
Breast Cancer

Umberto Veronesi • Aron Goldhirsch
Editors-in-Chief

Paolo Veronesi • Oreste Davide Gentilini
Maria Cristina Leonardi
Editors

Breast Cancer

Innovations in Research and Management

Editors-in-Chief

Umberto Veronesi
European Institute of Oncology
Milan
Italy

Aron Goldhirsch
European Institute of Oncology
Milan
Italy

Editors

Paolo Veronesi
European Institute of Oncology
Milan
Italy

Oreste Davide Gentilini
San Raffaele University and Research Hospital
Milan
Italy

Maria Cristina Leonardi
European Institute of Oncology
Milan
Italy

ISBN 978-3-319-48846-2 ISBN 978-3-319-48848-6 (eBook)
DOI 10.1007/978-3-319-48848-6

Library of Congress Control Number: 2017945756

© Springer International Publishing AG 2017

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, express or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

This book is dedicated to Umberto Veronesi, to his memory, and especially to his scientific and medical heritage.

Preface

The scientific and patient care communities have witnessed significant improvements in the diagnosis and treatment of breast cancer. Breast cancer is the leading cause of cancer morbidity and mortality in women worldwide. Screening, early diagnosis, and personalized treatments have provided better patient management, improved efficacy of therapies, and reduced mortality. Additional knowledge has been obtained by improving histopathological testing and conducting molecular and genetic investigations, which have also resulted in better therapies.

Progress in care of breast cancer patients has been achieved due to the clinical trials designed and conducted to demonstrate the efficacy and safety of therapies. This accumulation of evidence from randomized trials has resulted in a substantial improvement in patient care. Clinical trials can provide evidence indicating treatment efficacy but do not provide direct extrapolation on “how to treat the Individual Patient.” The required intellectual step for extrapolation of useful details needed for adapting information from clinical trial results for the purpose of patient care is the multidisciplinary approach, a relatively novel methodology for discussion and negotiation involving several professional perspectives to define a common modality of diagnosis and treatment. With this spirit in mind, this book has been created, touching on all aspects of innovation in the care of patients with breast cancer. The editors and authors of each section and chapter are scholars in the field of breast cancer and are experts in conducting multidisciplinary discussions.

Professor Umberto Veronesi, who conceived the idea of this book to summarize modern developments in the diagnosis and treatment of breast cancer, was an internationally renowned innovator of diagnosis and all modalities of therapy for women with breast cancer. In the 1960s, he introduced the concepts that breast cancer is a disease with widespread extension of micrometastasis, and that the least extensive treatment (either surgical, radiation, or systemic) might suffice for obtaining the optimal therapeutic result. This approach involves specifically maintaining efficacy while reducing the burden of side effects of therapeutic and diagnostic interventions. Clinical research was conducted by him and others to intensively investigate this personalized approach for women with the disease. Areas of these clinical trial investigations included use of quadrantectomy instead of mastectomy, partial intraoperative radiation therapy instead of whole breast irradiation, sentinel node biopsy instead of full axillary dissection, and assigning systemic therapies according to features that predict responsiveness to different treatments instead of using the “same therapy for all” approach. His dedication to prevention was also methodologically remarkable, from pioneering work in early diagnosis to investigating chemoprevention in clinical trials. This book is a comprehensive presentation of breast cancer research and treatment, describing past and present information and including thoughts about the future.

Professor Umberto Veronesi passed away on November 8, 2016. Although he did not survive to see the book’s birth, he was intensively involved in the editing until the last days of his life. He remained an example for all of us, insisting that the work should go on. This book is dedicated to him, to his memory, and especially to his scientific and medical heritage.

Special appreciation is extended by all editors and authors to Mrs. Lucia Racca, the backbone of Professor Veronesi’s office for many years, who maintained the coordination of the editorial office until the completion of the work, well beyond her retirement.

This book is an important resource covering all aspects of breast cancer carcinogenesis, prevention, diagnosis, and surgical, radiation, and systemic therapies. It is particularly suited for those who seek exposure to a broad spectrum of knowledge of a multidisciplinary approach to understand the disease and facilitate optimal patient care.

