



Brain metastasis-Evidence based management

G Biswas, R Bhagwat, R Khurana, H Menon, N Prasad, PM Parikh

Department of Medical Oncology, Tata Memorial Hospital, Parel, Mumbai-400 012, India.

For correspondence:

Purvish Parikh,
Department of Medical Oncology, Tata Memorial Hospital, Parel, Mumbai, India-400 012, Email: purvish@rediffmail.com drgbiswas@yahoo.com

ABSTRACT

Advances in cancer management have resulted in a significant increase in median survival of number of diseases. Consequently we are seeing more patients living long enough to develop symptomatic brain metastases. The management of such patients will be discussed here. The most important definitive investigation is contrast enhanced MRI scan of brain. Management consists of supportive care and disease directed treatment. Surgical resection remains the gold standard for the treatment of solitary brain metastases. Whole brain radiotherapy is considered standard treatment for all patients with brain metastases. The role of chemotherapy was limited in the past. Recently several new agents have been identified as potentially useful. Preliminary results indicate that drugs like temozolomide and topotecan have antitumor activity against the brain metastases as well as the primary systemic malignancies. The goal of multimodality treatment for brain metastases is to palliate local symptoms and prevent consequences of neurological involvement.

KEY WORDS: Brain Metastasis, Management, Temozolomide

INTRODUCTION

Brain metastasis is the most common intracranial tumor in adults. In the Caucasian population, approximately 100,000 patients have symptomatic intracranial metastases annually; a number that is six times more than the 17,000 patients with malignant primary brain tumors. Some autopsy reports indicate a 25% incidence of brain metastasis in patients who die of cancer.^[1] The American Cancer Society estimates that 170,000 cancer patients develop cerebral metastases each year in the United States^[2] and many of these patients harbor two or more metastases.

Most patients develop involvement of the brain late during the course of metastatic cancer. In some types of cancers, brain metastases may occasionally be the first presenting feature. Patients with lung cancer, breast ca and melanoma have a greater propensity for the same.^[3,4]

Pathophysiology

For metastatic cells to reach the brain, the primary tumor usually gets access to the circulation either by invading the venules or lymph channels. Before reaching the brain such circulating tumor cells necessarily pass through the right side of the heart and the first capillary bed they encounter, is the lung. Accordingly, patients with symptomatic brain metastasis usually have involvement of the lung (primary tumors or metastases).

Factors influencing intracranial metastases:^[5]

1) In the resting state, the brain receives 15%-20% of the body's blood flow. This high volume making it likely that circulating tumor cells will have greater chance of reaching the brain.

2) Tumor cells from certain primaries find the brain an appropriate place for metastatic colony formation and growth. This is one of the reasons that the probability of brain metastases varies among tumor types. In adults, the commonest primary tumor is lung, followed by breast, skin and colon [Table 1].^[6] In the younger age groups, sarcomas (osteogenic and Ewing's) and germ cell tumors are more common.^[6] Renal, colon and breast carcinomas generally produce single metastases whereas malignant melanoma and lung generally produce multiple secondary lesions.^[6]

3) The site distribution of brain metastases is also determined by the size of the region and its vasculature. Hence, about 85% of brain metastases are found in the cerebral hemispheres- in the watershed area between middle and posterior cerebral arteries. Approximately 10%-15% of metastases are found in the cerebellum and only about 3% of metastases are found in the brainstem. Renal-cell, gastrointestinal and pelvic cancers tend to metastasize to the infratentorial area, whereas breast carcinoma is commonly found in the posterior pituitary.

Clinical features

The signs and symptoms of brain metastasis are





related to the involved brain area [Table 2].^[7] Most patients presents with headache or focal neurological deficits. Common focal symptoms include muscle weakness, gait disturbances, visual field defects and aphasia.

Symptoms usually evolve over a few weeks. However, hemorrhage into the metastases can result in a more dramatic presentation. Such propensity to bleed is commonly seen with tumors like malignant melanoma, thyroid ca, renal cell ca and choriocarcinoma.

