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The purpose of this paper is to provide an overview of the clinical presentation, diagnosis, and treatment of brain metastases in patients with SCLC, with a focus on current trends and developments in the treatment of this disease.

ABSTRACT: Small cell lung cancer (SCLC) accounts for approximately 20% of all cases of lung cancer. It tends to disseminate earlier in the course of its natural history than non-small cell lung cancer and is clinically more aggressive. Approximately 10% of patients present with brain metastases at the time of initial diagnosis, and an additional 40% to 50% will develop brain metastases some time during the course of their disease. The prognosis of patients with brain metastases from SCLC is poor despite years of research. The standard of care remains appropriate medical management followed by whole brain radiation therapy. Current research is evaluating novel agents in an attempt to improve the survival and quality of life in these patients. However, the most effective treatment for brain metastases from SCLC is the prevention of the development of clinically detectable disease. For patients with a complete response to initial treatment, prophylactic cranial irradiation is an effective method of prevention.

Approximately 173,770 new cases of lung cancer will be diagnosed in the United States in 2004 with an estimated 160,440 deaths.[1] Small cell lung cancer (SCLC) accounts for approximately 20% of all cases of lung cancer.[2] It tends to disseminate earlier in the course of its natural history than non-small cell lung cancer (NSCLC) and is clinically more aggressive.[3] Patients with SCLC are classified as having either limited- or extensive-stage disease according to the system developed by the Veteran's Administration Lung Cancer Study Group.[4] Patients with tumors that can easily be encompassed within an acceptable radiation portal (historically defined as a hemithorax) are classified as having limited disease, and they represent approximately one-third of all new SCLC cases. In contrast, two-thirds of patients with SCLC present with extensive-stage disease, with frank distant sites of involvement that cannot be incorporated into a safe and tolerable radiation portal.[4] In that regard, metastases from SCLC have a particular predilection for the brain. Approximately 10% of patients present with brain metastases at the time of initial diagnosis, and an additional 40% to 50% will develop brain metastases some time during the course of their disease.[5-7] The purpose of this paper is to provide an overview of the clinical presentation, diagnosis, and treatment of brain metastases in patients with SCLC, with a focus on current trends and developments in the treatment of this disease.

Clinical Presentation

Brain metastases most frequently arise at the junction between the white and grey matter, or the so-called "watershed area" of the brain.[8] The signs and symptoms are not specific to the disease but rather reflect the location and number of metastatic lesions. Moreover, the severity of these symptoms may be a function of the degree of tumor-related vasogenic edema. The most common signs and symptoms include headache, focal weakness, mental disturbances, gait ataxia, seizures, speech difficulty, visual disturbance, sensory disturbance, and limb ataxia.[8]

Diagnosis

The diagnosis of brain metastases is based on patient history, neurologic examination, and diagnostic imaging. Imaging of the brain is very important in patients with SCLC who are suspected of having brain metastases, because these patients often have metabolic abnormalities or paraneoplastic syndromes that can produce symptoms that mimic those caused by intracranial metastases. In fact, SCLC is the most common histologic type of cancer associated with neurologic paraneoplastic...
syndromes.[9] These syndromes are thought to be related to an autoimmune process in which the tumor produces substances that are similar to those normally expressed by the nervous system. These substances lead to the production of autoantibodies that crossreact with neuronal antigens and ultimately damage normal tissue. One such disorder, Eaton-Lambert myasthenic syndrome, is seen in up to 3% of patients with SCLC and causes proximal muscle weakness, autonomic dysfunction, and paresthesias. Other neurologic syndromes seen in patients with SCLC include sensory neuropathies and paraneoplastic cerebellar degeneration.[9]

The most helpful imaging study is gadolinium-enhanced magnetic resonance imaging (MRI). When brain metastases from SCLC develop, they usually occur at multiple sites and tend to be located in the posterior cranial fossa.[6] The posterior fossa is better visualized on MRI, which can also detect small lesions not seen on a computed tomography (CT) scan.[8] Magnetic resonance imaging can also help identify leptomeningeal involvement—an uncommon finding in patients with SCLC.[4] In addition to establishing a diagnosis, MRI can also be used in treatment planning and as a baseline for gauging response to treatment.[10]

**Prognostic Factors**

**TABLE 1**

<table>
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<th>Classification of Brain Metastases</th>
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Although patients with brain metastases have a poor prognosis overall, certain factors have been identified that are predictive for an improved outcome. Gaspar et al performed a recursive partitioning analysis of 18 pretreatment characteristics and three treatment-related variables in three consecutive Radiation Therapy Oncology Group (RTOG) brain metastases trials conducted between 1979 and 1993.[11] The analysis included 1,200 patients, over 50% of whom had NSCLC. Only 51 patients included in this analysis had brain metastases from SCLC. The small number of patients with SCLC did not allow for this histology to be evaluated separately from other primaries. Based on this analysis, age, performance status, control of the primary tumor, and the presence or absence of extracranial metastatic disease were found to significantly influence survival. These factors were grouped into three prognostic classes (Table 1).[11]

