Cancer Neurology in Clinical Practice
Cancer Neurology in Clinical Practice comes in its third edition, now edited by David Schiff, Isabel Arrillaga, and Patrick Y. Wen. The overall aim remains to provide a comprehensive overview on neurologic complications of cancer and its treatment. The refined classification of many cancer entities to a molecular level has not only resulted in a better understanding of pathogenesis but also in the development of several rather specific molecularly targeted treatments. Moreover, the last years have seen a wave of new therapeutic approaches in the area of immunotherapy. These were associated not only with striking gains in survival, but also with a changing spectrum of complications from cancer treatment. These developments made a new edition of this textbook timely and necessary.

An overview on the general role of neurologic disease in cancer is followed by parts on diagnostic studies and the overall involvement of the nervous system by systemic cancer. This is then further detailed in a part on the neurologic complications of cancer and of its treatment, and all this with specific consideration of distinct types of cancer. Finally, the last chapter is dedicated to an area of increasing relevance, the neurologic symptoms and signs of long-term cancer survivors.

The editors and their team of distinguished contributors are to be congratulated for having provided an up-to-date and comprehensive source of knowledge of high value for all those involved in the management of patients with cancer.

Prof. Dr. Michael Weller
Department of Neurology
University Hospital Zurich
Zurich, Switzerland
It is estimated that cancer affects approximately 40% of the population at some time and is responsible for 20% of deaths. Recent years have witnessed substantial advances in the treatment of many malignancies. Targeted molecular therapies have improved outcomes for many cancers including HER2-positive breast cancer, EGFR and ALK-positive non-small cell lung cancer, BRAFV600E-positive melanoma, and a growing number of hematologic malignancies, among others. More recently, checkpoint inhibitor-based immunotherapy has dramatically changed the fortune of some patients with melanoma, non-small cell lung cancer, and a rapidly growing list of other cancers (7 FDA approvals in 2016 alone). However, as therapies for cancer improve and patients live longer, relapse within the nervous system is increasing. Additionally, prolonged survival has exposed more cancer survivors to the long-term neurologic sequelae of radiation therapy and systemic therapies. Finally, newly approved antineoplastic therapies bring new neurologic complications, as seen with immunotherapy. These neurologic complications detract significantly from patients’ quality of life.

The diagnosis and treatment of neurologic complications of the nervous system are shared among neuro-oncologists, medical and radiation oncologists, neurologists, and neurosurgeons. While neurologists and neurosurgeons have expertise in the diagnosis and management of neurologic complaints, they are generally less familiar with the biology, behavior, and management of cancer. Conversely, medical and radiation oncologists have expertise in the diagnosis and treatment of cancer but are less familiar with the diagnosis and management of neurologic complaints in cancer patients. The purpose of this Third Edition of Cancer Neurology in Clinical Practice is to provide clinicians from various backgrounds and levels of training with information that will allow them to optimally diagnose and manage neurologic complications of the nervous system. This volume begins with an overview of diagnostic studies for neurologic complications involving the nervous system. That is followed by parts on metastatic and non-metastatic complications of cancer involving the nervous system, and the interpretation, diagnosis, and management of common neuro-oncologic symptoms. The next part reviews the neurologic complications of cancer therapy, including corticosteroids, radiation therapy, chemotherapy, targeted molecular therapies, immunotherapies, hematopoietic stem cell transplantation, and infections involving the nervous system. The final part focuses on the most important neurologic complications in cancers arising from specific organs.

We hope that this volume will provide clinicians from varied backgrounds looking after cancer patients with readily accessible, relevant information that will allow them to optimally diagnose and manage neurologic complications in these patients. Prompt diagnosis and effective interventions will ameliorate neurologic outcomes of most of the complications discussed in this volume, translating into improved quality (and in some cases quantity) of life for patients suffering from cancer.