Diagnosis

Proper pretreatment evaluation is important in determining the optimum treatment strategy for patients with multiple brain metastases [Table 3]. For brain metastases, the term ‘solitary’ indicates the absence of extracranial metastatic disease, whereas the term ‘single’ merely indicates the presence of one brain metastasis with no implication as to the status of extracranial disease.^[9] Single brain metastases constitute up to 50% of all brain metastases presentations.

CT or MRI establishes the diagnosis of brain metastases. MRI is the superior test and should be performed whenever feasible in any patient being evaluated for metastatic brain disease. A high-quality, contrast-enhanced MR scan should be obtained to define the number of metastatic nodules and

to look for evidence of leptomeningeal disease. If MRI is unavailable, CT is adequate to exclude brain metastases in most patients, but it can miss small lesions or tumors located in the posterior fossa. PET scans have a sensitivity of only 75% and a specificity of 83% for identification of cerebral metastases. Therefore, they are less accurate than MRI, which remains the gold standard.^[10]

On CT or MRI, most brain metastases are enhancing lesions surrounded by edema, which extends into the white matter. Unlike primary brain tumors, metastatic lesions rarely involve the corpus callosum or cross the midline. The radiographic appearance of brain metastases is nonspecific and may mimic other processes, such as infection. Therefore, the CT or MR scan must always be interpreted within the context of the clinical picture of the individual patient, particularly since cancer patients are vulnerable to opportunistic CNS infections or may develop second primaries, which can include primary brain tumors.^[10]

Table 1: Five cancers with common occurrence of brain metastasis^[6]

Lung cancer	25-30%
Breast cancer	22-25%
Melanoma	11%
Renal cell cancer	<5%
Uterine cancer	<5%

Table 2: Signs and symptoms^[8]

Signs/ symptoms	% Of Patients
Generalized	
Headache	24
Cognition and behavioral abnormalities	14
Focal	
Hemiparesis	20
Gait disturbances	07
Others	
Seizure	
Visual field defect	
Aphasia	
Nausea/ Vomiting	
No symptoms	

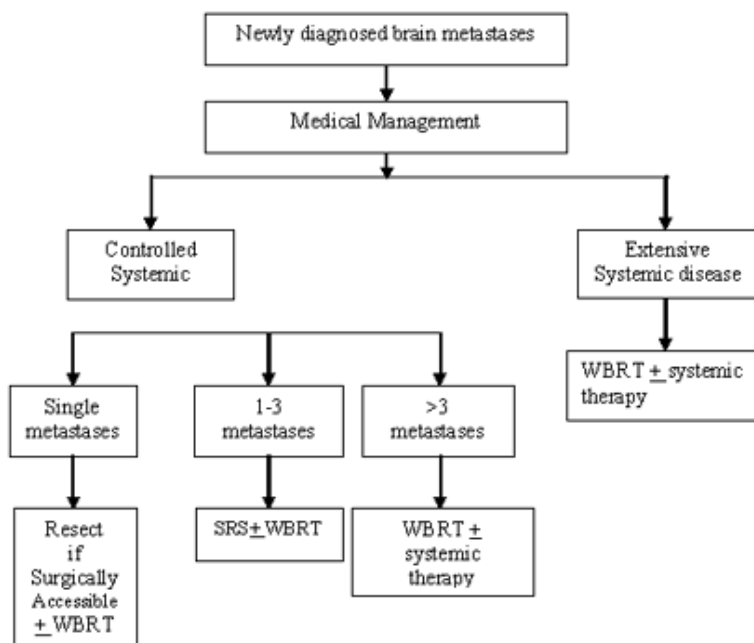


Figure 1: 1 Newly diagnosed brain metastasis management flowchart^[11]



Treatment modalities [Table 4]

Management consists of symptomatic care and definitive treatment [Figure 1]. Symptomatic management can result in a significant improvement in quality of life for patients with brain metastasis. The goals of surgery are to obtain immediate symptom relief, gain local control of the metastasis and histological confirmation. Whole brain radiotherapy delay progression of neurologic deficits and decrease steroid dependency. Chemotherapy currently has a limited role in the treatment of brain metastases.