**Treatment**

**Initial Management**

Brain metastases require prompt intervention to minimize progressive neurologic injury.[10] The aim of initial management is to control increased intracranial pressure if it is present. This can be accomplished with the use of corticosteroids such as dexamethasone, which decreases the brain-to-tumor capillary permeability, thereby reducing edema of the brain.[6] Patients are typically prescribed dexamethasone (8 to 16 mg) divided into two to four daily doses. Antiepileptic medications such as phenytoin are not used routinely in this setting unless the patient presents with seizures.

**Radiation**

**TABLE 2**
Brain Metastases in Small Cell Lung Cancer


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Median Survival of Patients After the Development of Brain Metastases From Small Cell Lung Cancer

- **External Beam Radiation Therapy**—Small cell lung cancer is very radiosensitive.[12] In vitro, SCLC cell lines have lower survival rates than squamous-cell carcinomas in singlefraction clonogenic assays.[12] Whole brain radiation therapy (WBRT) is the standard of care in managing brain metastases from SCLC because it is well tolerated and rapidly resolves symptoms. However, the prognosis of SCLC patients with brain metastases is poor. Reported median survival for these patients ranges from 1 to 14 months, but most survive only 3 to 4 months (Table 2.).[5,13-23] Although brain metastases from SCLC can cause significant morbidity, it is rarely the sole cause of death. Rather, the presence of brain metastases often heralds the development of systemic progression of disease.[5] Between 60% and 95% of SCLC patients with brain metastases are found to have extracranial disease at the time of or shortly after diagnosis.[24] Because of the aggressive systemic nature of SCLC, these patients have been historically excluded from participation in clinical trials that are exploring alternatives to conventional WBRT. As a result, few randomized trials have been conducted to guide the treatment evolution in this group of patients and to challenge the prevailing perspective that WBRT alone is the only effective treatment for brain metastases from SCLC.

**TABLE 3**

<table>
<thead>
<tr>
<th>Author</th>
<th>Median Survival Comments</th>
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<tr>
<td>Provenza et al.[10]</td>
<td>1.5 mo. Chemotherapy and whole body radiation therapy</td>
</tr>
<tr>
<td>Kato et al.[11]</td>
<td>8.0 mo. Median survival not known</td>
</tr>
<tr>
<td>Hoang et al.[12]</td>
<td>2.9 mo. Limited disease at initial diagnosis</td>
</tr>
<tr>
<td>Luza et al.[13]</td>
<td>2.0 mo. Extensive stage at initial diagnosis</td>
</tr>
<tr>
<td>Grammer et al.[14]</td>
<td>11 mo. Median survival not known</td>
</tr>
<tr>
<td>Coons et al.[15]</td>
<td>7.3 mo. Response to whole body radiation therapy</td>
</tr>
<tr>
<td>Department of Defense</td>
<td>10 mo. No response</td>
</tr>
<tr>
<td>Gammon et al.[16]</td>
<td>15 mo. Median survival not known</td>
</tr>
<tr>
<td>Kone et al.[17]</td>
<td>16 mo. Median survival not known</td>
</tr>
<tr>
<td>Berge et al.[18]</td>
<td>24 mo. Median survival not known</td>
</tr>
<tr>
<td>van Hoefer et al.[19]</td>
<td>16.8 mo. Extensive stage at initial diagnosis</td>
</tr>
<tr>
<td>Hagan et al.[20]</td>
<td>9.6 mo. Extensive stage at initial diagnosis</td>
</tr>
<tr>
<td>Provenza et al.[21]</td>
<td>6.8 mo. Extensive stage at initial diagnosis</td>
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The effectiveness of WBRT has been examined mainly in retrospective studies (Table 3).[13-20,25] Interpreting the data from these studies, however, is difficult because different criteria were used to measure response rates.[23] The response criteria used in the older studies were often based on symptomatic improvement rather than on objective measurements of tumor size on radiographic studies. In addition, many of the patients included in these studies were also treated with chemotherapy, either concurrently with radiation or shortly thereafter. Finally, the chemotherapy regimens varied widely from study to study. Another confounding factor is the use of corticosteroids. Symptomatic improvement is frequently seen after the initiation of such medications. Thus, in patients treated with corticosteroids, it is not known whether the clinical response should be attributed to the medical treatment or to WBRT.[23] Finally, some of these retrospective studies included patients presenting with brain metastases at the initial diagnosis as well as patients whose disease relapsed in the brain after initial treatment.[23] Some studies have found that patients presenting with brain metastases at diagnosis may have a better prognosis than patients who develop brain metastases at a later date. The largest series documenting the role of WBRT in SCLC was reported in 1988 by Carmichael et al,
who performed a retrospective review of 59 patients with proven brain metastases from SCLC treated with therapeutic irradiation from 1977 through 1983.[18] Although patients were treated with varying chemotherapy regimens, all those with brain metastases at presentation were given induction chemotherapy. However, the systemic treatment of patients with delayed presentation of brain metastases was individualized. The radiation dose and fractionation schedules depended on the patient’s performance and disease status and whether or not the patient had received previous prophylactic cranial irradiation (PCI).

