Progress in Neurological Surgery
Editor: L.D. Lunsford
Vol. 25

Current and Future Management of Brain Metastasis

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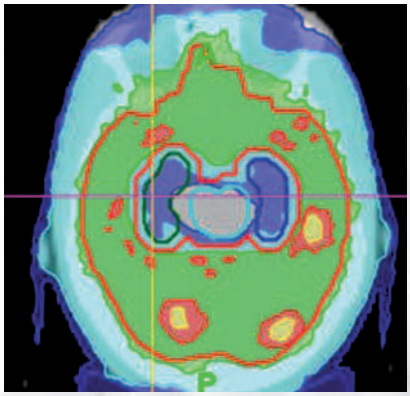

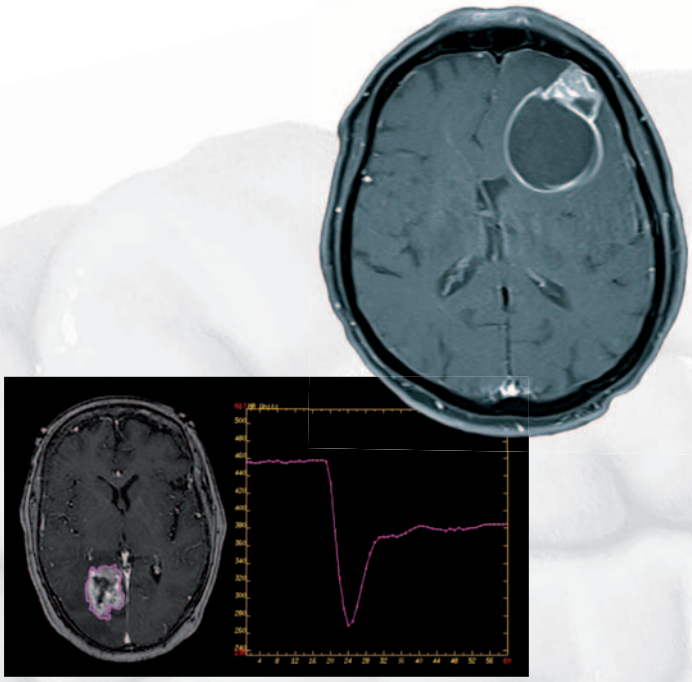

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Series Editor

L. Dade Lunsford Pittsburgh, Pa.

Current and Future Management of Brain Metastasis

Volume Editors

Dong Gyu Kim Seoul
L. Dade Lunsford Pittsburgh, Pa.

78 figures, 5 in color, and 27 tables, 2012

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Library of Congress Cataloging-in-Publication Data

Current and future management of brain metastasis / volume editors, Dong Gyu Kim, L. Dade Lunsford.
p. ; cm. -- (Progress in neurological surgery, ISSN 0079-6492 ; v. 25)
Includes bibliographical references and indexes.
ISBN 978-3-8055-9617-6 (hardcover : alk. paper) -- ISBN 978-3-8055-9618-3 (e-ISBN)
I. Kim, Dong Gyu. II. Lunsford, L. Dade. III. Series: Progress in neurological surgery ; v. 25. 0079-6492
[DNLM: 1. Brain Neoplasms--secondary. 2. Brain Neoplasms--therapy. 3. Neoplasm Metastasis--therapy. 4. Radiosurgery. W1 PR673 v.25 2012 / WL 358]

616.99'481--dc23

2011044588

Bibliographic Indices. This publication is listed in bibliographic services, including Current Contents® and Index Medicus.

www.karger.com
Printed on acid-free and non-aging paper (ISO 9706)
ISSN 0079–6492
e-ISSN 1662–3924
ISBN 978–3–8055–9617–6
e-ISBN 978–3–8055–9618–3