1. Medical Management

Vasogenic edema secondary to metastasis typically responds to treatment with corticosteroids. For initial symptom control, dexamethasone is administered at loading dose of 10-20mg followed by doses of 4mg four times a day.^[12] This usually results in rapid reduction of the edema and symptom control. Side effects associated with corticosteroids include myopathy, hyperglycemia, edema, weight gain, vascular necrosis and psychosis. All cancer patients on prolonged corticosteroids should receive prophylactic therapy for pneumocystis carini pneumonia^[9]. Steroids should be tapered as early as possible (decreasing the dose every three days, as tolerated) to minimize side effects.

Anticonvulsants are indicated for all patients who develop a seizure. Prophylactic anticonvulsants have not been shown to be beneficial except in metastasis to motor cortex, synchronous brain metastases and leptomeningeal metastasis.^[9] Prophylactic use has the potential to complicate patient management by increasing the risk of medication

Table 3: Investigations

Baseline	Definitive
CBC	Site specific
Biochemistry	CE CT Scan
Chest X-ray	MRI
Ultrasound	Others

Table 4: Treatment Modalities

Supportive care	Definitive
Medical	Surgery
Corticosteroids	Radio surgery
Anticonvulsants	WBRT
	Chemotherapy
	Others

Table 5: RTOG recommendations^[32]

RPA Class	Description	Median survival	Recommended
II	KPS ≥ 70 Age < 65 Controlled Primary No systemic metastases	7.1 mths	Aggressive focused therapy if possible + WBRT
III	KPS ≥ 70 and one or more of the following Age > 65 Uncontrolled Primary Systemic metastases	4.2 mths	WBRT
IIII	KPS < 70	2.3 mths	WBRT or Palliative care

related side effects and drug interactions.^[13] It is recommended to use non-hepatic-enzyme inducing anticonvulsants such as lamotrigine, levetiracetam and gabapentin to control seizures, as these do not increase the clearance of chemotherapeutic agents via the cytochrome P450 isoenzyme CYP3A system.

Vigilance for less common complications of brain metastasis, such as the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is critical.

2. Radiotherapy

Whole brain Radiotherapy (WBRT)

WBRT is considered standard treatment for the patients with brain metastases. WBRT was first described nearly 50 years ago by Chao et al.^[14] It may prevent or delay the progression of neurologic deficits, restore function and decrease steroid dependency.

A dose of 20Gy in 5 fractions or 30Gy in 10 fractions is recommended.^[15,16] Accelerated hyperfractionated regimens delivering up to 70.4 Gy focal radiation offer no additional benefit relative to the conventional schedule.^[17,18] Data suggests that early whole brain radiotherapy improves neurological control. But there is no clear survival benefit, with average survival 3-4 months in about 50% of the patients from brain metastases.^[19,20] As a result, many practitioners are inclined to defer WBRT until the disease in the brain becomes symptomatic.

Patients with low KPS scores and progressive systemic disease often receive WBRT alone. In patients with high KPS scores and systemic disease under control, WBRT is often considered if there are new or recurrent lesions following resection or radiosurgery.^[21]

The acute toxicities of WBRT include headache, nausea, vomiting, ear blockade, mild-to-moderate fatigue, temporary hair loss and skin hyperpigmentation.

Limited information exists about the long-term impact of WBRT. Larger fractions of radiation (3–6 Gy) can contribute to a greater incidence of late toxicities like progressive dementia, ataxia and even urinary incontinence.^[22] CT identified cortical atrophy and hypodense white-matter changes in one study.^[23] Those changes were most likely due

Table 6: Randomized Studies of Surgery (or SRS) Plus WBRT v WBRT alone

Study	No of brain mets	n	Median Survival (m)
Surgery			
Patchell et al, 1990 ^[36]	1	25/23	9.3 vs 3.5, p <.01
Vecht et al, 1993 ^[43]	1	32/31	10 vs 6, p =.04
Mintz et al, 1996 ^[44]	1	41/43	5.6 vs 6.3, p =.24
SRS			
Kondziolka et al, 1999 ^[45]	2-4	13/14	11 vs 7.5, p =.22
Chougule et al, 2000 ^[46]	3	36/37/31	7 vs 5 vs 9
Andrews et al, 2004 ^[47]	1-3	333	6.5 vs 5.7, p =.13



to demyelination secondary to irradiation of the brain.^[24]

