

Therapeutic Advances in the Treatment of Brain Metastases

Julie E. Chang, MD, H. Ian Robins, MD, PhD, and Minesh P. Mehta, MD

Dr. Chang is a Hematology/Oncology Fellow at the University of Wisconsin Hospital and Clinics; Dr. Robins is Professor in the Departments of Medicine, Neurology, and Human Oncology at the University of Wisconsin School of Medicine; and Dr. Mehta is Chairman and Professor in the Department of Human Oncology at the University of Wisconsin School of Medicine and Public Health, in Madison.

Address correspondence to:

Julie E. Chang, MD, Department of Hematology/Oncology, University of Wisconsin CSC H4/534, 600 Highland Avenue, Madison, WI 53792; E-mail: jchang@uwhealth.org.

Abstract: Brain metastases are a frequent sequelae of many solid tumors. Whole-brain radiotherapy (WBRT) has been the standard treatment for decades, with modest long-term complications observed using doses no greater than 3 Gy/fraction. Surgical resection may be beneficial in select populations of patients with single brain metastases, controlled systemic disease, and good performance status. Radiosurgery has demonstrated consistent improvement in local control, with some reports showing a survival benefit when combined with WBRT. However, the role of radiosurgery as a single modality is unclear, particularly given concerns that higher rates of distant brain relapse result in increased risk of neurologic compromise and death from neurologic causes. Increasingly, the importance of neurocognitive assessment with brain metastases is being recognized, and recent data have strongly correlated neurocognitive dysfunction with tumor progression. Systemic agents showing activity in brain metastases including temozolomide, RSR13, motexafin gadolinium, and lapatinib are being explored.

Brain metastases continue to pose a formidable challenge in the treatment of solid tumors. In the United States, approximately 170,000 new cases of brain metastases are diagnosed annually. The risk varies according to primary tumor type, with the highest rates of brain metastases observed with lung cancer (50%), breast cancer (15–20%), melanoma (10%), adenocarcinoma of unknown primary etiology (10–15%), and colon cancer (5%).¹ With the development of improved therapeutic options for management of systemic disease, there has been a shift in the natural history of several tumor types with prolongation of survival, increasing the incidence of brain metastases in these populations (eg, HER2/neu-positive breast cancer).² Another contributing factor is the increased incidence of several tumor types at high risk for brain metastases, such as melanoma and lung cancer in women.^{3–5} In addition, the availability of magnetic resonance imaging (MRI) has allowed for earlier detection, even when patients are asymptomatic.⁶ Although the mainstay of treatment for brain metastases remains whole-brain radiotherapy (WBRT), the role of other approaches including surgery, radiosurgery, chemotherapy, and targeted biologic therapies continues to evolve. This review focuses on recent and ongoing advances in the therapy of brain metastases from solid tumors.

Keywords: surgery, radiotherapy, radiosurgery, temozolomide, motexafin gadolinium, RSR13

Whole-Brain Radiotherapy

Historically, treatment of brain metastases has involved external-beam radiotherapy delivered to the whole brain; various fractionation and dosing schedules have been investigated (Table 1).^{7,8} Although no statistically significant differences have been shown among the various fractionation schedules and doses in terms of survival, 30 Gy administered in 10 fractions has become the standard in the United States due to its tolerability, brief treatment course, cost-effectiveness, and trend for improved survival (although not statistically significant). Additional experience reported by the Radiation Therapy Oncology Group (RTOG) with delivering accelerated hyperfractionated regimens at doses up to 70.4 Gy of focal radiotherapy have not demonstrated a significant survival benefit compared with more conventional dosing of radiotherapy.⁹⁻¹¹

Surgery

The role of surgery in the management of brain metastases is multifaceted. Surgical resection has a role in establishing the diagnosis, relieving mass effect, and achieving symptomatic resolution through debulking. Frequently, surgery is limited to cases in which one brain metastasis is present or in the case of multiple metastases in which one lesion is dominant or symptomatic. Multiple uncontrolled retrospective series have yielded conflicting results as to the benefit of surgery.¹²⁻²¹ Three randomized trials have investigated the role of surgery for single brain metastases from solid tumors, with two studies supporting the role of surgery in this setting (Table 2).²²⁻²⁴

Patchell and colleagues randomized 48 patients with single brain metastases to either WBRT alone (36 Gy) or surgical resection followed by adjuvant WBRT.²² The majority of enrolled patients (77%) had known diagnoses of non-small cell lung cancer (NSCLC) and a median Karnofsky performance status (KPS) of 90. Survival was improved with surgical resection, with a median survival of 40 versus 15 weeks ($P < .01$). In addition, surgical resection was associated with improved functional independence and lower rates of local recurrence.²² Noordijk and associates also reported favorable outcomes in surgical resection of single brain metastases, with a statistically significant improvement in survival favoring surgery followed by WBRT compared with WBRT alone (43 vs 26 weeks, $P = .04$).²³ The importance of controlled systemic disease was also clearly highlighted in this trial, with the largest difference in survival between treatment arms observed among patients with controlled systemic disease. Consistent with the experience of Patchell and colleagues,²² functional independence also appeared improved in patients undergoing surgery.²³

Table 1. Dose Fractionation and Schedules of Whole-Brain Radiotherapy for Treatment of Brain Metastases: RTOG Historical Experience

Years of Study	n	Gy/Fraction	Median Survival (weeks)
RTOG 1971–1973 ⁷	227	40/20	16
	233	40/15	18
	217	30/15	18
	233	30/10	21
RTOG 1973–1976 ⁷	447	20/5	15
	228	30/10	15
	227	40/15	18
RTOG 1979–1983 ⁸	193	30/10	19
	200	30/15*	18

Modified from Langer CJ, Mehta MP. *J Clin Oncol*; 2005.¹⁰³

*Delivered in 6 fractions of 5 Gy/fraction over 3 weeks.

RTOG=Radiation Therapy Oncology Group.

In contrast, Mintz and coauthors failed to demonstrate a survival advantage for surgical management of single brain metastases.²⁴ Median overall survival was not significantly different between the groups, although active extracranial disease again emerged as an important prognostic indicator.²⁴ The results of this study, in contrast to the survival advantage with surgery reported by Patchell²² and Noordijk,²³ may be related to a slightly higher proportion of patients with active extracranial disease.²⁴ The median KPS within the treatment populations of each of these trials was relatively similar.²²⁻²⁴ Although the randomized studies of surgery in management of single brain metastases do not unanimously support its role, these studies clearly demonstrate that surgery offers the most benefit in select patient populations with good performance status and controlled systemic disease.

Radiosurgery

Stereotactic radiosurgery (RS) is a specialized radiation technique in which a single dose of highly collimated radiation is delivered with submillimeter precision to one or more intracranial targets. Standard radiation doses are too low to produce sustained intracranial tumor control, and the high doses of conformal radiotherapy delivered with stereotactic radiosurgery allow for better local control than can be achieved with WBRT. In addition, there are fewer limitations with respect to location and number of brain metastases with the use of RS compared with neurosurgical resection. In order to safely target intracranial

Table 2. Randomized Trials of Surgical Resection of Single Brain Metastases

Reference	Treatment	n	Functional Independence (weeks)*	P	Median Survival (weeks)	P
Patchell et al ²²	S + WBRT (36 Gy)	25	38	<.005	40	<.01
	WBRT (36 Gy)	23	8		15	
Noordijk et al ²³	S + WBRT (40 Gy)	32	34	.06	43	.04
	WBRT (40 Gy)	31	21		26	
Mintz et al ²⁴	S + WBRT (30 Gy)	41	–	.98	24	.24
	WBRT (30 Gy)	43	–		27	

Modified from Langer CJ, Mehta MP. *J Clin Oncol*; 2005.¹⁰³

*Number of weeks in which the patient maintained a Karnofsky performance status \geq 70.

