based medicine, cancer informatics, oncology outcome reporting, symptom management, survivorship and end of life needs of cancer patients. Each disease-site chapter also incorporates cancer staging from the *UICC's TNM Classification of Malignant Tumours*, 7th Edition (2009) and a complete chapter is devoted to the history and principles of cancer staging that evolved at the UICC from the time it first introduced TNM more than 60 years ago.

Since publication of the 8th edition in 2004, there has been a necessary need to integrate knowledge about non-anatomical factors with traditional classification of disease extent into prognostic algorithms which also influence cancer diagnosis and therapy. Of particular importance are molecular characteristics, but other very relevant factors pertain to patient issues, such as age, co-morbidity and ability to tolerate treatment, as well as the health service environment, including access to care, education and skill/knowledge of practitioners. For this reason each disease-site chapter employs a standard classification format that identifies prognostic factors according to their current relevance in the clinic. This classifies factors as to whether they are *essential* to guide treatment decision-making, provide *additional* information that may facilitate research, teaching, or cancer programme management, or represent *new and promising* developments in oncology without yet having a firm foothold in overall cancer control. These concepts are emphasized using the UICC's standard tabular format in each anatomical site-specific chapter. The source for *essential* factors is from publicly available guidelines that mandate their requirement for treatment decision-making. They include internationally recognized guidelines such as those of NCCN, ESMO, ASTRO, ESTRO and ASCO, as well as published guidelines from individual cancer institutions or agencies where available. In addition, the cancer incidence and prevalence data are almost entirely from Globocan 2012 (http://globocan.iarc.fr/Default.aspx) and Surveillance, Epidemiology, and End Results Program (SEER) (http://SEER.cancer.gov).

Finally, and most importantly, I would like to thank our readers, whose efforts on behalf of oncology patients worldwide offer the very best hope for a future free of malignant disease. I hope you will enjoy this book as much as we, the editors and authors, enjoyed the global spirit of collaboration and interaction needed to prepare it for you and our patients.

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Acknowledgement

I would like to take this opportunity to thank my co-editors and all the authors of the *Manual* for their dedication in volunteering their time on behalf of this project.

Special thanks are also extended to the Editorial Coordinator, Shao Hui (Sophie) Huang, who volunteered tirelessly in supporting the editorial team, and to the staff at UICC and Wiley.

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PART 1

General principles of cancer diagnosis and management

1 Cancer epidemiology

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Introduction

Epidemiology is the study of the distribution and determinants of disease in specified populations, and the application of this information to the control of health-related problems. Cancer epidemiology thus encompasses understanding the distribution of cancer morbidity and mortality, identifying the causes of cancer and evaluating preventive measures and use of health services.

Distribution of disease refers to the identification, description and interpretation of the patterns of cancer among different populations over different time periods. This branch of cancer epidemiology, often referred to as *descriptive cancer epidemiology*, has provided insights into the disease burden of cancer and trends of cancer over time, and has also helped in generating hypotheses for aetiological research. Key to accurate descriptive cancer epidemiology is the availability of high-quality population-based cancer registries in many areas of the world.

The term *determinant of disease* refers to the study of disease aetiology. Knowledge about the causes and preventive strategies for cancer has largely arisen from carefully conducted epidemiological studies, often referred to as *analytical epidemiology*. The search for causes in an epidemiological setting is not limited to lifestyle factors, but also includes infectious agents and genetic factors. Over the past few decades, the field of epidemiology has evolved with the use of biomarkers, including genetic markers, to deepen our understanding of both exposure and outcome. This particular approach to understanding disease aetiology is often termed *molecular epidemiology*.

Along with the identification of the causes of cancer, epidemiological studies have been used to evaluate the success of primary and secondary prevention strategies in controlling the burden of cancer. These studies are often conducted as *field intervention trials* and assess the feasibility and success of primary preventive measures and screening programmes in different population settings.

Study designs in cancer epidemiology (Box 1.1 and Table 1.1)

Descriptive studies

A well-functioning cancer surveillance system which provides accurate information on cancer incidence, mortality and time trends is a key feature of an effective cancer control programme. The task of cancer surveillance is undertaken by population-based cancer registries (PBCRs). These registries collect cancer data by age, cancer site and date of diagnosis

Box 1.1 Introduction to cancer epidemiology

- Descriptive cancer epidemiology is the study of the distribution of cancer in different geographical areas over different time periods. This information is mainly derived from population-based cancer registries (PBCRs)
- Cancer epidemiology is also concerned with identifying the causes of cancer: this is mainly achieved through observational study designs such as case–control and cohort studies
- The branch of epidemiology that uses biomarkers of exposure and disease to understand the aetiology of cancer is referred to as 'molecular epidemiology'
- Since cancer is a relatively rare disease, case–control studies are often the study design of choice. Given the potential for selection and recall bias, these studies should be conducted with utmost care to minimize bias for meaningful interpretation of study results
- Although expensive and requiring longer follow-up, cohort or longitudinal studies are powerful study designs to understand the aetiology of cancer
- Experimental studies which involve randomization of individuals into two or more study groups are commonly used to study treatment efficacy ('clinical trials'). This design can also be used in the field to study the effectiveness of interventions such as vaccination (by randomization of individuals into vaccinated and non-vaccinated groups)