Charlottesville, USA  
David Schiff  
Boston, USA  
Isabel Arrillaga  
Boston, USA  
Patrick Y. Wen
I am very grateful for the addition of Isabel Arrillaga as co-editor; she has provided much-needed new energy, perspective, organization, and talent to this new edition. Patrick Wen, who is responsible for my choosing neuro-oncology as a specialty 25 years ago, remains a mentor, friend, and role model as well as a shining light in the field. My heartfelt appreciation goes to the many excellent chapter authors. Most importantly, I thank my patients and Tanya Nezzer, MD, for teaching me what matters in life.

David Schiff, MD

I am privileged to have worked on this Third Edition of Cancer Neurology in Clinical Practice alongside David Schiff and Patrick Wen, both leaders in the field of neuro-oncology and cancer neurology. I am particularly grateful to Patrick for the opportunity to collaborate on this text and for sharing so much of his time and talent over the years as a thoughtful and trusted mentor. I dedicate this book to my husband, Benjamin Rymzo, my greatest supporter and pillar, to my two young daughters, Celina and Camila, whom I hope I can one day inspire to pursue their own passions, and to my parents, Rafael Arrillaga and Celina Romany, who are ever-present sources of encouragement and confidence. Lastly, I humbly acknowledge the patients we treat and the many lessons they have offered about resilience, determination, and grace.

Isabel Arrillaga, MD, Ph.D.

This Third Edition of Cancer Neurology in Clinical Practice would not have been possible if not for all the efforts of David Schiff. I am very grateful for his hard work and encyclopedic knowledge of the field, which were both instrumental in making the three editions possible, and, most importantly, for his friendship, support, and always wise counsel over the years. We also were very lucky to have Isabel Arrillaga join us as an editor for this third edition. She is a wonderfully talented neuro-oncologist, and this edition would not have been possible without the hard work and the countless hours she devoted to it. I would also like to thank the expert group of chapter authors for their willingness to contribute to this book despite their very busy schedules. I dedicate this book to my parents, Hsiang-Lai Wen, MD, and Grace Wen, and to my family, May, Katherine, and Jessie.

Patrick Y. Wen, MD
# Contents

## Part I  Overview

1  **The Prevalence and Impact of Neurological Disease in Cancer** ........ ........ 3  
   Andrew L. Lin and Lisa M. DeAngelis

## Part II  Diagnostic Studies

2  **Imaging Neurologic Manifestations of Oncologic Disease** ................. 13  
   Raymond Huang and Patrick Y. Wen

3  **Other Diagnostic Tools for Neurological Disease in Cancer:**  
   EEG, EMG, and Lumbar Puncture .................................. 33  
   Crystal S. Janani and Edward K. Avila

## Part III  Nervous System Involvement of Systemic Cancers

4  **Brain Metastasis as Complication of Systemic Cancers** .................. 57  
   Riccardo Soffietti, Federica Franchino, and Roberta Rudà

5  **Leptomeningeal Metastasis as Complication of Systemic Cancers** .............. 81  
   Sophie Taillibert, Emilie Le Rhun, and Marc C. Chamberlain

6  **Spinal Metastasis as Complication of Systemic Cancers** .................. 113  
   Gregory Davis, Michaela Lee, Dawit Aregawi, Mark E. Shaffrey,  
   David Schiff, and Jonathan H. Sherman

7  **Peripheral Nervous System Metastases as Complications**  
   of Systemic Cancer ............................................... 127  
   Amanda C. Guidon

## Part IV  Neurological Complications of Cancer

8  **Headache as Complication of Cancer** ................................. 143  
   Surabhi Ranjan and David Schiff

9  **Seizures as Complications in Cancer** ................................. 153  
   Christa P. Benit, Melissa Kerkhof, Alberto Duran-Peña,  
   and Charles J. Vecht

10  **Cerebrovascular Complications of Cancer** ............................. 171  
    Lisa R. Rogers

11  **Elevated Intracranial Pressure and Hydrocephalus in Brain**  
    **Tumor Patients** .................................................. 193  
    Matthew E. Shuman and Mark D. Johnson

12  **Cognitive Dysfunction, Mood Disorders, and Fatigue**  
    **as Complications of Cancer** ..................................... 203  
    Jörg Dietrich and Michael W. Parsons
13 Paraneoplastic Syndromes of the Nervous System as Complications of Cancer ........................................ 221
   Myrna R. Rosenfeld and Josep Dalmau