S=neurosurgical resection; WBRT=whole-brain radiotherapy.

lesions, RS requires that lesions be no larger than 4 cm in size. Three types of devices have been commonly used for delivering radiosurgery: the multisource cobalt unit (known as the “gamma knife”), specially modified linear accelerators, and charged-particle irradiators.¹¹

Previous experience with RS in brain metastases reported from smaller retrospective series have suggested that RS improves local control²⁵⁻³⁵ and offers a survival advantage.^{27,29-37} The largest retrospective study of RS in brain metastases reported outcomes in 502 patients with no more than 3 brain metastases treated with RS plus WBRT.³⁷ All patients were stratified into three prognostic classes based on the recursive partitioning analysis (RPA) reported by Gaspar and colleagues using data from three previous Radiation Therapy Oncology Group (RTOG) trials.³⁸ Factors influencing the prognostic classes include KPS, age, controlled primary tumor site, and the presence of extracranial metastases. As shown in Figure 1, all patients receiving RS plus WBRT at each RPA class level had improved survival compared with patients receiving WBRT alone.³⁷

These promising retrospective data led to a large randomized study (RTOG 9508) comparing WBRT (37.5 Gy) alone versus WBRT plus RS in patients with 1–3 brain metastases.³⁹ A total of 331 patients were randomized, with patients stratified by the number of brain metastases (1 vs 2–3) and extracranial metastases (none vs present). The treatment groups were well-balanced with respect to primary tumor type (>60% lung cancer), RPA class I disease, controlled systemic disease, and solitary and single brain metastases. Of the patients randomized to RS plus WBRT, 15% and 24% of patients with 1 and 2–3 brain metastases, respectively, did not receive RS. There was no improvement in survival between the treatment groups for the study population as a whole, but the subset of patients with one brain metastasis demonstrated a sta-

tistically significant improvement in overall survival (6.5 vs 4.9 months; Table 3). In addition, post hoc analysis showed improved survival for patients younger than age 50 with 1–3 metastases, patients with 1–3 metastases with NSCLC, and patients with 1–3 metastases and RPA class I patients.³⁹ Previously, some clinicians had postulated that RS may increase edema and lead to higher rates of radiation necrosis; however, results from RTOG 9508 did not support such claims and actually showed improvement in edema and decreased steroid dependence with RS (Table 4).³⁹

It is of interest to note that an earlier trial of WBRT (30 Gy) with or without RS in patients with 2–4 brain metastases was stopped at an interim evaluation after 60% accrual.³⁵ After enrolling 27 patients, the study was closed

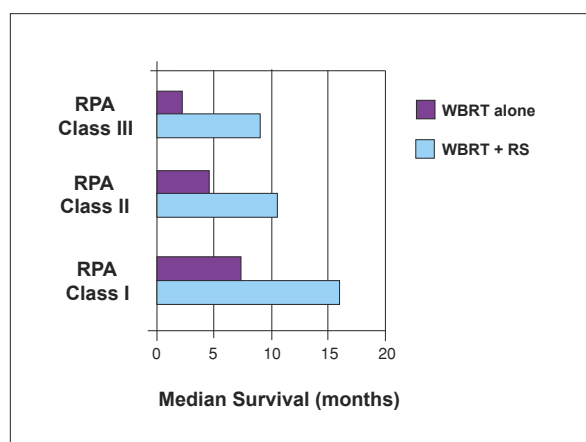


Figure 1. Radiosurgery by RPA class: retrospective multi-institution experience versus RTOG database.

Adapted from Sanghavi SN et al. *Int J Radiat Oncol Biol Phys*; 2001.³⁷ RPA=recursive partitioning analysis; RS=radiosurgery; RTOG= Radiation Therapy Oncology Group; WBRT=whole-brain radiotherapy.

Table 3. RTOG 9508: Survival Outcomes³⁹

Survival Analyses	Median Survival (months) WBRT + RS	Median Survival (months) WBRT	P
Overall	6.5	5.7	0.13
1 brain met	6.5	4.9	0.04
Post hoc subsets			
1–3 mets & age <50	9.9	8.3	0.04
1–3 mets & NSCLC	5.0	3.9	0.05
1–3 mets & RPA class I*	11.6	9.6	0.05

Table adapted from personal communication, Dr. Paul Sperduto, 2006.

*Recursive partitioning analysis based on outcomes reported by Gaspar et al.³⁸

Mets=metastases; NSCLC=non-small cell lung cancer; RPA=recursive partitioning analysis; RS=radiosurgery; WBRT=whole-brain radiotherapy in 2.5 Gy/fraction to 37.5 Gy (15 fractions).

prematurely because of a marked increase in local failure rate in the group receiving WBRT alone.³⁵

Further investigation has centered on outcomes when RS is used alone, in the hope that WBRT may be reserved for recurrence. Aoyama and associates reported results from 134 patients with 1–4 brain metastases treated with RS alone or RS plus WBRT.⁴⁰ Intracranial relapse at 12 months was significantly worse in patients who received RS alone (76.4% vs 46.8%, $P<.001$). In addition, rates of deterioration in neurologic function were worse in the group treated with RS alone (86% vs 59%, $P=.05$). Survival was comparable, but the study was not powered to detect a difference in this. These data suggest a strong association between intracranial relapse and decline in neurologic function, raising the concern that delayed WBRT may compromise the quality of a patient's survival. Similarly, high rates of intracranial relapse were reported in E6397, a phase II study of RS for treatment of 1–3 newly-diagnosed brain metastases from solid tumors.⁴¹ A local brain failure rate of 40% and a distant brain failure of 39% were observed in this study among patients treated with RS alone.

In a small single-institution review, Sneed and coauthors observed higher rates of local relapse when RS was used as a single modality, but similarly noted that successful salvage therapy for intracranial relapse did not appear to significantly alter survival.⁴² A larger multi-institution retrospective review including over 500 patients treated with RS plus WBRT or RS alone demonstrated lower rates of entire-brain freedom from progression with RS alone, but showed no difference in terms of survival, freedom from

Table 4. RTOG 9508: Outcome Results³⁹

Results	WBRT	WBRT + RS	P
KPS stable/improved at 3 mos	33%	50%	.02
KPS stable/improved at 6 mos	27%	43%	.03
Edema decreased at 3 mos*	62%	73%	.04
Tumor response at 3 mos	47%	70%	.0017
Grade 3/4 late toxicity	<2%	<3%	NS [†]

Table adapted from personal communication, Dr. Paul Sperduto, 2006

*Significantly lower steroid dependence on RS arm.

[†]Not stated.