Radiation Sensitization for Brain Metastases

a) RSR 13 (Efafproxiral) is an allosteric modifier of hemoglobin that decreases the affinity of hemoglobin binding to oxygen, permitting greater oxygenation of hypoxic tumor cells, to enhance radiation cell killing.^[25] A randomized, phase III study of WBRT with or without efafproxiral^[26] involving 538 patients did not demonstrate significant increase in median survival in the combined arm. A subset analysis of 115 breast cancer patients (20% of the study population) suggested a possible survival advantage.^[26]

b) Motexafin gadolinium is the first of a new class of drugs known as texaphyrins, which are porphyrin-like macrocyclic compounds that forms complex with large metal cations.^[27] MRI studies have shown that motexafin gadolinium is selectively retained in tumor cells.^[28] Inside the tumor cell, it generates reactive oxygen species and oxidizes various intracellular reducing metabolites in a process known as 'futile redox cycling'.^[27,29] This leads to altered cellular metabolism, inhibition of DNA repair and promotes apoptosis.^[27,30] Tumor cells containing motexafin gadolinium may therefore be more vulnerable to the ionizing effects of radiation or the effects of chemotherapy. It has been tested in phase I to III trials in patients with brain metastases.

A phase III study was conducted to determine whether motexafin gadolinium used with WBRT would improve neurologic function and survival.^[31] Time to neurologic progression, time to loss of functional independence and radiologic response rates were secondary efficacy end points. The results of this study^[31] suggest that motexafin gadolinium does not improve survival. Other end points, especially in NSCLC, may be improved like the median time to neurologic progression.

Recent work published by the Radiotherapy oncology group (RTOG) has delineated specific prognostic categories for patients with newly diagnosed brain metastases [Table 5].^[32] Based on these criteria following treatment algorithm has been proposed.

3. Surgery

The goals of surgery in the management of brain metastases are to obtain immediate symptom relief, gain local control and histological confirmation.^[33] Lesions surgically accessible have made improvements in stereotactic techniques, cortical mapping and the use of ultrasonography.^[34] Surgery is an important modality for patients with a single brain metastasis, particularly when favorable prognostic factors and systemic disease control are present.^[35]

A landmark trial demonstrated that selected patients with resectable single brain metastases randomized to undergo resection and WBRT survived longer than did those who

underwent biopsies and WBRT alone^[36] [Table 6]. This randomized trial and a confirmatory trial have established surgery and postoperative irradiation as the standard approach for such patients.^[37] Retrospective data from the Memorial Sloan-Kettering Cancer Center^[38] and the M.D. Anderson Cancer Center^[39] on the surgical management of brain metastases from breast cancer showed a median survival of approximately 16 months.

The role of surgery in patients with multiple brain metastases is controversial. In a retrospective review,^[40] in patients with multiple metastases who underwent resection of all their lesions, a longer survival length (median 14 months) was found as compared with those with multiple metastases not resected (median 6 months) ($p = 0.003$).

4. Stereotactic Radiosurgery (SRS)

Stereotactic radiosurgery, in which high doses of focused radiation are delivered by a linear accelerator or by gamma knife to the brain metastases,^[3] has emerged as a treatment for patients with metastatic brain disease with or without WBRT [Table 6].

The hallmark of SRS is the rapid dose fall off at the target edges, permitting a clinically significant dose to be given to the target while a clinically insignificant dose is delivered to the surrounding normal brain.^[33]

The advantages of SRS include lower risk of hemorrhage, infection and tumor seeding. Surgery immediately relieves the mass effect, provides a tissue diagnosis and has no risk of radiation necrosis.^[42]

The effect of SRS combined with WBRT in patients harboring two to four metastases has been shown to be superior to WBRT alone^[45-47] in the control of metastatic brain disease [Table 6]. The largest and most credible randomized study to date was conducted by the RTOG [Table 6]. In this trial, 333 patients were randomly assigned to WBRT or WBRT plus SRS. The overall trial demonstrated no significant improvement in survival. The prespecified group of patients with a single metastasis, however, experienced significant improvement in median survival (6.5 v 4.9 months; $P = .05$). In this study, radiosurgery technique (ie, linear accelerator v gamma knife) had no impact on outcome.