Part V Neurological Complications of Cancer Therapy

14 Neurologic Complications of Radiation Therapy ................................................................. 241
   Damien Ricard, Thomas Durand, Arnault Tauziède-Espariat, Delphine Leclercq, and Dimitri Psimaras

15 Neurological Complications of Chemotherapy ................................................................. 275
   Craig A. Vargo, Leslie A. Ray, and Herbert B. Newton

16 Neurological Complications of Targeted Therapies ......................................................... 311
   Deborah A. Forst and Patrick Y. Wen

17 Neurological Complications of Immune-Based Therapies ........................................... 335
   Martha R. Neagu, Russell W. Jenkins, and David Reardon

18 Neurologic Complications of Hematopoietic Stem Cell Transplantation ............... 345
   Eudocia Q. Lee and Patrick Y. Wen

19 Neurologic Complications of Corticosteroids in Cancer Therapy .......................... 359
   Erin M. Dunbar, Yue Wang, and Santosh Kesari

20 Central Nervous System Infections in Patients Receiving Cancer Therapies ............. 377
   Amy A. Pruitt

Part VI Neurological Complications of Specific Malignancies

21 Neurological Complications of Primary Brain Tumors .............................................. 399
   Justin T. Jordan, Thomas N. Byrne, and Tracy Batchelor

22 Neurological Complications of Lung Cancer ................................................................. 417
   Ming Chi and Manmeet S. Ahluwalia

23 Neurological Complications of Breast Cancer and Its Treatment ......................... 435
   Emilie Le Rhun, Sophie Taillibert, and Marc C. Chamberlain

24 Neurologic Complications of Gastrointestinal Cancer .............................................. 471
   Rajiv Magge and Eli L. Diamond

25 Neurologic Complications of Genitourinary Cancer ...................................................... 485
   Jennie W. Taylor

26 Neurologic Complications of Female Reproductive Tract Cancers .......................... 497
   K. Ina Ly and Maciej M. Mrugala

27 Neurological Complications of Sarcomas ................................................................... 515
   Megan L. Kruse and David M. Peereboom

28 Neurologic Complications of Head and Neck Cancer ................................................. 527
   Sepideh Mokhtari and Thomas J. Kaley

29 Neurological Complications of Malignant Melanoma ............................................... 541
   Hamza Malek, Annise Wilson, and Jeffrey Raizer

30 Neurological Complications of Leukemia ..................................................................... 559
   Joachim M. Baehring and Amy M. Chan

31 Neurologic Complications of Lymphoma .................................................................... 571
   Lakshmi Nayak and Christian Grommes
32 Neurologic Complications of Plasma Cell Dyscrasias ................. 583
   Elie Naddaf and Michelle L. Mauermann

33 Neurologic Complications of Pediatric Systemic Cancer .............. 597
   Elizabeth S. Duke, Scott L. Pomeroy, and Nicole J. Ullrich

Part VII  Neurological Complications in Long Term Cancer Survivors

34 Neurological Complications of Cancer and Cancer Therapies
   in Long-Term Survivors .......................................... 617
   Isabel Arrillaga

Index ................................................................. 627
Contributors