KPS=Karnofsky performance status; RS=radiosurgery; WBRT=whole-brain radiotherapy in 2.5 Gy/fraction to 37.5 Gy (15 fractions).

local progression, or ability to provide salvage therapy at relapse.⁴³ However, measures assessing changes in neurologic function or performance status during treatment of brain metastases were not available in these retrospective studies.^{42,43} In another report by Regine and colleagues, an increased rate of symptomatic recurrences and neurologic deficits with intracranial relapse was observed among 36 patients with one brain metastasis treated with RS alone.⁴⁴ A 47% rate of local brain recurrence was observed, with 71% of these recurrences associated with symptoms and 59% of these recurrences associated with some type of neurologic deficit.⁴⁴ Experience to date suggests that RS alone results in higher local failure rates, analogous to what is observed when local control with surgery is utilized without adjunctive WBRT (Table 5).

Although the experience to date does not suggest a survival disadvantage with RS as a single modality (and none of the studies were actually powered to detect this), there is concern that the higher rates of observed local relapse translate into symptomatic recurrences with neurologic deficits and impairment in quality of life. In a multi-institution trial of 95 patients randomized post-resection of a single brain metastasis to WBRT (n=49) or observation (n=46), patients treated with postoperative radiotherapy had lower rates of local brain recurrence and were less likely to die of neurologic causes (14% vs 44% for deaths from neurologic causes with WBRT vs observation, respectively).⁴⁵ Overall, there was no difference in median survival between the 2 groups, but the lower rates of death from neurologic causes suggests that WBRT may allow for better quality of neurologic function, and

Table 5. Rates of Salvage Brain Therapy in Patients Treated With Up-front Surgery/RS Alone or With Adjuvant WBRT

Study	Surgery or RS + WBRT	Surgery or RS Alone	Relative Risk
Patchell (1998) ⁴⁵ (n=95) Surgery, randomized	8%	63%	7.9
Sneed (1999) ⁴² (n=105) Single institution, retrospective	19%	40%	2.1
Sneed (2002) ⁴³ (n=569) Multi-institution, retrospective	7%	37%	5.3
Aoyama (2006) ⁴⁰ (n=132) Phase III RS vs RS + WBRT	15%	43%	2.9

RS=radiosurgery; WBRT=whole brain radiotherapy.

by extrapolation, quality of life.⁴⁵ A similar limitation of salvage WBRT may apply to patients treated with RS, as local recurrence rates parallel those observed with surgical resection alone (Table 5).

Several ongoing RS studies should better define the role of RS, particularly with respect to effects not only on survival, but also in terms of quality of life and impact on neurocognitive function. RTOG 0320 is randomizing patients to WBRT and RS either alone, with temozolomide (TMZ; Temodar, Schering), or with erlotinib (Tarceva, Genentech/OSI); patients are stratified by RPA class, number of metastatic lesions, and controlled versus active extracranial disease. An NCCTG-led intergroup study is comparing RS alone versus RS plus WBRT in patients with 1–3 brain metastases, with attention to quality of life and neurocognitive function endpoints in addition to endpoints of survival and relapse.

Neurocognitive Dysfunction Associated With Brain Metastases

For decades, there has been underlying concern as to the neurocognitive effects of therapy for brain metastases, with little data available to quantify the effect of treatment on this outcome. Until recently, much of what was known of toxicity from WBRT in brain metastases came from a retrospective study of 47 patients who were 1-year survivors following WBRT for brain metastases treated at

Memorial Sloan-Kettering Cancer Center.⁴⁶ Five of the 47 patients (11%) were found to have severe dementia at 1 year, with the observation that patients with severe dementia received higher fractions of RT. Four of these 5 patients received fractions greater than 3 Gy, with the fifth patient receiving 3 Gy fractions in combination with a radiosensitizer. The remaining 15 patients without dementia had all received WBRT at doses no greater than 3 Gy/fraction.⁴⁶ This observed relationship between higher dose fractionation and risk for dementia has led to ongoing strategies to deliver WBRT at doses no greater than 3 Gy/fraction.

Another retrospective study reported by Patchell and colleagues suggested that WBRT given as initial therapy for brain metastases actually improved neurologic outcomes in patients receiving WBRT after resection of a single brain metastasis.⁴⁵ Patients randomized to observation had a greater chance of dying from neurologic causes than patients who received upfront WBRT, despite the fact that 88% of patients in the observation group received WBRT at progression.⁴⁵ Data from this retrospective report suggest that withholding WBRT until relapse in the hopes of sparing patients from potential neurologic toxicity from WBRT may ultimately lead to the greater risk of neurologic decline from the underlying disease and local progression of tumor. Such reports promote the idea that upfront WBRT is associated with a favorable risk:benefit ratio with the use of lower fractionation schedules.

Only recently has interest begun to focus on the baseline neurocognitive dysfunction present with brain metastases and the impact of treatment on these outcomes. Data from the SMART trial⁴⁷ demonstrated significant baseline neurocognitive abnormalities in the setting of brain metastases, with 90.5% of the 401 enrolled patients with brain metastases showing impairment in at least one neurocognitive test at baseline (prior to WBRT).⁴⁸ With reassessment following WBRT with or without the radiosensitizer motexafin gadolinium (MGd; Xcytin, Pharmacyclics), further decline in neurocognitive function was found to strongly correlate with progression of central nervous system (CNS) disease. In contrast, improvement in neurocognitive function was observed in the 109 patients showing at least a partial response to therapy, suggesting that neurocognitive decline is correlated to tumor growth and not to radiotherapy.⁴⁸

Chemotherapy for Brain Metastases

Blood-Brain Barrier in Highly Chemotherapy-Responsive Diseases

Systemic chemotherapy for brain metastases is rapidly evolving as a therapeutic modality. Many complicating factors arise in delivering systemic chemotherapy for

Table 6. Ability of Selected Agents to Cross the Blood-Brain Barrier.⁵²

Therapeutic Agent	Penetration into CSF*	Therapeutic Agent	Penetration into CSF*
Nitrosureas		Topoisomerase inhibitors	
BCNU (carmustine)	+++	Topotecan	+++
CCNU (lomustine)	+++	Etoposide	+
Alkylating agents		Irinotecan	None
Cyclophosphamide	None	Anthracyclines	
Dacarbazine	++	Doxorubicin	None
Procarbazine	+++	Idarubicin	None
Temozolomide	+++	Cytokines	
Antimetabolites		Interferon- α , Interleukin-2	None
Capecitabine	++	Mitotic inhibitors	
Cytarabine	++	Vincristine	+
Gemcitabine	None	Vinorelbine	+
Hydroxyurea	+++	Paclitaxel	None
Methotrexate†	++	Docetaxel	None
Platinum agents		Targeted agents	
Carboplatin	+	Lapatinib	++
Cisplatin	+	Trastuzumab	+

*Penetration into CSF: Very good +++, Good ++, Poor +.

†High-dose methotrexate at doses ≥ 1 g/m².

brain metastases, including overcoming the blood-brain barrier (BBB) and choosing an agent or regimen that is appropriate for the primary neoplasm (particularly in the setting of relapsed disease when patients have already received first- and second-line chemotherapy agents). The BBB is of particular interest in brain metastases from solid tumors as this barrier may fluctuate during treatment,⁴⁹ posing complex issues in terms of treatment of primary tumors and consideration of CNS prophylaxis.