The treatment dose to the tumor margin typically is between 15 to 20 Gy and is based on tumor size, location, history of prior radiotherapy and dose overlap from the treatment of other radiosurgical metastases.

5. Chemotherapy

The primary hurdle in developing chemotherapy regimens for patients with brain metastases is that the intact blood-brain barrier (BBB) is largely impermeable to most chemotherapeutic drugs. However, the microcirculation of





cerebral metastases differs substantially from that of the normal blood-brain barrier. This is inferred from the leakage of gadolinium or iodinated contrast into brain metastases observed in MRI or CT scans, respectively.

By the time most patients develop brain metastases, they have already been exposed to the most effective chemotherapeutic agents and the metastatic clones are relatively chemo resistant. Although BBB is disrupted in patients with brain metastases, water-soluble chemotherapy may not penetrate sufficiently to attain a therapeutic concentration. Newly diagnosed patients who are chemotherapy naive and neurologically asymptomatic may respond favorably to systemic chemotherapy.

Treatment efficacy is determined by the sensitivity of tumor cells to chemotherapeutic agents and whether or not these drugs can cross the BBB. Among the various tumor types, brain metastases from small-cell lung cancer, germ cell tumors and lymphoid malignancies are perhaps the most sensitive to chemotherapy, whereas brain metastases from non-small-cell lung cancer (NSCLC) and breast cancer are somewhat less sensitive to chemotherapy.^[1]

An objective response rate (ORR) of 82% and a median survival time of 34 weeks^[49] were reported in patients with chemosensitive brain metastases from SCLC who was treated initially with cyclophosphamide, doxorubicin, vincristine and etoposide. In patients with brain metastases from breast cancer at initial diagnosis, cisplatin and etoposide yielded a high ORR of 55% in the central nervous system (CNS), whereas response rates of 17%-59% were seen in those treated with combination chemotherapeutic regimens that included: cyclophosphamide, doxorubicin and prednisolone; cyclophosphamide, doxorubicin, prednisone, methotrexate and vincristine; methotrexate, vincristine and prednisolone; cyclophosphamide and doxorubicin; cyclophosphamide, methotrexate and 5-fluorouracil; and cyclophosphamide, doxorubicin and 5-fluorouracil.^[50-52]

Although the role of chemotherapy for brain metastases still remains controversial, a new generation of chemotherapeutic agents those have the ability to cross an intact or physiologically normal BBB, hold promise.

a) Temozolomide (TMZ)

This small molecule is a third generation alkylating agent, which is 100% bioavailable when taken orally. Because of its

Table 7: Single agent activity of TMZ^[57,59,61 62]

Disease	Prev CT	n	ORR(%)	Response duration(m)	Median survival (m)
Breast ca	Yes				
SCLC	Yes	5	0	NR	NR
NSCLC	Yes	22	9	NR	NR
NSCLC	Yes	12	8	3	4.5
Melanoma	No	156	13	6	7.7

small size and lipophilic properties, it crosses the BBB.^[53] Concentrations in the central nervous system are approximately 30% of plasma concentrations. Once it has entered the central nervous system, TMZ can be spontaneously converted to the active metabolite (MTIC).^[54]

Unlike, nitrosoureas and other alkylating agents that chemically cross-link the DNA and are associated with severe, dose limiting, cumulative hematological toxicity, TMZ is associated with generally mild, noncumulative myelosuppression.^[55]

Based on the favorable toxicity profile observed in early clinical trials, subsequent studies have investigated doses of 150 mg/m²/day for 5 days for patients who had previously been treated with cytotoxic chemotherapy with a planned increase to 200 mg/m²/day if no major myelosuppression was evident on day 22 of the 28-day cycle. For previously untreated patients, the initial dose is typically 200 mg/m²/day for 75 days. The most common nonhematologic adverse events are nausea, vomiting, headache, fatigue and constipation. These events are generally mild to moderate in severity.^[55]

Limited response rates have been obtained in metastatic melanoma (13.5%) and NSCLC (0-8%)^[56-58] [Table 7]. In newly diagnosed brain metastases patients with progression after WBRT show ORRs between 5 and 10%.^[59,60]