A total of 19 patients (32.2%) achieved a complete response to WBRT, and an additional 18 patients (30.5%) had a partial response. However, of the 37 patients with an objective response, 24 (8/19 complete responders and 16/18 partial responders) developed recurrent or progressive intracranial disease prior to death. The median duration of the response was 10 months in patients with a complete response and 5 months in patients with a partial response. The median survival of patients presenting with brain metastases was 7 months, compared with 3 months in patients with delayed development of metastatic disease. Patients who received radiation doses of more than 40 Gy had longer response durations than those given lower doses. The authors concluded that the irradiation schedules customarily used to treat brain metastases in SCLC are unlikely to eradicate intracranial tumors in the occasional patient whose systemic cancer has a durable complete response. They suggested that it may be appropriate to consider treatment with doses greater than 40 Gy.

The European Organization for Research and Treatment of Cancer (EORTC) conducted a prospective, phase II study between 1989 and 1995 that accrued 22 patients with SCLC and brain-only metastases to evaluate the efficacy of WBRT as a single treatment modality.[23] Radiation consisted of 30 Gy in 10 fractions to the whole brain. Six patients had a complete response, and five had a partial response. The median response duration in patients with an objective response was 5.4 months, and the median survival of all patients was 4.7 months. This trial confirmed a major finding from the previous retrospective studies—that a significant number of patients respond to WBRT, but the response duration and survival are short.

• **Attempts to Improve WBRT Results**—Investigators have attempted to improve the results of WBRT by increasing the total radiation dose using altered fractionation schedules. Bach et al performed a retrospective review of 101 patients with brain metastases from SCLC that compared extended-course with short-course brain irradiation.[26] Extended-course irradiation consisted of > 45 Gy in > 4 weeks, with most patients receiving 50.4 Gy in 28 fractions. Short-course irradiation consisted of < 30 Gy in < 1 week, with most patients receiving 22 Gy in four fractions. Extended-course irradiation significantly improved median survival (5.3 vs 2.9 months, \( P = .00001 \)). However, 40% of patients who received short-course brain irradiation had evidence of extracranial progressive disease at the time of treatment, whereas all patients who received extended-course brain irradiation were in partial or complete remission outside the brain.

Many prospective trials have been conducted to identify the optimal dose and fractionation schedule in the treatment of patients with brain metastases. Although these issues have not been addressed in a prospective fashion in the SCLC population alone, these patients were not specifically excluded from participation in these trials. The RTOG has been very active in exploring different fractionation schedules for WBRT. The first two trials evaluated different accelerated fractionation regimens, including 40 Gy in 4 weeks, 40 Gy in 3 weeks, 30 Gy in 3 weeks, 30 Gy in 2 weeks, 10 Gy in one fraction, and 12 Gy in two fractions over 3 days.[27,28] The overall response to treatment was equivalent in all arms. However, the duration of neurologic improvement was shorter in patients treated with 10 or 12 Gy.[28]

RTOG 9104 was a phase III study comparing accelerated hyperfractionation with standard accelerated fractionation in 429 patients with unresected brain metastases.[29] In this study, 39 patients had SCLC. Standard accelerated fractionation consisted of 30 Gy in 10 fractions. For those receiving accelerated hyperfractionation, the entire brain was treated with 1.6 Gy bid to a total dose of 32 Gy in 20 fractions. This was followed by an additional 22.4 Gy in 14 fractions to clinically visible lesions with a 2-cm margin, for a total dose of 54.4 Gy in 34 fractions. Median survival was 4.5 months in both arms, with a 1-year overall survival rate of 19% in the accelerated fractionation arm and 16% in the accelerated hyperfractionation arm. Given that higher radiation doses and altered fractionation schedules have not been shown to improve outcome in prospective trials, 30 Gy in 10 fractions continues to be one of the most commonly used fractionation schedules in WBRT.