Even among chemotherapy-sensitive tumors (eg, small-cell lung cancer, germ cell tumors, medulloblastoma/primitive neuro-ectodermal tumor, and lymphoma), metastatic disease to the CNS responds ultimately less well to chemotherapy compared with systemic sites of disease. This is presumably related to the BBB, with data suggesting that it is compromised and relatively permeable at presentation with brain metastases but quickly reconstitutes with ongoing therapy.^{49,50} For example, in a prospective study of newly diagnosed small-cell lung cancer, 22 patients were found to have asymptomatic synchronous brain metastases. With systemic therapy, a response rate of 27% for CNS disease was observed compared with a response rate of 73% for systemic disease.⁵¹ Again, one probable explanation for this variability in response may

be related to reconstitution of the BBB after an initial response with treatment. This phenomenon related to the BBB was dramatically illustrated using serial PET scanning during the treatment of lymphoma in the CNS with chemotherapy.⁴⁹

Table 6 summarizes earlier reports regarding the potential for various agents crossing the BBB.⁵²

Specific Agents

Temozolomide TMZ is a novel alkylating agent that is highly bioavailable after oral administration, with effective penetration of the BBB and achievement of therapeutic levels in the cerebrospinal fluid.^{53,54} The dose-limiting toxicity is myelosuppression, which tends to be readily reversible with less cumulative toxicity in comparison with other alkylating agents.⁵⁵ TMZ has reported activity in the treatment of high-grade primary or recurrent gliomas and in metastatic melanoma.⁵⁶⁻⁶¹ Recently, Stupp and coauthors reported a clear survival benefit with TMZ in combination with radiotherapy for newly diagnosed glioblastoma multiforme.⁶² In this large phase III trial, TMZ 75 mg/m² was administered for 6–7 weeks during radiotherapy followed by 6 months of adjuvant therapy. Median survivals of 14.6 months and 12.1 months were

Table 7. Trials of TMZ Plus RT in Newly Diagnosed Brain Metastases

Study	Patients	Dose TMZ and RT	Responses
Antonadou (2002) ⁶⁷ Phase III TMZ + RT vs RT alone	N=108 Lung 82%	TMZ 75 mg/m ² /day + RT (30 Gy WBRT) → TMZ 200 mg/m ² /day D1–5 q28 days (6 cycles)	TMZ + RT 53% RT 33% Patients <60 yrs: TMZ + RT 77% RT alone 37%
Antonadou (2002) ⁶⁶ Phase II TMZ + RT vs RT alone	N=48 Lung 83% Breast 10%	TMZ 75 mg/m ² /day + RT (40 Gy WBRT) → TMZ 200 mg/m ² /day D1–5 q28 days (6 cycles)	TMZ + RT 96% RT alone 67%
Siena (2003) ⁶³ TMZ alone	N=63 Lung 33% Breast 33% Melanoma 33%	TMZ 150 mg/m ² /day D1–3 and D15–21 q28 days (maximum of 1 year)	Lung 24% Breast 19% Melanoma 40%
Dardoufas (2001) ⁶⁵ Phase II TMZ + RT → adjuvant TMZ	N=20 Lung 55% Rectal 15% Breast 15% Melanoma 10%	TMZ 60 mg/m ² /day + RT (WBRT 36–39 Gy) → TMZ 200 mg/m ² /day D1–5 q28 days (6 cycles)	After 3 cycles: CR 20%, PR 35% After 6 cycles: CR 15%, PR 40%
Verger (2005) ¹⁰²	N=82 Lung 51% Breast 16%	TMZ 75 mg/m ² /day + RT (WBRT 30 Gy) → TMZ 200 mg/m ² /day D1–5 q28 days (2 cycles)	TMZ + RT: CR 5%, PR 27% RT alone: CR 5%, 27%

CR=complete response; PR=partial response; RT=radiotherapy; TMZ=temozolomide; WBRT=whole-brain radiotherapy.

reported for the group receiving TMZ plus radiotherapy versus radiotherapy alone, respectively.⁶²

Recent experience with TMZ has shown promising results in patients with newly diagnosed brain metastases (Table 7).^{63–67} For example, Sienna and colleagues reported a response rate of 24% among NSCLC patients with brain metastases not previously irradiated who were treated with TMZ.⁶³ Antonadou and associates reported a statistically significant increase in responses with TMZ plus WBRT (96%) versus WBRT alone (67%), with a trend toward improved survival.⁶⁶ Preliminary results of a confirmatory phase III study of WBRT and TMZ in a series of 108 patients (82% with NSCLC) found that the difference in response rates for brain metastasis was again statistically significant favoring WBRT plus TMZ (response rate, 53%) versus WBRT alone (response rate, 33%), with a trend toward improved survival (8.3 vs 6.3 months).⁶⁷ Response rates in this phase III study were not as impressive as the 96% response rates of TMZ plus radiotherapy reported in the phase II setting, suggesting that patient selection plays a significant role in outcomes. Further, recently reported data have demonstrated modest

disease responses to TMZ for treatment of brain metastases following postradiotherapy relapses (Table 8).^{68–74}

Based on recent observations in patients with lung cancer, there is additional interest in using TMZ to prevent or delay the occurrence of brain metastases. In a phase II study of TMZ in NSCLC, Adonizio and coauthors observed a 3% incidence of brain metastases (1/38).⁷⁵ Similarly, Choong and colleagues observed that only 6.5% (3/46) of NSCLC patients treated with TMZ and irinotecan as second-line therapy developed brain metastasis, and 9 patients with treated brain metastases at enrollment did not demonstrate progression or new metastases during treatment.⁷⁶ As 30–50% of NSCLC patients are expected to develop brain metastasis,^{77–80} based on these data, Robins and associates argued that TMZ may play a role in chemoprevention of brain metastases.⁸¹ This observation has led to ongoing development of clinical trials evaluating TMZ for prophylaxis of brain metastasis in NSCLC.⁸¹

In summary, TMZ has modest single-agent activity for treatment of brain metastases from a variety of solid tumor primaries. Recent data suggest improved response rates occur when TMZ is combined with WBRT, but it

Table 8. Temozolomide for Progressive CNS Disease at Relapse Postradiotherapy

Study	Patients	TMZ dose	Response
Friedman (2003) ⁷⁰	N=52 Lung 56% Breast 10% Melanoma 6%	TMZ 150 mg/m ² /day × 7 days, then 7 days off (continuously until progression)	PR = 3 (2 lung, 1 melanoma) SD = 33 (duration 2–7+ mos)
Giannitto-Giorgio (2002) ⁷²	N=9 All NSCLC	TMZ 200 mg/m ² /day D1–5 q28 days	CR = 3 SD = 3 PD = 3
Mangiameli (2001) ⁷³	N=8 All NSCLC	TMZ 150 mg/m ² /day D1–5 with gemcitabine/vinorelbine or cisplatin	CR = 3 Response = 5
Christodoulou (2001) ⁶⁸	N=28 Lung 61% Breast 14%	TMZ 150 mg/m ² /day D1–5 q28 days	PR = 4% (1/24) SD = 17% (4/24) Improved neurologic status = 37% (10/24)
Abrey (2001) ⁶⁹	N=41 Lung 59% Breast 24% Melanoma 7%	TMZ 150–200 mg/m ² /day D1–5 q28 days	PR = 5% (2/41) SD = 37% (15/41)

CNS=central nervous system; CR=complete response; NSCLC=non-small cell lung cancer; PD= progressive disease; PR=partial response; SD=stable disease; TMZ=temozolomide.

remains to be determined if a survival benefit occurs or if this improved response translates into improved neurocognitive function and quality of life. In the setting of relapsed brain metastases, TMZ provides a small benefit in term of response, and additional studies are planned to investigate the benefit of TMZ in chemoprevention of brain metastasis in high-risk populations.