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Foreword

It has long been considered that brain metastases are the terminal stage of cancer progression and their management had mostly been focused on the palliative aspects of treatment. However, taking quality of life into account, the treatment of brain metastases, the most common intracranial solid tumors identified in adults, needs to be reconsidered. Moreover, the incidence of brain metastasis is on the increase thanks to advances in diagnostic imaging tools, easy-available opportunities of screening for metastasis, population growth of cancer survivors, and extension of survival period in cancer patients. Radiation therapy, surgery, radiosurgery and conservative management have been the mainstay of brain metastasis management only to reveal that not a single modality is perfect. Recent advances in management strategies combining multiple modalities and development of their appropriate indications has opened a new field of brain metastasis management focusing on disease control. The current purpose of the management of brain metastasis is no longer confined to palliation. Moreover, the management of brain metastasis in modern times not only requires prolonged survival but also preservation of quality of life. To meet those requirements, radiosurgery has become a key modality in the management of brain metastasis. Many new guidelines and protocols of multidisciplinary approaches have been tried and suggested during last two decades. While plenty of data have accumulated on the knowledge and promising outcomes of brain metastases there is still confusion and impulse decision-making in clinical practice. So, this book is most opportune to wrap up the erstwhile knowledge on brain metastasis management in order to provide clinicians with the currently best management strategies and to encourage researchers to take a new leap forward.

Current and Future Management of Brain Metastasis offers the most up-to-date guidelines. In this comprehensive volume, almost every aspect of brain metastasis management is covered and practical points on difficult situations in daily clinical practice are suggested. Each chapter encompasses extensive reviews and broad perspectives on specific topics. The contributors to this comprehensive volume are the most renowned personages in this rapidly progressing field who, due to their devotion and hard work, have continuously shown their excellence. I would like to

thank Professor L. Dade Lunsford for his valuable advice and for taking the initiative to realize the publication of this book. I would also like to express my gratitude to Dr. Dan Leksell for his dedicated support. I hope this volume will be of help to all clinicians who are involved in the management of cancer patients regardless of their major field.

Dong Gyu Kim
Seoul, Korea

Introduction

Come writers and critics
Who prophesize with your pen
And keep your eyes wide
The chance won't come again
And don't speak too soon
For the wheel's still in spin
And there's no tellin' who
That it's namin'
For the loser now
Will be later to win
For the times they are a-changin'.
Bobby Dylan, *The times they are a changin'*
Second Stanza

It is likely that no new technology has had a greater impact on the management of metastatic brain cancer than stereotactic radiosurgery (SRS). The use of cross-fired and precisely focused radiation to achieve a tumor controlling response without the need to open a patient's head has been revolutionary. Most often done in a single procedure as an outpatient, and associated with both a strong therapeutic window – tumor control and satisfactory risk profile – reproducibility, and ever-increasing evidence-based medicine outcome analysis, SRS has changed the entire paradigm of care of patients when cancer spreads to the brain.

In prior years, metastatic brain cancer was in essence the beginning of the end. Patients, treating physicians, and families all realized that such an ominous event started the time clock. Most patients could expect only a few months if no additional treatment was offered. Those who opted for conventional management with fractionated external beam radiation therapy might average 6 months for responsive cancers such as lung or breast, and even fewer months for more resistant cancers such as renal cell or melanoma. The pursuit of aggressive systemic treatments – newer surgical, chemotherapeutic, or immunological therapies – was thought to be of little value once the clock started ticking. Withdrawal of active treatment and conversion to palliative care became the routine.

Whole-brain radiation became a standard management, based in part because of the limited benefit of systemic chemotherapy, and in part because of the lack of value of other options. In the absence of widely available and beneficial alternatives, most research looked at fractionation schemes, sensitizers, or brain protection strategies. Whole-brain radiation therapy became the standard of care supported by a distinct reimbursement stream in most societies. Over the years we came to recognize that most patients who survive for more than 6 months after fractionated whole-brain radiation therapy begin to pay a significant price. Concomitant with the emerging development of progressive white matter leukoencephalopathy, patients and their families began to see a gradual deterioration in cognitive skills. Executive decision making and recent memory abilities gradually worsened. These changes can be explained not only on the impact of radiation therapy on the relatively radiation-sensitive oligodendroglia critical for white matter function, but also on the effective annihilation of periventricular progenitor cells that might be the source of brain repair mechanisms.

Surgical removal of metastatic tumors proved to have limited impact because many cancer patients were already ill and poor candidates for craniotomy. Many tumors were recognized in deep-seated locations unsuitable for even image-guided approaches. Of the 200,000–400, 000 patients in the United States newly diagnosed with metastatic brain cancer, probably less than several thousand per year were reasonable candidates for craniotomy. Most had solitary brain tumors associated with significant mass effect in surgically reachable lobar locations. Magnetic resonance imaging facilitated the revolution in thinking. Earlier recognition coupled with a reliable diagnostic imaging technique that sorted out solitary from multiple tumors required an effective therapeutic partner. SRS filled that requirement and was applicable to many more patients than craniotomy could provide.