Manmeet S. Ahluwalia MD  Cleveland, OH, USA
Dawit Aregawi MD  Department of Neurosurgery, Penn State Milton S. Hershey Medical Center, Penn State College of Medicine, Hershey, PA, USA
Isabel Arrillaga MD, Ph.D.  Department of Neurology/Neuro-Oncology, Massachusetts General Hospital, Boston, MA, USA
Edward K. Avila DO  Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, NY, USA
Joachim M. Baehring MD, DSc  Departments of Neurology and Neurosurgery, Yale School of Medicine, New Haven, CT, USA
Tracy Batchelor MD, MPH  Department of Neurology, Massachusetts General Hospital, Boston, MA, USA
Christa P. Benit MD  Department of Neurology, The Hague Medical Center, The Hague, The Netherlands
Thomas N. Byrne MD  Massachusetts General Hospital, Neurology, Boston, MA, USA
Marc C. Chamberlain MD  Department of Neurology and Neurological Surgery, Seattle Cancer Care Alliance, University of Washington, Seattle, WA, USA; Cascadian Therapeutics, Inc., Seattle, WA, USA
Amy M. Chan MD  Department of Neurology, Yale School of Medicine, New Haven, CT, USA
Ming Chi MD  Atlanta Cancer Care, Northside Hospital, Atlanta, GA, USA
Josep Dalmau MD, Ph.D.  Hospital Clinic, Institució Catalana de Recerca i Estudis Avançats (ICREA), Institut d’ Investigació Biomedica August Pi i Sunyer (IDIBAPS), Barcelona, Catalonia, Spain
Gregory Davis MD  Department of Neurological Surgery, George Washington University Hospital, Washington, DC, USA
Lisa M. DeAngelis MD  Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, NY, USA
Eli L. Diamond MD  Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, NY, USA
Jörg Dietrich MD, Ph.D.  Department of Neurology, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA
Elizabeth S. Duke MD  Department of Neurology, Boston Children’s Hospital, Boston, MA, USA
Erin M. Dunbar MD  Piedmont Hospital, Brain Tumor Center, Atlanta, GA, USA

Alberto Duran-Peña MD  Department of Neurology Mazarin, Pitié Salpetrière Hospital, Paris, France

Thomas Durand M.Sc.  UMR MD 8257 Cognition and Action Group, Paris, France

Deborah A. Forst MD  Department of Neuro-Oncology, Massachusetts General Hospital, Boston, MA, USA

Federica Franchino MD  Department of Neuroscience, University of Turin and City of Health and Science Hospital, Turin, Italy

Christian Grommes MD  Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Amanda C. Guidon MD  Department of Neurology, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA

Raymond Huang MD, Ph.D.  Department of Radiology, Brigham and Women’s Hospital, Boston, MA, USA

Crystal S. Janani MD  Department of Neurology, St. Agnes Hospital, Baltimore, MD, USA

Russell W. Jenkins MD, Ph.D.  Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA

Mark D. Johnson MD, Ph.D.  Department of Neurological Surgery, University of Massachusetts Medical School and UMass Memorial Hospital, Worcester, MA, USA

Justin T. Jordan MD  Department of Neurology, Massachusetts General Hospital, Boston, MA, USA

Thomas J. Kaley MD  Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Melissa Kerkhof M.Sc., MD  Department of Neurology, The Hague Medical Center, The Hague, The Netherlands

Santosh Kesari MD, Ph.D.  Department of Translational Neuro-Oncology and Neurotherapeutics, John Wayne Cancer Institute at Providence Saint John’s Health Center, Santa Monica, CA, USA

Megan L. Kruse MD  Department of Hematology/Oncology, Cleveland Clinic, Cleveland, OH, USA

Emilie Le Rhun MD  Department of Neurosurgery and Neuro-oncology, University Hospital, Lille Cedex, France; Breast unit, Department of Medical Oncology, Oscar Lambert Center, Lille Cedex, France; PRISM Inserm U1192, Villeneuve-d’Ascq, France

Delphine Leclercq MD  Department of Neuroradiology, Pitié Salpetrière Hospital, Paris, France

Eudocia Q. Lee MD, MPH  Center for Neuro-Oncology, Dana-Farber/Brigham and Women’s Cancer Center, Boston, MA, USA

Michaela Lee MD  Department of Neurosurgery, George Washington University Medical Center, Washington, DC, USA

Andrew L. Lin MD  Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, NY, USA
K. Ina Ly MD  Stephen E and Catherine Pappas Center for Neuro-Oncology, Massachusetts General Hospital, Boston, MA, USA; Center for Neuro-Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

Rajiv Magge MD  Weill Cornell Medicine/New York Presbyterian, Weill Cornell Brain Tumor Center, New York, NY, USA

Hamza Malek MD  Department of Neurology, Northwestern University, Chicago, IL, USA