Methotrexate High-dose methotrexate is an active agent in multiple tumor types and has been observed to produce responses in the setting of brain metastases. High-dose methotrexate achieves good penetration of the BBB, is easily administered, and is fairly well tolerated, with myelosuppression and hepatic transaminitis representing the most common adverse effects. Lassman and colleagues reported results of a retrospective analysis of 32 solid tumor patients with brain metastases treated with high-dose intravenous methotrexate.⁸² The majority of patients had primary breast cancer (91%), and 9 patients had received concurrent radiotherapy, intrathecal chemotherapy, or chemotherapy. A 28% partial response and 28% stable disease rate were observed, with a median overall survival of 19.9 weeks. The response rate among 23 patients who received high-dose methotrexate monotherapy was similar, with a 22% partial response rate.

Other Chemotherapy Agents Additional chemotherapy drugs have been investigated as single agents or

in combination therapy for brain metastases from solid tumors. Combination therapy with etoposide and cisplatin has shown activity as initial therapy for brain metastases from breast carcinoma, NSCLC, and melanoma.⁸³ Teniposide (Vumon, Bristol-Myers Squibb) demonstrates modest activity in brain metastases from lung cancer when administered as a single agent⁸⁴ or in combination with WBRT.⁸⁵ Topotecan produced responses in small-cell lung cancer relapsed after WBRT.⁸⁶ Combination therapy with vinorelbine, gemcitabine (Gemzar, Lilly), and carboplatin as well as cisplatin and vinorelbine has demonstrated activity in brain metastases from NSCLC.^{87,88}

In this regard, a randomized phase III study by Robinet and associates tested the concept of delaying WBRT for brain metastases up to 8 weeks in patients with NSCLC.⁸⁸ The patients in the experimental arm were treated with cisplatin and vinorelbine prior to WBRT. Results demonstrated no survival difference between arms, with an overall median survival of 23 weeks. It is of interest in this study that the intracranial response rate to chemotherapy was remarkably high at 27%, and the WBRT-related response rate was perhaps somewhat low at 33%.⁸⁸ Notably, survival was considerably shorter than predicted based on the retrospective experience of the Southwest Oncology Group (SWOG) in NSCLC patients with brain metastases. In the SWOG experience, the poorest prognostic group with both active brain metastases and systemic disease survived 12 months.⁸⁹

Lapatinib The tyrosine kinase inhibitor lapatinib (Tykerb, GlaxoSmithKline) blocks signaling of EGFR1 and HER2. Recent experience suggests this drug probably crosses the BBB and may have activity in the setting of brain metastases from HER2/neu-positive breast cancer.⁹⁰ Among 39 women with brain metastases from HER2/neu-positive breast cancer (all had developed CNS disease while on trastuzumab and 38 patients had progressed after prior radiotherapy), partial responses and stable disease were observed in 2 and 5 patients, respectively. In addition, volumetric analysis of response in 20 patients demonstrated an improvement of at least 30% in 5 patients and an improvement of 15–30% in 3 patients.⁹⁰

RSR13 RSR13 (Efaproxiral, Allos) is synthetic allosteric modifier of hemoglobin that noncovalently binds to the hemoglobin tetramer and decreases the hemoglobin-oxygen binding affinity, resulting in an increase in tissue pO₂.^{91–93} In contrast to other hypoxic radiosensitizing agents, the radiation-enhancing effect does not rely on direct diffusion of the agent into a tumor cell.⁹² Previous experience with RSR13 in brain metastases from solid tumors has been promising,⁹⁴ leading to the recent reporting of a phase III study of RSR13 plus radiotherapy versus radiotherapy alone in brain metastases (REACH study).⁹³ Although median survival was not significantly prolonged between the groups, overall response rate, median survival, and performance status at 3 months were improved in the subgroup of patients with breast cancer. Among 115 patients with breast cancer, patients randomized to RSR13 demonstrated a median survival of 8.7 months compared with 4.6 months in the control group ($P=.006$). At 3 months posttreatment, 35% of breast cancer patients treated with RSR13 demonstrated stable-to-improved KPS compared with 18% of patients receiving radiotherapy alone ($P=.001$).^{93,95} This has led to a recently completed phase III trial of RSR13 with or without radiotherapy in breast cancer patients with brain metastases (ENRICH study).

Motexafin Gadolinium MGd is a metallotexaphryin that catalyzes the oxidation of intracellular reducing metabolites and generates reactive oxygen species. These reactive oxygen species selectively concentrate in tumor cells and promote apoptosis.^{96,97} Tumor cells that have taken up MGd are visualized by MRI due to the paramagnetism of gadolinium.^{98,99} Based on a promising 72% radiologic response rate observed in a phase I/II study in patients with brain metastases,¹⁰⁰ a large phase III study was performed to determine whether MGd combined with WBRT resulted in improved survival and neurocognitive function in patients with brain metastases from solid tumors.⁴⁷ The SMART trial enrolled 401 patients (251

with NSCLC) who were treated with WBRT to 30 Gy with or without MGd. Although no significant difference was observed between the treatment groups in terms of overall survival (median 5.2 months for MGd plus radiotherapy vs 4.9 months for WBRT; $P=.48$) or neurologic progression, a statistically significant improvement in time to neurologic progression was observed in the subgroup of patients with NSCLC.⁴⁷ These promising results have led to a recently completed industry-sponsored trial of WBRT with or without MGd in NSCLC brain metastases, and preliminary results suggest that in patients receiving timely therapy, neurologic progression is significantly delayed with the use of MGd (10 vs 15.4 months).¹⁰¹

Summary

WBRT remains the standard treatment for brain metastases from solid tumors, although additional options continue to be explored. Experience to date suggests that surgery is an effective treatment option for a select population of patients with stable systemic disease and good performance status. Radiosurgery has shown decreased rates of local relapse as a single intervention with improved survival reported when radiosurgery is combined with WBRT, but ongoing investigation is needed to optimize patient outcomes with radiosurgery as a single agent or in combination with other treatment modalities. Recent data with agents such as TMZ in primary brain tumors offer promise for treatment of brain metastases, and newer radiosensitizing agents (RSR13, MGd) have shown activity in combination with radiotherapy. Equally important is the recent emphasis on preserving neurocognitive function and quality of life during therapy of brain metastases, and ongoing trials are increasingly considering this outcome in the assessment of treatment benefit.