Milan, Italy
September 2017

Aron Goldhirsch

Contents

Part I An Integrated View of Breast Cancer Biology

- 1 Fundamental Pathways in Breast Cancer 1: Signaling from the Membrane** 3
Yekaterina Poloz, Ryan J.O. Dowling, and Vuk Stambolic
- 2 Fundamental Pathways in Breast Cancer 2: Maintenance of Genomic Stability** 13
Chiara Gorrini and Tak W. Mak
- 3 Fundamental Pathways in Breast Cancer 3: Estrogen Biology** 19
Luca Magnani and Darren K. Patten
- 4 Fundamental Pathways in Breast Cancer 4: Signaling to Chromatin in Breast Development** 27
Luca Mazzearella and Pier Giuseppe Pelicci
- 5 Breast Cancer Microenvironment and the Metastatic Process** 39
George Sflomos and Cathrin Brisken
- 6 Mouse Models of Breast Cancer: Deceptions that Reveal the Truth** 49
Joana Pinto Couto and Mohamed Bentires-Alj

Part II Epidemiology, Genetics and Prevention

- 7 Epidemiology, Lifestyle, and Environmental Factors** 63
Patrick Maisonneuve
- 8 Breast Cancer Genetics** 73
Ana Carolina Ribeiro Chaves de Gouvea and Judy E. Garber
- 9 Chemoprevention** 87
Andrea De Censi, Bernardo Bonanni, and Massimiliano Cazzaniga
- 10 Surgical Prevention** 95
Paolo Veronesi and Nickolas Peradze

Part III Pathology: Standard and Molecular Diagnostics

- 11 Premalignant and Pre-invasive Lesions of the Breast** 103
Elena Guerini-Rocco and Nicola Fusco
- 12 Prognostic and Predictive Role of Genetic Signatures** 121
Giancarlo Pruneri and Francesca Boggio
- 13 Special Types of Breast Cancer and Non-epithelial Tumors** 133
Giovanni Mazzarol and Sara Pirola

14	Pathology After Neoadjuvant Treatments	141
	W. Fraser Symmans	
15	Breast Cancer Genomics	149
	Maurizio Scaltriti	
16	The Pathology Report	157
	Andrea Vingiani and Giuseppe Viale	
Part IV Imaging		
17	Radiological Screening of Breast Cancer: Evolution	171
	Alfonso Frigerio, Francesco Sardanelli, and Franca Podo	
18	Innovation in Breast Cancer Radiology	205
	Rumana Rahim, Michael J. Michell, Viviana Londero, Chiara Zuiani, Martina Zanotel, Massimo Bazzocchi, and Christiane K. Kuhl	
19	Nuclear Medicine in the Clinical Management (ROLL, SNB, and PET)	247
	Giovanni Paganelli, Federica Matteucci, and Laura Gilardi	
20	One-Step Systemic Staging for Patients with Breast Cancer	265
	Giuseppe Petralia and Anwar R. Padhani	
21	Imaging Findings After Surgery	277
	Silvia Pérez Rodrigo and Elizabeth A. Morris	
22	Integrated Breast Biopsy for Best Radiological Diagnosis of Breast Cancer	317
	Enrico Cassano and Chiara Trentin	
Part V Oncological Surgery		
23	Conservative Surgery	335
	Umberto Veronesi	
24	The Conservative Mastectomy	345
	Alberto Luini	
25	Surgical Treatment of Local Recurrence in Breast Cancer Patients	349
	Jose Vila, Francisco Ripoll, and Oreste D. Gentilini	
26	Management of the Axilla	357
	Viviana Galimberti	
27	Management of Intraepithelial Disease	365
	Antonio Toesca	
28	Breast-Conserving Surgery After Neoadjuvant Therapy	369
	Mahdi Rezaei and Stefan Kraemer	
29	Surgical Treatment of the Primary Tumor in Patients with Metastatic Breast Cancer (Stage IV Disease)	385
	Mattia Intra	
30	Breast Cancer in Lymphoma Survivors	399
	Mattia Intra and Denise Mattar Fanianos	
31	Surgery of Metastases in Stage IV Breast Cancer	415
	Elisabetta Pennacchioli, Gianluca Varano, Franco Orsi, Pierpaolo Prestianni, Gianmarco Orsolini, and Angela Cioffi	