• **Re-treatment With External Beam Radiation Therapy**—Although many patients with brain metastases from SCLC experience a good initial response to WBRT, many develop recurrent or progressive intracranial disease prior to death. The treatment options for these patients are often limited, and some authors have advocated repeat WBRT for palliation of symptoms.
Wong et al reported on the Mayo Clinic experience with reirradiation for brain metastases.[30] From 1975 through 1993, 86 patients were reirradiated because their neurologic function had deteriorated or findings on imaging studies were consistent with progressive disease after an initial course of WBRT, or both. The most common primary sites were the breasts and lung, but the proportion of patients with SCLC was not identified. The median time interval between the first and second courses of irradiation was 7.6 months. The median dose of the first course of WBRT was 30 Gy, which was usually given in 10 fractions. The median dose of the second course was 20 Gy, most commonly given in 10 fractions.

Neurologic symptoms were resolved in 27% of patients, 43% experienced a partial improvement, and 29% had either no change or their condition worsened after reirradiation. The median survival following reirradiation was 4 months. Most patients had no significant toxicity secondary to reirradiation. Radiographic abnormalities consistent with radiation changes appeared in five patients, and one patient developed symptoms of dementia, which was attributed to radiation therapy. From this review, the authors concluded that reirradiation should be offered to patients who develop progressive brain metastases.

Imanaka et al used reirradiation therapy in three patients with recurrent brain metastases from SCLC.[31] The initial therapy varied among the three patients. Two patients were treated with 30 Gy in 10 fractions to the whole brain, followed by a boost consisting of 10 Gy in four fractions for one patient and 9 Gy in three fractions for the other patient. The third patient was initially treated with 38 Gy in 14 fractions. Re-treatment consisted of 20 Gy and was administered to two patients with hyperfractionation (20 fractions) and to one patient with conventional fractionation (10 fractions). The time interval between the two treatments ranged from 4 to 8 months. Of the re-treated patients, two achieved a partial response and the third had no response. The survival after reirradiation was 4 months for all patients. No radiation injury was observed during follow-up. Therefore, the authors suggested that whole brain reirradiation is useful and safe for brain recurrence of SCLC.

**Stereotactic Radiosurgery**—With this external irradiation technique, multiple collimated beams of radiation are stereotactically aimed at a target to deliver a single, high dose of radiation to a small volume of tissue.[32] Brain metastases are ideal targets for stereotactic radiosurgery because they are usually relatively small when they are diagnosed, and they are often spherical in shape. They are also minimally invasive and displace normal brain parenchyma, which reduces the risk of injury to healthy tissue.

Numerous retrospective studies have evaluated the effectiveness of stereotactic radiosurgery in the treatment of brain metastases. These studies have suggested that radiosurgery improves both control of intracranial metastases and survival.[33] However, the survival benefit suggested by these studies may have been due to bias because patients with known favorable prognostic factors were selected.

Sanghavi et al performed a retrospective review of 502 patients with brain metastases treated with radiosurgery and external beam radiation therapy at 10 institutions from January 1988 through May 1998.[33] Patients with brain metastases from any primary tumor treated with WBRT and a stereotactic radiosurgery boost to all visible lesions were included in this analysis. Patients in this study were stratified according to their recursive partitioning analysis classification based on the RTOG's phase III brain metastases database reported by Gaspar et al (Table 1).[11] With this stratification system, current results can be compared with prior RTOG results. In addition, the recursive partitioning analysis system attempts to remove the potential bias resulting from patient selection. The median external beam dose was 37.5 Gy, and 97% of patients received ≥ 30 Gy. Radiosurgery was delivered using a modified linear accelerator or via Gamma Knife. The dose and prescription line varied depending on each institution's preference.

On multivariate analysis, performance status, controlled primary disease, and absence of
extracranial metastases were significant predictors of improved survival. The median survival of all patients was 10.7 months. No specific comments were made regarding survival based on histology. Median survival for recursive partitioning analysis class I, II, and III patients was 16.1, 10.3, and 8.7 months, respectively. The median survival times were longer in this study for each recursive partitioning analysis class than they were in the RTOG studies. Therefore, this study suggested that radiosurgery may improve survival in all patients with brain metastases regardless of recursive partitioning analysis class.

Serizawa et al performed a retrospective review of 245 patients with brain metastases from either SCLC (34 patients) or NSCLC (211 patients) treated with Gamma Knife radiosurgery.[34] The inclusion criteria included: (1) no prior brain tumor treatment; (2) 25 or fewer lesions; (3) a maximum of 3 tumors with a diameter of 20 mm or more; (4) no surgically inaccessible tumor ≥ 30 mm in diameter; and (5) a life expectancy > 3 months. Tumors > 30 mm in diameter were surgically resected. All other smaller brain metastases were treated using the Gamma Knife system, with a mean prescription dose of 21.3 Gy. New brain metastases detected on follow-up MRI scans were treated with repeat Gamma Knife radiosurgery. Chemotherapy was administered according to the referring physician’s protocol.