This monograph is designed to review the evidence based medicine that supports the firm integration of radiosurgery into the treatment paradigm of metastatic brain cancer. At the same time we want to provide evidence for the appropriate use of fractionated radiation therapy and surgery in properly selected patients. We have enlisted the talents of well known authorities in cancer to review our understanding of brain metastases, the histopathologic nature of such tumors, and their potential radiobiological response. The various current management strategies including surgery, radiation therapy, chemotherapy, and radiosurgery are reviewed. The results of SRS for selected tumor types and using various technologies are discussed. The recognition of treatment related side effects and their management are pursued. Finally, the role of SRS after craniotomy or after failure of radiation therapy or prior SRS, and emerging strategies for SRS are analyzed. At the end I and my colleagues will attempt to summarize the past, present, and future management of metastatic brain cancer. By the appropriate use of radiosurgery, we believe that cancer that spreads to the brain can become a chronic disease. Oncologists can pursue more effective treatment of the systemic disease. Patients and their families will no longer need to push the time

clock. Radiosurgery, performed once or many times, can end the concept that metastatic brain cancer is always the cause of fatality. Instead we can control such disease in more than 80% of patients. Quality of life is maintained. Radiosurgery has only a brief impact on the patient's life and allows the oncologist to pursuit ever more successful treatment for the primary disease.

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Pittsburgh, Pa., USA

Kim DG, Lunsford LD (eds): Current and Future Management of Brain Metastasis.
Prog Neurol Surg. Basel, Karger, 2012, vol 25, pp 1–12

Historical Background

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Abstract

Surgery, radiation therapy, chemotherapy, steroid therapy and radiosurgery have been the mainstream of management of brain metastasis and the trend has been continuously changed along with the advancement of cancer management, development of new technology and changing in perception of quality of life. A glance at the historical perspective on brain metastasis management clearly shows two major shifts which have been made in last two decades. One is the changes of leading treatment modalities from whole-brain radiation therapy to multimodal management focusing on radiosurgery, and the other is changes of the attitude of the treatment from palliative purpose to disease control. The epoch-making change in the understanding of brain metastasis is that brain metastasis is no longer a death sentence as considered in the past.

It is obvious that there had already been a clear recognition of brain metastases in late 19th century as can be inferred from Hare's [1] description. However, it was not until the early 1930s that brain metastasis was established as a separate entity from other brain tumors [2]. Since then, it took about half a century for brain metastases to come into the spotlight as the target of active treatment. Brain metastases were initially considered to be rare and relatively little attention was paid to their management owing to their very dismal prognosis. However, it is well recognized that brain metastases are the most common intracranial tumors in adults. The higher incidence of brain metastases reported in modern series reflects the introduction of new diagnostic imaging tools, prolonged patient survival by improvement of primary site treatment outcome, and a broader indication of active treatment thanks to the development of management modalities for the multimodal approach. Classic management for brain metastases had long comprised steroid therapy and palliative whole-brain radiation therapy (WBRT). However, the recent rapid advancement of radiosurgery and neurosurgery together with the development of brain-permeable