Part VI Plastic and Reconstructive Surgery

32 Oncoplastic Surgery	427
Cicero Urban and Mario Rietjens	
33 Delayed Breast Reconstruction	435
Cicero Urban and Flavia Kuroda	
34 Immediate Breast Reconstruction (Direct to Implant)	443
Mario Rietjens, Pietro Loschi, and Leonardo Pires Novais Dias	
35 Breast Reconstruction with Tissue Expander and Definitive Implant Replacement	457
Thomas H.S. Fysh and R. Rainsbury	
36 The Pedicled TRAM Flap in Breast Reconstruction	465
Glyn Jones	
37 Breast Reconstruction with Free Flaps	485
Fabio Santanelli di Pompeo, Benedetto Longo, and Rosaria Laporta	
38 Contralateral Breast Management	495
Marco Klinger, Luca Maione, Silvia Giannasi, Valeria Bandi, Barbara Banzatti, Alessandra Veronesi, Barbara Catania, Valeriano Vinci, Andrea Lisa, Guido Cornegliani, Micol Giaccone, Mattia Siliprandi, Fabio Caviggioli, and Francesco Klinger	
39 Lipofilling	503
J.Y. Petit, V. Lohsiriwat, and M. Rietjens	
40 Breast Reconstruction with Biological and Non-biological Meshes and Matrices	513
Rachel Rolph and Jian Farhadi	
41 How to Manage Complications in Breast Reconstruction	521
Francesca De Lorenzi	

Part VII Medical Oncology

42 Adjuvant Systemic Therapies by Subtypes: Guidelines	535
Antonella Palazzo and Marco Colleoni	
43 Primary Systemic Therapies: Guidelines	541
Jenny Furlanetto and Gunter von Minckwitz	
44 Treatment of Advanced Disease: Guidelines	549
Rosario Andre, Simona Ruxandra Volovat, and Fatima Cardoso	
45 Endocrine Therapies in the Adjuvant and Advanced Disease Settings	557
Olivia Pagani	
46 Chemotherapy Regimens in the Adjuvant and Advanced Disease Settings	569
Christopher D. Hart, Laura Biganzoli, and Angelo Di Leo	
47 Anti-HER2 Therapies in the Adjuvant and Advanced Disease Settings	577
Elisabetta Munzone	
48 Adjuvant Treatment with Bone-Targeting Agents (Bisphosphonates and Anti-RANK-Ligand Antibody)	593
Michael Gnant	

- 49 Systemic Treatment for Specific Medical Situations** 599
Silvia Dellapasqua

Part VIII Radiotherapy

- 50 Conceptual Basis and Principles of Radiation Oncology** 611
Roberto Orecchia
- 51 Whole-Breast Irradiation Following Breast-Conserving Surgery for Invasive Breast Cancer** 621
Anna Kirby
- 52 Whole-Breast Radiation Following Breast-Conserving Surgery in Noninvasive Cancer** 631
Beryl McCormick
- 53 Postmastectomy Radiation Therapy of Early Breast Cancer** 637
Birgitte Vrou Offersen and Mette Skovhus Thomsen
- 54 Concurrent Use of Radiation Therapy and Targeted Molecules in the Breast Cancer Treatment** 645
Youlia M. Kirova and Alain Fourquet
- 55 Accelerated Partial Breast Irradiation** 655
Nina N. Sanford and Alphonse G. Taghian
- 56 Intraoperative Radiotherapy with Electrons (ELIOT)** 671
Maria Cristina Leonardi
- 57 Radiotherapy for Metastatic Lesions** 685
Per Karlsson and Dan Lundstedt