UICC Manual of Clinical Oncology, Ninth Edition. Edited by Brian O'Sullivan, James D. Brierley, Anil K. D'Cruz, Martin F. Fey, Raphael Pollock, Jan B. Vermorken and Shao Hui Huang.

Table 1.1 Summary of the scope of cancer epidemiology

Main goal	Approach	Statistical measures
Distribution of cancer	Population-based cancer registries (PBCRs)	Incidence rates, mortality rates, cumulative risk
Determinants of cancer (lifestyle, environmental, infection, genetic)	Case–control studies, cohort studies, molecular epidemiology (including genetic markers)	Odds ratio, relative risk, attributable risk
Public health (screening, primary prevention measures)	Field intervention trials	Hazard ratio, mortality ratio

for populations in well-defined geographical areas. PBCRs can also provide data on population-based survival for different cancer sites in different populations. The quality and completeness of the data depends upon the availability and utilization of health services by cancer patients, and proper documentation by various facilities in which cancer is diagnosed and treated. Key requirements for a well-functioning PBCR are: accurate census data for the population covered by the registry by age and gender; access to various sources of cancer diagnosis and treatment; and support from local policy-makers as well as leading cancer diagnostic and treatment centres. While the numbers of high-quality PBCRs have been increasing worldwide, the large majority is still located in high-income countries. In the absence of PBCRs, many countries depend upon data from hospital-based cancer registries (HBCRs) and pathology-based cancer registries to estimate cancer burden. Data from these registries, however, are not suitable for cancer control planning, given the potential biases due to referral patterns and underestimation of incidence for cancer sites where histology is uncommon. In order to promote descriptive epidemiology research and increase the number of cancer registries in low resource settings, the International Agency for Research on Cancer (IARC), in collaboration with a number of global partners, including UICC, the U.S. National Cancer Institute and Centers for Disease Control and Prevention (CDC), has launched the Global Initiative for Cancer Registry Development' (GICR; www.gicr.iarc.fr). The GICR functions with the help of IARC regional hubs which provide assistance in the establishment of cancer registries.

Analytical studies

Analytical studies fall into two main categories: *observational* and *experimental*.

Observational studies

An observational study is a non-interventional investigation of disease causation in a human population. Such studies are based on observing associations between the exposure(s) and disease(s) of interest. Measurement of exposure is usually based on some combination of lifestyle data from questionnaires, external monitoring of exposure (e.g. for air pollutants) and biomarkers of exposure. New advances in microchip technologies and informatics are being used to understand the role of genetics as well as the interaction between environmental exposures and genes. Observational studies yield measures of association between exposure and disease, but interpretation of causality requires further information, including the following considerations:

- *Temporality*. Does exposure precede disease? For a factor to be causal for a disease, it must occur before the disease.
- *Strength* of the association, measured by the relative risk or odds ratio. The stronger the association, the more likely that the relationship is causal.
- Existence of a *dose–response* relationship. If the risk of disease increases with exposure dose, this provides further evidence for causality.
- *Replication* of findings. If an association is observed in various studies and settings, this provides further support for causality.
- *Biological plausibility* of the association. A relationship is more likely to be causal if the existing biological literature supports the finding.
- *Ruling out alternative explanations*. Alternative explanations for the observed results should be considered to rule out the possibility of spurious associations due to confounding or bias (see below).

As individuals are not randomly assigned to exposure groups in observational study settings, these designs can lead to non-causal associations, particularly due to:

- Confounding
- Selection bias
- Misclassification.

Confounding occurs when a variable that is not part of the disease causal pathway is associated with both disease and outcome. Confounding can be addressed by appropriate study design, data collection and analysis. In order to statistically control for confounders during analysis, it is essential to obtain information on potential confounding variables during data collection. For example, in a study measuring the effect of alcohol intake on lung cancer, results could be confounded by smoking, as smoking is associated with both the exposure under investigation (alcohol intake) and is also independently a risk factor for the disease (lung cancer); therefore, the confounding effect of smoking needs to be addressed either at the design stage (e.g. matching for smoking status or restricting the study to non-smokers) or at the analysis stage (by adjusting for smoking information in statistical models).

Most observational studies rely on data collected from accurate reporting of information, e.g. by study participants, physician records or laboratory procedures. Errors in classification of exposure or disease can occur if this information is not properly