The tumor control rate was 94.5% in the SCLC group and 98% in the NSCLC group. The median survival was 9.1 months in the SCLC group and 8.6 months in the NSCLC group. There was no significant difference between the two groups for any type of survival. Therefore, the results of this study suggest that Gamma Knife radiosurgery appears to be as effective in treating brain metastases from SCLC as for those from NSCLC.

RTOG 9508 was a phase III trial comparing WBRT alone vs WBRT followed by stereotactic radiosurgery for patients with one to three unresected brain metastases ≤ 4 cm from any primary tumor except for leukemia or lymphoma.[35] Patients were not stratified according to histology. Whole brain radiation therapy consisted of 37.5 Gy delivered in 15 fractions. The radiosurgery doses were based on a previous RTOG trial and depended on the size of the lesion. For lesions ≤ 2 cm, patients were treated with 24 Gy. Lesions measuring 2.1 to 3 cm were treated with 18 Gy, and lesions measuring 3.1 to 4 cm were treated with 15 Gy.

Patients treated with stereotactic radiosurgery were found to have a statistically significant improvement in the 1-year local control rate (82% vs 71%, \( P = .01 \)). Furthermore, all subsets of patients treated with stereotactic radiosurgery were more likely to have a stable or improved performance status than those receiving WBRT alone. There was no improvement in survival overall, but it did improve for recursive partitioning analysis class I patients, patients < 50 years of age, and patients with SCLC, any squamous cell cancers, or solitary brain metastases. The authors concluded that stereotactic radiosurgery can prolong survival in select patients with brain metastases only by 1 to 2 months. Systemic disease remained the primary cause of death in more than two-thirds of the patients. Improved systemic therapies are needed to significantly lengthen survival.

• **Brachytherapy**—In this treatment, radioactive sources are used to deliver radiation at a short distance by interstitial, intracavitary, or surface application.[36] With this technique, a high dose of radiation can be delivered locally to the tumor with rapid dose fall-off in the surrounding healthy tissue. Brachytherapy can be used as a primary treatment, as a means of delivering a boost in conjunction with conventional radiation therapy, or as a treatment for recurrent lesions.[37] Brachytherapy can be divided into two categories, low dose rate (LDR) and high dose rate (HDR).[37] In LDR brachytherapy, the radioactive sources are typically placed in catheters that are spaced evenly within the tumor or in the center of the tumor to deliver 5 to 60 Gy/h. Another approach to LDR brachytherapy involves permanent interstitial implants in which iodine (I)-125 sources that are embedded in suture material are inserted or implanted directly into a tumor cavity. In HDR brachytherapy, a dose rate of 100 to 200 Gy/min is delivered through temporary catheters that are placed within the tumor; high-activity radioactive sources are inserted into the catheters. The relatively discrete nature of brain metastases suits the physical dose parameters of brachytherapy. Nonetheless, it remains an invasive procedure. Patients with a single brain metastasis whose greatest dimension measures < 5 cm are candidates for brachytherapy.[38] Because patients with SCLC rarely present with a single brain metastasis, experience with brachytherapy in these patients is limited.

McDermott et al reported on the University of California, San Francisco, experience in 30 patients with a single brain metastasis who underwent temporary I-125 implantation.[38] One of the patients included in this study had SCLC. Of the 25 patients treated for recurrence of their metastasis, 4 received brachytherapy as a boost, and 1 had brachytherapy alone after resection without external irradiation. The median implant dose was 4,901 cGy delivered at a median dose rate of 45 cGy/h.
The median survival for the entire group was 14.7 months. The median survival for patients treated at recurrence was 13.9 vs 68.2 months for those treated with a boost. The authors concluded that their experience with interstitial brachytherapy using I-125 implants was favorable and that interstitial brachytherapy is particularly useful in salvaging metastases that recur after prior therapies.