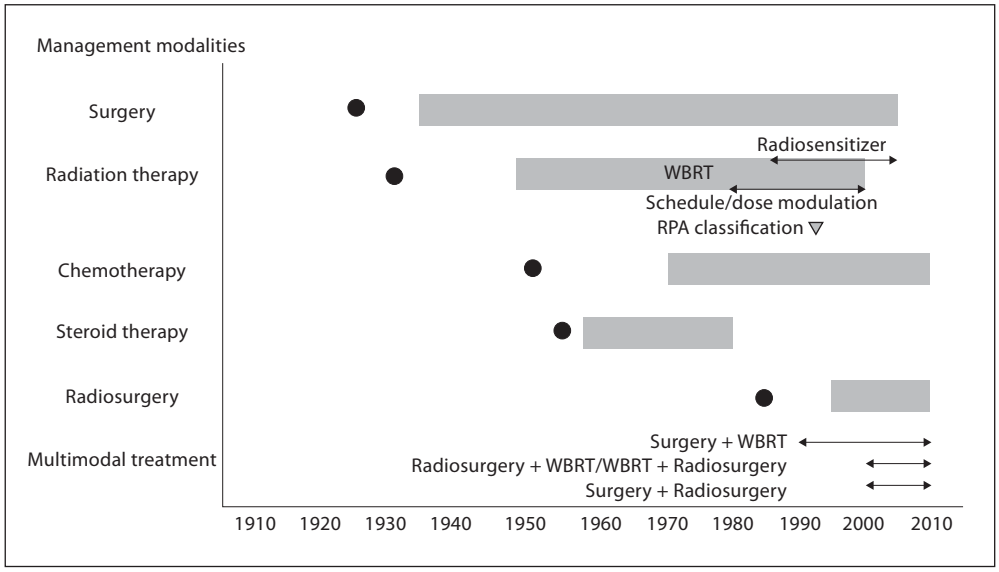

Fig. 1. Historical developments in the management trends of brain metastasis based on published articles. Filled circle = Time at the first description; grey bar = period of active publication; arrow line = period of the publication of advanced studies.

targeted anticancer drugs are orienting brain metastases toward a controllable disease. A chronological diagram of the trend in brain metastases management modalities based on major published reports clearly shows a remarkable development in the last two decades (fig. 1).

Surgery

The first report of a surgical series for the treatment of brain metastases was published in 1926 by Grant [3]. As he concluded 'that neither radical nor palliative surgery for brain metastases is of any permanent value', surgery was initially considered to be only beneficial in the condition of urgent increased intracranial pressure [2, 3]. In 1933, Oldberg [4] described long-term survivors of brain metastases after surgical resection which seems to be the first description of its optimistic role. However, resection of the metastatic brain lesion was so uncommon prior to the emergence of modern imaging techniques such as computed tomography or magnetic resonance images that it became the standard option during the 1980s [5]. Only several studies had reported on the limited role of surgical resection with trivial survival gains (median survival less than 6 months) and unacceptable postoperative mortality (10–30%) before the 1980s [6–11]. Surgical mortality has declined dramatically ever since thanks to the improvement of surgical techniques [12].

In 1990, the benefit of surgical resection of single brain metastasis in combination with adjuvant WBRT was validated for the first time in a randomized trial [13]. The result of this landmark study was confirmed by subsequent randomized trials when the extracranial disease was stable [14–16]. Although there had been controversies as to the selection of appropriate surgical candidates and the role of adjuvant WBRT [17–20], follow-up large-scale analysis or systematic review confirmed positive proof of the beneficial role of surgical resection both in terms of survival and quality of life especially in single lesions [21–23]. Limited evidence is available for direct comparison between surgery alone and radiosurgery alone. However, when surgical resection is possible, it may have a superior, at least comparable, survival gain as radiosurgery despite the surgical risk in itself [24–28].

Radiation Therapy

Radiation therapy for brain metastases might have been tried in the late 1920s [2]. In 1931, Lenz and Freid [29] described the palliative effect of radiation therapy in breast cancer patients with increased intracranial pressure due to brain metastases. However, it was in the report published in 1954 by Chao et al. [30] that the first systematic analysis of WBRT for brain metastases management was performed. They recommended WBRT as a primary treatment for brain metastases based on its good palliative effect shown in more than 60% of the cases [30]. During the subsequent two decades, several clinical analytic studies and randomized prospective clinical trials subsequently demonstrated the favorable effect of WBRT in palliation and a slight survival gain (median survival less than 6 months) [31–40].

It was from the 1980s that the Radiation Therapy Oncology Group (RTOG) undertook a series of controlled trials to determine the best dosage and schedule of WBRT for the treatment of brain metastases [2]. The studies testing schedules for WBRT, ranging from 10 to 54.4 Gy in 1–34 fractions, drew the conclusion of a standard scheme which is 30 Gy in 10 fractions [41–48]. Based on the database of multiple consecutive studies by RTOG, a classification of prognostic groups for brain metastases was established using recursive partitioning analysis [49]. Recursive partitioning analysis classes for brain metastases are of importance in that factors such as performance status, primary disease status, age and extracranial metastases rather than treatment modality dominate the patient's prognosis. During the same period, diverse efforts were made to find the radiosensitizer for the improvement of efficacy of WBRT for brain metastases, with limited success [50–57]. With these continuing efforts, WBRT have historically been the standard of care for brain metastases for the decades thorough the mid-1990s, although alone it still remains for palliative purposes [18, 58–59]. However, concerns on the late side effects of WBRT have come to the fore with longer survival of cancer patients thanks to the remarkable advancement of cancer management.