Michelle L. Mauermann MD  Department of Neurology, Mayo Clinic, Rochester, MN, USA

Sepideh Mokhtari MD  Department of Neurology, H. Lee Moffitt Center, Tampa, FL, USA

Maciej M. Mrugala MD, Ph.D., MPH  Department of Neurology, University of Washington Medical School, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; Department of Neurology and Division of Medical Oncology, Mayo Clinic, Phoenix, AZ, USA

Elie Naddaf MD  Department of Neurology, Mayo Clinic, Rochester, MN, USA

Lakshmi Nayak MD  Department of Neuro-Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

Martha R. Neagu MD, Ph.D.  Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA

Herbert B. Newton MD, FAAN  Neuro-Oncology Center, Florida Hospital Cancer Institute & Florida Hospital Orlando, Orlando, FL, USA

Michael W. Parsons Ph.D.  Burkhardt Brain Tumor Center and Section of Neuropsychology, Cleveland Clinic, Cleveland, OH, USA

David M. Peereboom MD, FACP  Burkhardt Brain Tumor and Neuro-Oncology Center, Cleveland Clinic, Cleveland, OH, USA

Scott L. Pomeroy MD, Ph.D.  Department of Neurology, Boston Children’s Hospital, Boston, MA, USA

Amy A. Pruitt MD  Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Dimitri Psimaras MD  Department of Neurology, Pitié Salpetrière Hospital, Paris, France

Jeffrey Raizer MD  Department of Neurology, Northwestern University, Chicago, IL, USA

Surabhi Ranjan MBBS  Department of Neurology, University of Virginia, Charlottesville, VA, USA

Leslie A. Ray Pharm.D., BCOP  Department of Pharmacy, The James Cancer Hospital, The Ohio State University, Columbus, OH, USA

David Reardon MD  Center for Neuro-Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

Damien Ricard MD  Department of Neurology, Hôpital d’Instruction des Armées Percy, Clamart, France

Lisa R. Rogers DO  Department of Neurology, University Hospitals Cleveland Medical Center, Cleveland, OH, USA

Myrna R. Rosenfeld MD, Ph.D.  Institut d’Investigació Biomedica August Pi i Sunyer (IDIBAPS), Barcelona, Catalonia, Spain

Roberta Rudà MD  Department of Neuroscience, University of Turin and City of Health and Science Hospital, Turin, Italy
David Schiff MD  Neuro-oncology center, University of Virginia, Charlottesville, VA, USA

Mark E. Shaffrey MD  Department of Neurological Surgery, University of Virginia Hospital, Charlottesville, VA, USA

Jonathan H. Sherman MD  Department of Neurosurgery, The George Washington University Hospital, Washington, DC, USA

Matthew E. Shuman BA  Department of Neurosurgery, Brigham and Women’s Hospital, Boston, MA, USA

Riccardo Soffietti MD  Department of Neuroscience, University of Turin and City of Health and Science Hospital, Turin, Italy

Sophie Taillibert MD  Department of Neurology and Department of Radiation Oncology, Pitié-Salpêtrière Hospital, UPMC-Paris VI University, Paris, France

Arnault Tauziède-Espariat MD  Laboratory of Neuropathology, Sainte-Anne Hospital, Paris, France

Jennie W. Taylor MD, MPH  Department of Neurology and Neurosurgery, University of California, San Francisco, CA, USA

Nicole J. Ullrich MD, Ph.D., MMSci  Department of Neurology, Boston Children’s Hospital, Boston, MA, USA

Craig A. Vargo Pharm.D.  Department of Pharmacy, The James Cancer Hospital, The Ohio State University, Columbus, OH, USA

Charles J. Vecht MD, Ph.D.  Department of Neurology Mazarin, Pitié Salpêtrière Hospital, Paris, France

Yue Wang MD, Ph.D.  Department of Neurology, University of Florida, Gainesville, FL, USA

Patrick Y. Wen MD  Center for Neuro-Oncology, Dana-Farber/Brigham and Women’s Cancer Center, Boston, MA, USA

Annise Wilson MD  Department of Neurology, Northwestern University, Chicago, IL, USA