**Chemotherapy**

Chemotherapy was not utilized in the treatment of brain metastases in the past because it was thought that the brain is a pharmacologic sanctuary site due to the blood-brain barrier.[39,40] The blood-brain barrier restricts the transport of certain molecules between the blood and the central nervous system (CNS) as a result of tight intercellular junctions between the endothelial cells of capillaries within the brain.[39] Substances that have a high solubility in the lipid component of the endothelial cell membranes are better able to cross the capillary wall, so the rate of penetration of an agent from the blood to the brain has been related to its lipid solubility.[41] While the blood-brain barrier seems to be preserved in the presence of micrometastatic CNS disease, it appears to be interrupted in patients with macroscopic brain metastases, which derive their blood supply from new capillaries growing into the tumor.[39-42] These new vessels have endothelial fenestrations and gaps that increase the permeability of these vessels.[42] In fact, this increased permeability is essential to the radiologic diagnosis of brain metastases, which relies on contrast dyes that normally do not cross the blood-brain barrier.[42,43]

**TABLE 4**

Response Rates of Brain Metastases at Initial Presentation Treated With Chemotherapy

Several studies have evaluated the efficacy of chemotherapy in the treatment of brain metastases from SCLC. Five studies reported on the response rates of various chemotherapy regimens in the treatment of patients with SCLC presenting with brain metastases at the time of diagnosis.[42-46] The reported response rates in these studies ranged from 53% to 100% (Table 4). Six studies reported the results of treatment with single-agent chemotherapy in patients who developed brain metastases after the initial diagnosis of SCLC.[47-52] These studies reported response rates that ranged from 32.5% to 50% (Table 5).

The higher response rates seen in the former group of patients may be related to the fact that these patients had not been exposed to previous chemotherapy.[39-40] Patients who have been previously treated with chemotherapy are more likely to exhibit resistance to additional chemotherapy than patients who are chemotherapy naive.[40] In addition, patients included in the first group of studies were treated with combination chemotherapy regimens rather than single agents, which may also have contributed to their improved response rates.[39]

**TABLE 5**

Response Rates of Delayed Brain Metastases Treated With Chemotherapy

• **Temozolomide**—One novel chemotherapeutic agent that has shown promise in the treatment of brain tumors is temozolomide (Temodar), a second-generation alkylating agent that is an imidazotetrazine derivative of dacarbazine (DTIC-Dome).[53] Temozolomide essentially has 100%
Chemotherapy and WBRT

and biologic agents in an attempt to improve these results. In addition, temozolomide has shown to have a favorable toxicity profile. The only dose-limiting toxicity is noncumulative myelosuppression, which occurs in < 5% of patients.[54] Ant

Antonadou et al performed a phase II randomized trial in 52 patients with previously untreated brain metastases in which treatment with concurrent temozolomide and WBRT was compared with WBRT alone.[55] A total of 48 patients completed radiation therapy and were assessable for efficacy and safety, and 45 patients were assessable for response. Of the patients included in this study, nine had brain metastases from SCLC. Whole brain irradiation consisted of 40 Gy delivered in 20 fractions. Temozolomide was administered orally at a dose of 75 mg/m²/d during radiation treatment, and 200 mg/m²/d for 5 days after radiation was complete. Treatment cycles were repeated every 28 days for a maximum of six additional cycles. The response rate in the combined-modality group was significantly superior to that achieved with radiation alone (96% vs 67%, P = .017). Patients treated with temozolomide plus radiation therapy had a slight improvement in median survival (8.6 vs 7.0 months). However, the difference was not statistically significant. The authors did not comment on the efficacy of temozolomide in the treatment of patients with SCLC in particular. From this study, the authors concluded that temozolomide is safe and significantly improves the response rate when administered in combination with radiotherapy in patients with previously untreated brain metastases. Two phase II trials have evaluated the safety and efficacy of temozolomide in the treatment of recurrent brain metastases. One of these trials was conducted at Memorial Sloan-Kettering Cancer Center and enrolled 41 patients, including 2 patients with brain metastases from SCLC.[56] All patients had been treated with previous WBRT (median dose: 30 Gy), and one patient had received two courses of WBRT. Stereotactic radiosurgery had been performed in 9 patients, and 11 had undergone prior surgical resection of their brain metastases. All but six patients had previously been treated with chemotherapy. Patients who had received prior chemotherapy were given temozolomide at 150 mg/m²/d for 5 days, and patients who were chemotherapy-naive received 200 mg/m²/d for 5 days. Treatment cycles were repeated every 28 days. Of the 34 evaluable patients, 2 had a partial response, 15 had stable disease, and 17 had progressive disease. The two partial responders had brain metastases from NSCLC. The median time to tumor progression was 1.97 months. The median survival for all patients was 6.62 months. The small number of patients with brain metastases from SCLC did not allow for a definitive conclusion about the efficacy of temozolomide in the treatment of this subgroup of patients. However, the authors concluded that treatment with single-agent temozolomide compares favorably with other therapeutic options available and, therefore, may provide a useful alternative therapy for patients with recurrent brain metastases.