References

1. Wen PY, Black PM, Loeffler JS: Metastatic Brain Cancer, in DeVita V, Hellman S, Rosenberg SA (eds): *Cancer: Principles and Practice of Oncology* (ed 6). Philadelphia, PA, Lippincott, Williams, & Wilkins, 2001, pp 2655–2670.
2. Clayton AJ, Danson S, Jolly S, et al. Incidence of cerebral metastases in patients treated with trastuzumab for metastatic breast cancer. *Br J Cancer*. 2004;91:639–643.
3. Burton RC, Coates MS, Hersey P, et al. An analysis of a melanoma epidemic. *Int J Cancer*. 1993;55:765–770.
4. Dennis LK. Analysis of the melanoma epidemic, both apparent and real: data from the 1973 through 1994 surveillance, epidemiology, and end results program registry. *Arch Dermatol*. 1999;135:275–280.
5. Thomas L, Doyle LA, Edelman MJ. Lung cancer in women: emerging differences in epidemiology, biology, and therapy. *Chest*. 2005;128:370–381.
6. Schellinger PD, Meineck HM, Thron A. Diagnostic accuracy of MRI compared to CCT in patients with brain metastases. *J Neurooncol*. 1999;44:275–281.
7. Borgelt B, Gelber R, Kramer S, et al. The palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys*. 1980;6:1–9.
8. Komarnicky LT, Phillips TL, Martz K, et al. A randomized phase III protocol for the evaluation of misonidazole combined with radiation in the treatment of patients with brain metastases (RTOG 7916). *Int J Radiat Oncol Biol Phys*. 1991;20:53–58.
9. Sause WT, Scott C, Krusch R, et al. Phase I/II trial of accelerated fractionation in brain metastases (RTOG 8528). *Int J Radiat Oncol Biol Phys*. 1993;26:653–657.

10. Murray KJ, Scott C, Greenberg HM, et al. A randomized phase III study of accelerated hyperfractionation versus standard fractionation in patients with unresected brain metastases: a report of the Radiation Therapy Oncology Group (RTOG 9104). *Int J Radiat Oncol Biol Phys.* 1997;39:571-574.
11. Mehta MP, Tsao MN, Whelan TJ, et al. The American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based review of the role of radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys.* 2005;63:36-46.
12. Störtebecker TP. Metastatic tumors of the brain from a neurosurgical point of view: a follow-up study of 158 cases. *J Neurosurg.* 1954;11:84-111.
13. Vieth RG, Odom GL. Intracranial metastases and their neurosurgical treatment. *J Neurosurg.* 1965;23:375-383.
14. DiStefano A, Yong Yap Y, Hortobagyi GN, Blumenschein GR. The natural history of breast cancer patients with brain metastases. *Cancer.* 1979;44:1913-1918.
15. Hendrickson FR, Lee MS, Larson M, Gelber RD. The influence of surgery and radiation therapy on patients with brain metastases. *Int J Radiat Oncol Biol Phys.* 1983;9:623-627.
16. Sundaresan N, Galicich JH, Beattie EJ Jr. Surgical treatment of brain metastases from lung cancer. *J Neurosurg.* 1983;58:666-671.
17. Patchell RA, Cirincione C, Thaler HT, et al. Single brain metastases: surgery plus radiation or radiation alone. *Neurology.* 1986;36:447-453.
18. Mandell L, Hilaris B, Sullivan M, et al. The treatment of single brain metastasis from non-oat cell lung carcinoma: surgery and radiation versus radiation therapy alone. *Cancer.* 1986;58:641-649.
19. Montana GS, Meacham WF, Caldwell WL. Brain irradiation for metastatic disease of lung origin. *Cancer.* 1972;29:1477-1480.
20. Berry HC, Parker RG, Gerdes AJ. Irradiation of brain metastases. *Acta Radiol Ther Phys Biol.* 1974;13:535-544.
21. Markesbery WR, Brooks WH, Gupta GD, Young AB. Treatment for patients with cerebral metastases. *Arch Neurol.* 1978;35:754-756.
22. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med.* 1990;322:494-500.
23. Noordijk EM, Vecht CJ, Haaxma-Reiche H, et al. The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age. *Int J Radiat Oncol Biol Phys.* 1994;29:711-717.
24. Mintz AH, Kestle J, Rathbone MP, et al. A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. *Cancer.* 1996;78:1470-1476.
25. Sturm V, Kober B, Hover KH, et al. Stereotactic percutaneous single dose irradiation of brain metastases with a linear accelerator. *Int J Radiat Oncol Biol Phys.* 1987;13:279-282.
26. Loeffler JS, Kooy HM, Wen PY, et al. The treatment of recurrent brain metastases with stereotactic radiosurgery. *J Clin Oncol.* 1990;8:576-582.
27. Fuller BG, Kaplan ID, Adler J, et al. Stereotactic radiosurgery for brain metastases: the importance of adjuvant whole brain irradiation. *Int J Radiat Oncol Biol Phys.* 1992;23:413-418.
28. Mehta MP, Rozental JM, Levin AB, et al. Defining the role of radiosurgery in the management of brain metastases. *Int J Radiat Oncol Biol Phys.* 1992;24:619-625.
29. Flickinger JC, Kondziolka D, Lunsford LD, et al. A multi-institutional experience with stereotactic radiosurgery for solitary brain metastasis. *Int J Radiat Oncol Biol Phys.* 1994;28:797-802.
30. Alexander E, Moriarty TM, Davis RB, et al. Stereotactic radiosurgery for the definitive non-invasive treatment of brain metastases. *J Natl Cancer Inst.* 1995;87:34-40.
