Brain Metastases in Non–Small-Cell Lung Cancer

David E. Dawe,[1] Jeffrey N. Greenspoon,[2] Peter M. Ellis[2]

Abstract

Up to 50% of patients with advanced non-small-cell lung cancer will develop brain metastases at some point during their illness. These metastases cause a substantial burden in morbidity and mortality, which has motivated research and technological innovation over the past 2 decades. Surgery, radiotherapy, and systemic therapies have each played a role in management, with the greatest changes associated with the popularization of stereotactic radiosurgery. In this review, the evidence behind each modality used in the management of brain metastases for non–small-cell lung cancer patients is examined, and recommendations regarding the current standards of care and areas of future research focus are provided.

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Introduction

Brain metastases represent a significant burden of illness among people with cancer, in North America and worldwide, as a consequence of the relatively high incidence and substantial effect on morbidity and quality of life. It is estimated that between 20% and 40% of cancer patients will develop brain metastases at some point during their disease course.[1] Among patients with lung cancer, this estimate is as high as 50%.[1-3] Historically, the development of brain metastases predicted a short survival for patients with lung cancer and this became the dominant factor in determining patient management. However, more sensitive radiological imaging, earlier diagnosis, and improvements in the approach to treatment of brain metastases all increase the complexity of management of brain metastases for oncologists involved in the treatment of patients with lung cancer. This article provides an evidence-based overview of the current management of brain metastases.

Lung cancer is the leading cause of cancer-related death worldwide.[4] Despite a declining incidence in North America, worldwide rates of lung cancer have been increasing because of escalating smoking rates in developing nations.[4] This review will focus on the management of brain metastases in non–small-cell lung cancer (NSCLC), which constitutes approximately 85% of all lung cancers.[5] The approach to the management of brain metastases from NSCLC has evolved over the past 10 years. Improvements in systemic treatment have resulted in improved control of extracranial disease and modest gains in overall survival. This improvement in treatment of disease outside of the brain has correlated with more frequent diagnosis of cerebral metastases.[6] The brain is often the first site of distant relapse in stage III patients treated with multimodality approaches.[7,8]

The development of brain metastases carries a high risk of morbidity and mortality. Common symptoms include headache, localizing weakness, seizures, altered mental status, and ataxia.[9] Severity of these manifestations can vary from minimal symptoms to debilitating and are likely to worsen as the disease progresses. Neurocognitive effects are an insidious problem, with careful testing demonstrating that > 90% of patients might have impairment in at least 1 of memory, verbal fluency, and fine motor control.[10] The presence of brain metastases increases the risk of seizure, which affects patients' lifestyle including the ability to drive.

Preventing the Development of Brain Metastases

In small-cell lung cancer prophylactic cranial irradiation (PCI) is routinely considered, because randomized trials have demonstrated not only that PCI decreases the risk of developing intracranial metastases, but is also associated with improved overall survival for patients with limited- and extensive-stage disease.[11,12] However, similar data do not exist for patients with NSCLC. Three different groups have investigated whether PCI can reduce the incidence of brain metastases and improve survival of NSCLC patients. A German group demonstrated a decrease in intracranial relapse with

[1]Department of Internal Medicine, University of Manitoba, Winnipeg, Manitoba, Canada
[2]Department of Oncology, McMaster University, Hamilton, Ontario, Canada

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Address for correspondence: David E. Dawe, MD, FRCPC, Internal Medicine, University of Manitoba, 675 McDermot Ave, Winnipeg, Manitoba R3E 0V9, Canada
E-mail contact: david.dawe@cancercare.mb.ca

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PCI in a phase II trial of patients who received trimodality therapy for stage III NSCLC.[13] Similar findings were observed in a phase III trial, although the inclusion of PCI was only 1 of several differences between the treatment arms and the trial lacked statistical power to evaluate survival.[14] The Radiation Therapy Oncology Group (RTOG; 0214) conducted a trial of PCI in patients with stage III NSCLC. Unfortunately, this trial suffered from low enrollment and failed to meet its recruitment target. The study was closed after 4.5 years, when only 356 of a planned 1058 patients were randomized.[15] Overall survival and disease-free survival at 1 year did not differ statistically between the groups. However, patients who received PCI had a lower risk of developing brain metastases than the control group (7.7% vs. 18%, $P = .004$). Quality of life outcomes were almost equivalent between the 2 groups, although receipt of PCI was associated with greater declines in immediate and delayed recall on the Hopkins Verbal Learning Test.[15] Because of the lack of randomized evidence of survival benefit for PCI, it should not form part of standard of care treatment for patients with NSCLC.