The second phase II study of temozolomide for recurrent brain metastases was conducted by the Hellenic Cooperative Oncology Group.[57] A total of 28 patients were enrolled in this trial, including 5 with brain metastases from SCLC; 22 patients had had one or more courses of chemotherapy, and 23 had undergone previous WBRT. Temozolomide at 150 mg/m²/d for 5 days was administered every 4 weeks until unacceptable toxicity or disease progression occurred. Of the 24 patients who received temozolomide treatment and had measurable disease, 1 patient with NSCLC achieved a partial response in both the lung and the brain, 4 patients had stable disease, and 4 patients had progressive disease. In 14 patients, the disease rapidly progressed or death from progressive disease occurred soon after the start of therapy. Two patients with SCLC who had both received prior chemotherapy and WBRT achieved disease stabilization under temozolomide therapy for 8.2 and 4.3 months, respectively. The median survival for all patients was 4.5 months, and the median time to progression was 3 months. The authors concluded that temozolomide demonstrated encouraging activity in the treatment of brain metastases in heavily pretreated patients with solid tumors, and was safe and well tolerated. Larger, phase III randomized trials are needed to verify the results of these phase II studies. Because temozolomide has shown synergistic activity in combination with other chemotherapeutic agents, future studies should focus on the use of temozolomide in combination with other chemotherapeutic and biologic agents in an attempt to improve these results.

Chemotherapy and WBRT
Although WBRT produces good response rates in patients with brain metastases from SCLC, most patients with tumor progression in the brain also have concurrent systemic failure.[5] These patients are therefore likely to be treated with chemotherapy. Some have questioned the need for WBRT in patients receiving systemic chemotherapy.

The EORTC conducted a phase III trial comparing teniposide (Vumon) alone vs teniposide plus WBRT (30 Gy in 10 fractions) in 120 patients with brain metastases and extracranial metastatic disease from SCLC.[5] The response rate of 57% in the combined-modality arm vs 22% in the teniposide-only arm was statistically significant. Time to progression in the brain was significantly longer with the addition of WBRT. However, the median survival was only 3.5 months in the combined-modality arm vs 3.2 months in the teniposide-only arm. The authors concluded that although the addition of WBRT results in a much higher response rate and a longer time to progression of brain metastases, chemotherapy does not seem to alter outcomes.

**Surgery**

Given the highly radiosensitive nature of SCLC and the fact that most patients with brain metastases from SCLC present with multiple lesions in the brain, surgical resection as a primary form of treatment is not routinely offered for these patients. In most cases in which surgical resection has been performed, SCLC was not the suspected diagnosis at the time of surgery. On the other hand, surgical resection plays a major role in the management of patients with a single brain metastasis from solid tumors such as NSCLC or breast cancer. In these patients, the addition of surgical resection to WBRT has been found to be superior to WBRT alone.[58,59]

Some case reports have reported long-term survival in patients undergoing surgical resection of a single brain metastasis from SCLC. Abratt et al reported on a patient presenting with a solitary brain metastasis 36 months after completing treatment for limited-stage SCLC.[60] The patient underwent gross total resection followed by WBRT consisting of 20 Gy in five daily fractions. Twenty-seven months after completing WBRT, the patient had no evidence of disease.

A second case report from Imai et al reported on a patient with extensive-stage SCLC with a single brain metastasis at initial diagnosis.[61] The patient was treated with subtotal resection of the brain metastasis followed by 56 Gy in 28 fractions to the brain. Thoracic irradiation was also given, along with one cycle of etoposide and cisplatin chemotherapy. The patient had a complete response to treatment and remained alive and well for 5 years without evidence of disease recurrence.

The randomized trials evaluating the role of surgery in the treatment of brain metastases have excluded patients with radiosensitive tumors such as SCLC. Therefore, there are no randomized data available to define the role of surgical resection of brain metastases in this group of patients. However, one could conceivably extrapolate from the data available for patients with a single brain metastasis from NSCLC. In these patients, adding surgical resection to WBRT improved median survival in two prospective randomized trials.[58,59]

In the trial reported by Patchell et al, local control and functional independence also significantly improved with the addition of surgical resection.[58] Therefore, one might hypothesize that surgical resection may provide similar benefits in the rare patient with a single brain metastasis from SCLC. However, given that this is such an unusual presentation of the disease, it is unlikely that a randomized trial could be completed to answer this question.