Part IX Special Conditions Requiring Multidisciplinary Approaches

- 58 Emergencies in Breast Cancer** 697
Lorenzo Gianni, Maria Vittoria Stefania Nicoletti, and Valentina Arcangeli
- 59 Breast Cancer (Diagnosed) During Pregnancy: Adapting Recent Advances in Breast Cancer Care for Pregnant Patients** 709
Sibylle Loibl, André Schmidt, Oreste D. Gentilini, Bella Kaufman, Christine Kuhl, Carsten Denkert, Gunter von Minckwitz, Anastasia Parokonnaya, Hanne Stensheim, Christoph Thomssen, Kristel van Calsteren, Philip Poortmans, Paul Berveiller, Udo Markert, and Frederic Amant
- 60 Chest Wall Disease: The Clinical Continuum Between Inflammatory and Lymphangitic Breast Cancer** 719
Giuseppe Curigliano
- 61 Fertility Issues in Patients with Breast Cancer or Survivors** 729
Matteo Lambertini, Hatem A. Azim Jr, and Fedro A. Peccatori
- 62 Breast Cancer and Sexuality with Focus in Young Women: From Evidence-Based Data to Women's Wording to Treatment Perspectives** 739
Alessandra Graziottin
- 63 Male Breast Cancer** 753
Laura Ottini and Carlo Capalbo

64 Treatment of Central Nervous System Involvement	763
E. Munzone, C. Casali, M. Del Bene, and F. Di Meo	
65 Follow-Up of Patients with Breast Cancer	769
Lorenzo Gianni, Alessandra Affatato, and Davide Tassinari	
Part X Investigating New Drugs and Immunological Agents in Breast Cancer	
66 Targeting Immune Checkpoint	781
Angela Esposito and Giuseppe Curigliano	
67 Targeting PI3K/AKT/mTOR Pathway	787
Carmen Criscitiello and Giuseppe Curigliano	
68 Targeting Genome Instability and DNA Repair	795
Marzia Locatelli and Giuseppe Curigliano	
69 Targeting the CDK4/6 Pathway in Breast Cancer	807
Luca Malorni, Ilenia Migliaccio, Cristina Guarducci, Martina Bonechi, and Angelo Di Leo	
70 Targeting FGFR Pathway in Breast Cancer	819
Carmen Criscitiello, Angela Esposito, and Giuseppe Curigliano	
71 Integrating Next-Generation Sequencing Data in Trial Design	823
Giuseppe Curigliano, Angela Esposito, Marzia Locatelli, and Carmen Criscitiello	
Part XI Investigational and Miscellaneous Approaches	
72 Lifestyle and Breast Cancer	831
Rowan T. Chlebowski	
73 Psychological Support in Breast Cancer Patients: A Personalized Approach	841
Chiara Fioretti, Ketti Mazzocco, and Gabriella Pravettoni	
74 HIFU and Radio Frequency as Alternatives to Surgery	849
Franco Orsi and Giovanni Mauri	
75 Hyperthermia with Radiotherapy and with Systemic Therapies	855
J. van der Zee and G.C. van Rhooen	
76 Electrochemotherapy of Breast Cancer	863
Luca G. Campana, Louise Wichmann Matthiessen, Marko Snoj, and Gregor Sersa	
77 Circulating miRNA in Early Diagnosis	875
Fabrizio Bianchi	
78 Relevance of Stem Cells	883
Salvatore Pece, Maria Grazia Malabarba, Pier Paolo Di Fiore, and Daniela Tosoni	
Part XII Biostatistics and Bioinformatics	
79 Subgroup Analyses and Information from Clinical Trials on Breast Cancer	891
Wai-Ki Yip	

80	The Methodology of Meta-Analyses and Its Potential Contribution to Patient Care	905
	di Sara Gandini	
81	Trial Designs and Biostatistics for Molecular-Targeted Agents	915
	William T. Barry	
82	Bioinformatics for Clinical Use in Breast Cancer	925
	Fabrizio Bianchi	