31. Auchter RM, Lamond JP, Alexander E, et al. A multi-institutional outcome and prognostic factor analysis of radiosurgery for resectable single brain metastasis. *Int J Radiat Oncol Biol Phys.* 1996;35:27-35.
32. Engenhardt R, Kimmig BN, Hover K, et al. Long-term follow-up for brain metastases treated by percutaneous stereotactic single high-dose irradiation. *Cancer.* 1993;71:1353-1361.
33. Kihlstrom L, Karlsson B, Lindquist C, et al. Gamma knife surgery for cerebral metastases: the importance of adjuvant whole brain irradiation. *Acta Neurochir Suppl.* 1991;52:89.
34. Shiau CY, Sneed PK, Shu HK, et al. Radiosurgery for brain metastases: relationship of dose and pattern of enhancement to local control. *Int J Radiat Oncol Biol Phys.* 1997;37:375-383.
35. Kondziolka D, Patel A, Lunsford LD, et al. Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. *Int J Radiat Oncol Biol Phys.* 1999;45(2):427-434.
36. Shu HK, Sneed PK, Shiau CY, et al. Factors influencing survival after gamma knife radiosurgery for patients with single and multiple brain metastases. *Cancer J Sci Am.* 1996;2:335-342.
37. Sanghavi SN, Miranpuri SS, Chappell R, et al. Radiosurgery for patients with brain metastases: a multi-institutional analysis, stratified by the RTOG recursive partitioning analysis method. *Int J Radiat Oncol Biol Phys.* 2001;51:426-434.
38. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys.* 1997;37:745-751.
39. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomized trial. *Lancet.* 2004;363:1665-1672.
40. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs. stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA.* 2006;295:2483-2491.
41. Manon R, O'Neill A, Knisely J, et al. Phase II trial of radiosurgery for one to three newly diagnosed brain metastases from renal cell carcinoma, melanoma, and sarcoma: an Eastern Cooperative Oncology Group study (E6397). *J Clin Oncol.* 2005;23:8870-8876.
42. Sneed PK, Lamborn KR, Forstner JM, et al. Radiosurgery for brain metastases: is whole brain radiotherapy necessary? *Int J Radiat Oncol Biol Phys.* 1999;43:549-558.
43. Sneed PK, Suh JH, Goetsch SJ, et al. A multi-institutional review of radiosurgery alone vs. radiosurgery with whole brain radiotherapy as the initial management of brain metastases. *Int J Radiat Oncol Biol Phys.* 2002;53:519-526.
44. Regine WF, Huhn JL, Patchell RA, et al. Risk of symptomatic brain tumor recurrence and neurologic deficit after radiosurgery alone in patients with newly diagnosed brain metastases: results and implications. *Int J Radiat Oncol Biol Phys.* 2002;52:333-338.
45. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA.* 1998;280:1485-1489.
46. DeAngelis LM, Mandell LR, Thaler HT. The role of postoperative radiotherapy after resection of single brain metastases. *Neurosurgery.* 1989;24:798-805.
47. Mehta MP, Rodrigues P, Terhaard CH, et al. Survival and neurologic outcomes in a randomized trial of motexafin gadolinium and whole-brain radiation therapy in brain metastases. *J Clin Oncol.* 2003;21:2529-2536.
48. Meyers CA, Smith JA, Bezjak A, et al. Neurocognitive function and progression in patients with brain metastases treated with whole-brain radiation and motexafin gadolinium: results of a randomized phase III trial. *J Clin Oncol.* 2004;22:157-165.
49. Ott RJ, Brada M, Flower MA, et al. Measurements of blood-brain barrier permeability in patients undergoing radiotherapy and chemotherapy for primary cerebral lymphoma. *Eur J Cancer.* 1991;27:1356-1361.
50. Stewart DJ. A critique of the role of the blood-brain barrier in the chemotherapy of human brain tumors. *J Neurooncol.* 1994;20:121-139.
51. Seute T, Leffers P, Wilmink JT, et al. Response of asymptomatic brain metastases from small cell lung cancer to systemic first-line chemotherapy. *J Clin Oncol.* 2006;24(13):2079-2083.
52. Kortmann RD, Jeremic B, Weller M, et al. Radiochemotherapy of malignant gliomas in adults: Clinical experiences. *Strahlenther Onkol.* 2003;179:219-232.
53. Patel M, McCully C, Godwin K, et al. Plasma and cerebrospinal fluid pharmacokinetics of temozolomide. *Proc Am Soc Clin Oncol.* 1995;14:461a.
54. Agarwala S, Reyderman L, Statkevich P, et al. Pharmacokinetic study of temozolomide penetration into CSF in a patient with dural melanoma. *Ann Oncol.* 1998;9(suppl 4):138a.
55. Brada M, Judson I, Beale P, et al. Phase I dose-escalation and pharmacokinetic study of temozolomide (SCH 52365) for refractory or relapsing malignancies. *Br J Cancer.* 1999;81:1022-1030.
56. Newlands ES, O'Reilly SM, Glaser MG, et al. The Charing Cross Hospital experience with temozolomide in patients with gliomas. *Eur J Cancer.* 1996;32:2236-2241.
57. Newlands ES, Blackledge GR, Slack JA, et al. Phase I trial of temozolomide. *Br J Cancer.* 1992;65:287-291.
58. O'Reilly SM, Newlands ES, Glaser MG, et al. Temozolomide: a new oral cytotoxic chemotherapeutic agent with promising activity against primary brain tumors. *Eur J Cancer.* 1993;29:940-942.
59. Yung WK, Prados MD, Yaya-Tur R, et al. Multicenter phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. *J Clin Oncol.* 1999;17:2762-2771.