**Prophylactic Cranial Irradiation**

Given the high rate of brain failure in patients with SCLC, it is clear that subclinical intracranial disease must be present at the time of initial diagnosis.[12] This has led to the use of PCI in patients with limited-stage SCLC who have had a complete response to initial treatment. The effectiveness of PCI is based on the premise that moderate doses of radiation can be very effective in preventing clinically detectable metastases in a significant number of patients. Clinical trials have corroborated this premise—brain failure rates in complete responders were cut in half in one study, and a meta-analysis suggested that PCI lengthened survival by 5% at 3 years.[62-64] Although neurocognitive toxicity has been a concern and has been used as an argument against the use of PCI, the results of trials with prospective neuropsychologic testing have shown that PCI does not negatively affect neurocognitive function.[12]

**Future Directions**

Despite the fact that numerous clinical trials have been conducted in an attempt to improve the survival of patients with brain metastases, the outcome of these patients remains poor. One way in
which outcome could potentially be improved is by increasing the sensitivity of tumor cells to radiation with the use of a radiation sensitizer. Over the past 2 decades, randomized trials have evaluated several potential radiation sensitizers such as lonidamine, misonidazole, bromodeoxyuridine, nimustine, and fluorouracil/nimustine, but none have been shown to be effective.[65] More recently, two new radiation sensitizers, efaproxiral (RSR13), and motexafin gadolinium (Xcytrin), have shown promise in improving outcome in patients with brain metastases. Patients with brain metastases from SCLC were not eligible for these trials.

**Efaproxiral**

Hypoxic tumor cells are more resistant to DNA damage by ionizing radiation because oxygen is needed to "fix" the damage produced by free radicals.[66] In the absence of oxygen, the ionized target molecules could repair themselves and recover the ability to function normally.[66] Oxygen measurements in human tumors have confirmed tumor hypoxia in brain metastases.[65] Efaproxiral is an allosteric modifier of hemoglobin that decreases the hemoglobin-oxygen binding affinity, thereby facilitating the release of oxygen from hemoglobin and increasing tissue $pO_2$.[65] A phase II study conducted by Shaw et al included 57 recursive partitioning analysis class II patients with brain metastases from breast cancer, NSCLC, melanoma, or genitourinary or gastrointestinal primaries.[65] These patients were given concurrent efaproxiral and WBRT consisting of 30 Gy in 10 fractions. This phase II study led to a phase III randomized trial that was completed in August 2002.

**Motexafin Gadolinium**

Motexafin is a redox active drug that targets tumor cells and has been shown to increase radiation response in preclinical models.[67] A phase I/II study in patients with brain metastases from solid tumors treated with motexafin and WBRT found a potentially favorable effect on local tumor control.[67] Therefore, Mehta et al conducted a phase III randomized trial of 401 patients with brain metastases from solid tumors other than SCLC, lymphoma, or germ-cell tumors, comparing 30 Gy of WBRT therapy plus 5 mg/kg/d of motexafin vs WBRT alone.[67] Although there was no improvement in overall survival, motexafin was found to possibly improve time to neurologic and neurocognitive progression in patients with NSCLC. Therefore, a second phase III randomized trial is currently under way to further evaluate the potential benefits of motexafin in this subgroup of patients.

**RTOG Trials**

Consideration should be given to the inclusion of SCLC patients in similar trials in the future, given the persistently poor outcomes to date. In that regard, two recent trials of patients with brain metastases conducted by the RTOG have enrolled patients with brain metastases from SCLC: RTOG BR-0118 and RTOG BR-0119.

RTOG BR-0118 is a current phase III study for patients with brain metastases from any primary tumor. In this study, patients are being randomized to one of two treatment arms: WBRT with thalidomide (Thalomid) and WBRT alone.[68] Thalidomide has been shown to be an extremely effective inhibitor of angiogenesis, both in vitro and in animal systems, and is thought to work by inhibiting the angiogenic activity of bFGF. Angiogenesis is required for tumor growth beyond microscopic size. Many angiogenic factors have been identified in primary malignant tumors and their metastases, and antiangiogenic therapies are thought to be promising methods to control tumors because of the relative rarity of angiogenesis and neovascularization in normal tissues. RTOG BR-0119 is a randomized phase II study of melatonin administered either in the morning or the evening for brain metastases in RPA class II patients. Melatonin is a hormone secreted by the pineal gland in response to darkness.[69] It has been shown to be an important nocturnal circadian growth inhibitory signal to rodent tumors in vivo. In addition, small randomized trials have suggested that melatonin may improve survival in patients with brain metastases.

**Conclusions**

The prognosis of patients with brain metastases remains poor despite years of research. The standard of care remains appropriate medical management of the patient followed by WBRT. Because SCLC is an extremely radiosensitive and chemosensitive tumor, it was often thought that patients with brain metastases from SCLC have a better prognosis than patients with brain metastases from other primary malignancies. However, the literature suggests otherwise. Because older trials have often excluded patients with brain metastases from SCLC, there has been little evidence to alter current practice. Given the similarly poor outcomes for all brain metastases
patients, SCLC patients should be encouraged to participate in future studies. Current research is evaluating novel agents in an attempt to improve survival and quality of life in these patients. However, the most effective treatment for brain metastases from SCLC is the prevention of the development of clinically detectable disease. For patients with a complete response to initial treatment, PCI is an effective method of prevention.

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