Detecting Brain Metastases

Because there is no defined method of preventing brain metastases in NSCLC patients and they carry a substantial risk of morbidity and mortality, it is important to detect these lesions early on and maximize the opportunity for treatment. Computed tomography (CT) formed the historical standard for brain metastasis detection, but use of magnetic resonance imaging (MRI) has been increasing for 20 years.[16] MRI has consistently been demonstrated to be more sensitive than CT for detecting brain metastases.[16-19] More accurate detection of brain metastases facilitates more appropriate treatment, especially in the context of a potentially solitary brain metastasis.[16,20] For these reasons, MRI is recommended as a standard component of staging work-up in patients with clinically stage III or IV disease, although there is no level 1 evidence.[21] Studies testing for improved survival due to MRI imaging of the brain have not been completed, therefore CT brain remains an option if MRI is not adequately available.

Approach to the Management of Patients With Brain Metastases

Establishing the Goal of Treatment

Significant neurological symptoms and signs often accompany the diagnosis of brain metastases in lung cancer. Survival of patients is poor, with a median prognosis of 4 months and ranges from 2 to 10 months in early studies, then more recently a median of 7 months with a range of 3 to 15 months depending on patient factors.[22-24] Therefore, a need exists to provide a clear understanding of prognosis to identify which patient groups might benefit from aggressive treatment and help clarify provider and patient time frame expectations. A number of tools have been developed to predict outcomes for patients with brain metastases. The RTOG's recursive partitioning analysis (RPA) classes were developed to stratify patients in clinical trials and inform treatment decisions. The RPA was derived from a database of 1200 patients who had participated in 3 RTOG trials conducted between 1979 and 1993.[25] This analysis defined 3 categories using: Karnofsky performance status (KPS), control of primary disease, age < 65 years, and location of metastases (brain only or other sites). Lung cancer patients comprised 61% of the cohort. A summary of the 4 most popular scores is shown in Table 1.[18-21,24,25] It should be noted that in all of these scoring systems age older than 65 years is associated with poorer survival. However, by itself age does not appear to be a significant enough factor to change the intention of treatment.

Although multiple studies have validated RPA in the NSCLC population, there remains some concern regarding its utility.[26,27] The main weakness of the RPA classification is that substantial variability remains within each class. RPA class I is the most homogeneous population because these patients were young, fit to undergo surgery, and had limited brain disease.[28] Several groups have attempted to refine the RPA to improve precision. Nieder et al published a comparative analysis of 7 prognostic scores for NSCLC patients in 2009.[29] They showed that the RPA classes, the Basic Score for Brain Metastases,[30] and the Graded Prognostic Assessment (GPA) each discriminated prognostically between groups. The GPA performed better than the others, effectively stratifying 4 groups with 1-year survivals of 43, 20, 8, and 0%. The GPA consists of 4 prognostic factors, including age, KPS, extracranial metastases, and number of brain metastases.[24] Although the initial publication reported median survival based on a variety of primary cancers, subsequent analysis of a multi-institutional database refined the GPA and created disease-specific scores.[31]

Supportive Care

Treatment with steroids is a mainstay of pharmacologic management for symptomatic brain metastases and might be the only appropriate therapy for patients with poor prognosis. Some authors have suggested that such patients could represent up to 50% of those seen in everyday practice and are best managed supportively.[32,33] Glucocorticoids improve symptoms by controlling cerebral edema and marked neurological improvement is expected within 24 to 72 hours of treatment.[34] Dexamethasone is typically the steroid of choice because of its minimal mineralocorticoid effect. An early study showed an improvement in performance status and neurological symptoms for at least 60% of patients receiving prednisone,[35] but few controlled studies have been completed in the past 20 years.[34] Some questions exist regarding the appropriate dose of steroids to be used. Two small older studies examined high-dose versus lower doses of dexamethasone, but showed no statistically significant difference in outcomes.[36,37] A systematic review in 2010 concluded that corticosteroids are recommended to provide symptom relief in patients with symptomatic brain metastases and that dexamethasone is the steroid of choice, but that the recommendations are based on level 3 evidence.[34]

Similarly, the literature regarding the use of prophylactic anticonvulsants is scant. The only randomized controlled trial (RCT) was reported by Forsyth et al in 2003 and included only 100 patients.[38] This trial enrolled patients with any form of brain tumor and was stopped early because of low rates of seizure (10%) in the observation group and greater than expected mortality within 3 months of randomization. In the absence of evidence supporting their use, anticonvulsants are primarily indicated for patients who develop seizures.

Surgery for Brain Metastases

Surgery is the oldest therapy for brain metastases and is still used in select cases.[39] A systematic review of NSCLC patients receiving