60. Yung WK, Albright RE, Olson J, et al. A Phase II study of temozolomide versus procarbazine in a patient with glioblastoma multiforme at first relapse. *Br J Cancer*. 2000;83:588-593.
61. Middleton MR, Grobb JJ, Aaronson N, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patient with advanced metastatic malignant melanoma. *J Clin Oncol*. 2000;18:158-166.
62. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352:987-996.
63. Siena S, Landonio G, Baietta E, et al. Multicenter phase II study of temozolomide therapy for brain metastases in patients with malignant melanoma, breast cancer, and non-small cell lung cancer. *Proc Am Soc Clin Oncol*. 2003. Abstract 407.
64. Biasco G, Pantaleo MA, Casadei S. Treatment of brain metastases of malignant melanoma with temozolomide. *N Engl J Med*. 2001;345:621-622.
65. Dardoufas C, Miliadou A, Skarleas C, et al. Concomitant temozolomide (TMZ) and radiotherapy (RT) followed by adjuvant treatment with temozolomide in patients with brain metastases from solid tumors. *Proc Am Soc Clin Oncol*. 2001. Abstract 2048.
66. Antonadou D, Paraskevaidis M, Sarris G, et al. Phase II randomized trial of temozolomide and concurrent radiotherapy in patients with brain metastases. *J Clin Oncol*. 2002;20:3644-3650.
67. Antonadou D, Coliarakis N, Paraskevaidis M, et al. Whole brain radiotherapy alone or in combination with temozolomide for brain metastases: a phase III study. *Int J Radiat Oncol Biol Phys*. 2002;54(suppl 1):93-94.
68. Christodoulou C, Bafaloukos D, Kosmidis P, et al. Phase II study of temozolomide in heavily pretreated cancer patients with brain metastases. *Ann Oncol*. 2001;12:249-254.
69. Abrey LE, Olson JD, Raizer JJ, et al. A phase II trial of temozolomide for patients with recurrent or progressive brain metastases. *J Neurooncol*. 2001;53:259-265.
70. Friedman HS, Evans B, Reardon D, et al. Phase II trial of temozolomide for patients with progressive brain metastases. *Proc Am Soc Clin Oncol*. 2003. Abstract 408.
71. Giannitto-Giorgio C, Giuffrida D, Cordio S, et al. Oral temozolomide may induce prolonged survival in patients affected by non-small cell lung cancer brain recurrences that progressed after whole-brain radiotherapy. *Ann Oncol*. 2002;13(suppl 5). Abstract 541.
72. Giannitto-Giorgio C, Cordio S, Di Blasi C, et al. Temozolomide shows promising activity against pretreated brain recurrences of non-small cell lung cancer. Preliminary results of a phase II trial. *Proc Am Soc Clin Oncol*. 2002;21. Abstract 2779.
73. Mangiameli A, Giuseppe M, Guglielmo MT, et al. Temozolomide (TMZ) in patients with brain metastases from NSCLC in combination with gemcitabine-cisplatin (GEM-CDDP) or gemcitabine-vinorelbine (GEM+VNB). *Proc Am Soc Clin Oncol*. 2001;20:261b.
74. Ebert BL, Niemierko E, Shaffer K, Salgia R. Use of temozolomide with other cytotoxic chemotherapy in the treatment of patients with recurrent brain metastases from lung cancer. *Oncologist*. 2003;8:69-75.
75. Adonizio CS, Babb JS, Maiale C, et al. Temozolomide in non-small cell lung cancer: preliminary results of a phase II trial in previously treated patients. *Clin Lung Cancer*. 2002;3:254-258.
76. Choong NW, Mauer AM, Hoffman PC, et al. Phase II trial of temozolomide and irinotecan as second line treatment for advanced non-small cell lung cancer. *J Thorac Oncol*. 2006;1(3):245-251.
77. Sorensen JB, Hansen HH, Hansen M, Dombrowsky P. Brain metastases in adenocarcinoma of the lung: frequency, risk groups, and prognosis. *J Clin Oncol*. 1988;6:1474-1480.
78. Newman SJ, Hansen HH. Proceedings: frequency, diagnosis, and treatment of brain metastases in 247 consecutive patients with bronchogenic carcinoma. *Cancer*. 1974;33:492-496.
79. Stuschke M, Eberhardt W, Pottgen C, et al. Prophylactic cranial irradiation in locally advanced non-small-cell lung cancer after multimodality treatment: long-term follow-up and investigations of late neuropsychologic effects. *J Clin Oncol*. 1999;17:2700-2709.
80. Robnett TJ, Machtay M, Stevenson JP, et al. Factors affecting the risk of brain metastases after definitive chemoradiation for locally advanced non-small-cell lung carcinoma. *J Clin Oncol*. 2001. 19:1344-1349.
81. Robins HA, Traynor AM, Mehta MP. Temozolomide as prophylaxis for brain metastasis in non-small cell lung cancer. *J Thorac Oncol*. 2006;1:732-733.
82. Lassman AB, Abrey LE, Shah GD, et al. Systemic high-dose intravenous methotrexate for central nervous system metastases. *J Neurooncol*. 2006;78:255-260.
83. Franciosi V, Cocconi G, Michiara M, et al. Front-line chemotherapy with cisplatin and etoposide for patients with brain metastases from breast carcinoma, nonsmall cell lung carcinoma, or malignant melanoma: a prospective study. *Cancer*. 1999;85:1599-1605.
84. Boogerd W, van der Sande JJ, van Zandwijk N. Teniposide sometimes effective in brain metastases from non-small cell lung cancer. *J Neurooncol*. 1999;41:285-289.
85. Postmus PE, Haaxma-Reiche H, Smit EF, et al. Treatment of brain metastases of small-cell lung cancer: comparing teniposide and teniposide with whole-brain radiotherapy: a phase III study of the European Organization for the Research and Treatment of Cancer, Lung Cancer Cooperative Group. *J Clin Oncol*. 2000;18:3400-3408.
86. Korfel A, Oehm C, von Pawel J, et al. Response to topotecan of symptomatic brain metastases of small-cell lung cancer also after whole-brain irradiation: a multi-center phase II study. *Eur J Cancer*. 2002;38:1724-1729.
87. Bernardo G, Cuzzoni Q, Strada MR, et al. First-line chemotherapy with vinorelbine, gemcitabine, and carboplatin in the treatment of brain metastases from non-small-cell lung cancer: a phase II study. *Cancer Invest*. 2002;20:293-302.
88. Robinet G, Thomas P, Breton JL, et al. Results of a phase III study of early versus delayed whole brain radiotherapy with concurrent cisplatin and vinorelbine combination in inoperable brain metastasis of non-small-cell lung cancer: Groupe Francais de Pneumo-Cancerologie (GFPC) Protocol 95-1. *Ann Oncol*. 2001;12:59-67.
89. Gaspar LE, Chansky K, Albain KS, et al. Time from treatment to subsequent diagnosis of brain metastases in stage III non-small-cell lung cancer: a retrospective review by the Southwest Oncology Group. *J Clin Oncol*. 2005;23:2955-2961.
90. Lin NU, Carey LA, Liu MC, et al. Phase II trial of lapatinib for brain metastases in patients with HER2+ breast cancer. *J Clin Oncol*. 2006;24(18S). Abstract 503.
91. Kleinberg L, Grossman SA, Carson K, et al. Survival of patients with newly diagnosed glioblastoma multiforme treated with RSR13 and radiotherapy: results of a phase II New Approaches to Brain Tumor Therapy CNS Consortium safety and efficacy study. *J Clin Oncol*. 2002;20:3149-3155.
92. Teicher BA, Ara G, Emi Y, et al. RSR13: effects on tumor oxygenation and response to therapy. *Drug Dev Res*. 1996;38:1-11.
93. Suh J, Stea B, Nabid A, et al. Standard whole brain radiation therapy (WBRT) with supplemental oxygen (O2), with or without RSR13 (efaproxiral) in patients with brain metastases: results of the randomized REACH (RT-009) study. *Proc Am Soc Clin Oncol*. 2004. Abstract 1534.
94. Shaw E, Scott C, Suh J, et al. RSR13 plus cranial radiation therapy in patients with brain metastases: comparison with the Radiation Therapy Oncology Group Recursive Partitioning Analysis Brain Metastases Database. *J Clin Oncol*. 2003;21:2364-2371.
95. Suh JH, Stea B, Nabid A, et al. Phase III study of efaproxiral as an adjunct to whole-brain radiation therapy for brain metastases. *J Clin Oncol*. 2006; 24:106-114.
96. Rodrigo P. Motexafin gadolinium: a possible new radiosensitizer. *Expert Opin Investig Drugs*. 2003;12:1205-1210.
97. Magda D, Lepp C, Gerasimchuk N, et al. Redox cycling by motexafin gadolinium enhances cellular response to ionizing radiation by forming reactive oxygen species. *Int J Radiat Oncol Biol Phys*. 2001;51:1025-1036.
98. Viala J, Vanel D, Meingan P, et al. Phases Ib and II multidose trial of gadolinium texaphyrin, a radiation sensitizer detectable at MR imaging: preliminary results in brain metastases. *Radiology*. 1999;212:755-759.
99. Rosenthal DI, Nurenberg P, Becerra CR, et al. A phase I single-dose trial of gadolinium texaphyrin (Gd-Tex), a tumor selective radiation sensitizer detectable by magnetic resonance imaging. *Clin Cancer Res*. 1999;5:739-745.
100. Carde P, Timmerman R, Mehta MP, et al. Multicenter Phase Ib/II trial of the radiation enhancer motexafin gadolinium in patients with brain metastases. *J Clin Oncol*. 2001;19:2074-2083.
101. Mehta MP, Carrie C, Mahe MA, et al. Motexafin gadolinium (MGd) combined with prompt whole brain radiation therapy (RT) prolongs time to neurologic progression in non-small cell lung cancer (NSCLC) patients with brain metastases: results of a Phase 3 trial. *Int J Radiat Oncol Biol Phys*. 2006;66(suppl). Abstract 41.
102. Verger E, Gil M, Yaya R, et al. Temozolomide and concomitant whole brain radiotherapy in patients with brain metastases: a phase II randomized trial. *Int J Rad Oncol Biol Phys*. 2005;61:185-191.
103. Langer CJ, Mehta MP. Current management of brain metastases with a focus on systemic options. *J Clin Oncol*. 2005;23:6207-6219.