Several phase II trials suggest that single-agent temozolomide

Table 8: Phase II Studies of Temozolomide in Brain Metastases Patients

Study	Tmz dose (mg/m ² /d)	n	ORR/SD (%)	Median survival (m)
Single agent				
Christodoulou et al, 2001 ^[61]	150 x 5 d, q 4wk	27	4/17	4.5
Abrey et al, 2001 ^[62]	150 x 5 d, q 4 wk	41	6/44	6.6
Dziedziszko et al, 2003 ^[57]	200 x 5 d, q 4 wk	13	0/23	NR
Friedman et al, 2003 ^[59]	150 x 7 d, q 2 wk	52	6/23	NR
Siena et al, 2003 ^[60]	150 x 7 d, q 2 wk	63	24 (PR+SD)	NR
Agarwal et al, 2004 ^[66]	200 x 5 d, q 4 wk	117	6/26	3.5
Giorgio et al, 2005 ^[67]	150 or 200 x 5 d, q 4 wk	30	10/10	NR
With WBRT				
Dardoufas et al, 2001 ^[65]	60 + WBRT 36-39 Gy	20	55/30	NR
Antonadou et al, 2002 ^[63]	75 + WBRT 40 Gy	48	96/4	8.6
Verger et al, 2002 ^[64]	75 + WBRT 30 Gy	44	NR/50	3.5
With cisplatin (CDDP)				
Christodoulou et al, 2005 ^[68]	150 or 200 + CDDP 75 mg / m ² , d 1, q 4 wk	32	31/16	5.5





[Table 7] has modest activity in patients with recurrent or progressive brain metastases. The efficacy and safety of using temozolomide concurrently with WBRT for patients with newly diagnosed brain metastases was evaluated in four recent phase II studies [Table 8]. The largest of these trials enrolled 134 patients, 82% with lung cancer. Patients were randomly assigned to receive temozolomide (75 mg/m²/d) plus WBRT (10 fractions of 3 Gy each) or WBRT alone. In addition, patients in the combined therapy group continued to receive temozolomide (200 mg/m² days 1 through 5 every 4 weeks for six cycles) beginning 1 month after completing WBRT. The group receiving WBRT plus temozolomide experienced a significant improvement in response rate compared with those receiving WBRT alone (53% v 33%; *P* = .039). Patients younger than 60 years and those with KPS more than 90 realized even greater relative benefit (*P* = .003). There was no significant difference in neurologic response. The temozolomide arm yielded a nonsignificant trend toward improved survival compared with WBRT alone (8.3 v 6.3 months; *P* = .179) [Table 8].

Chemoradiation studies with temozolomide have shown encouraging results with an objective response rate in 96% of patients versus 66% in the WBRT group^[63] [Table 8]. This impressive data is not seconded by other trials.

b) Topotecan

Topotecan is a semisynthetic camptothecin derivative that selectively inhibits topoisomerase I in the S phase of the cell cycle. The activity, tolerability and symptom improvement associated with topotecan has established the clinical value of topotecan as second-line therapy in patients with SCLC and ovarian cancer.^[69,70]

Topotecan freely penetrates the BBB and measurable levels of topotecan and its metabolite can be detected in CSF.^[71] This may be attributed to its low protein binding in serum (20% of less) relative to other camptothecins.^[71] The emerging data suggest that systemically administered topotecan has antitumor activity against brain metastases.

The potential antitumor activity of topotecan against brain metastasis has been investigated in several studies [Table 9]. These studies support the use of topotecan as a first line treatment for newly diagnosed brain metastases in SCLC particularly in platinum-sensitive patients. A comparison of the responses of cerebral and extracerebral lesions to topotecan treatment suggests that the responses in the former occurred more rapidly.^[78] This may be explained by the lack of exposure of brain metastasis to prior cytotoxic agents. Responses or disease stabilization in the brain often occurred in patients with progressive extracerebral lesions suggesting that cranial and extracranial metastases may have heterogenous topotecan sensitivities.

The feasibility of topotecan as a radiosensitizer has been

Table 9: Trials with Single agent Topotecan in brain metastasis^[72-77]

Disease	Prev CT	Dose	n	ORR	Median OS	Toxicity
Breast cancer	yes	1.5mg/m ² d1-5 q 3 wks	16	6 (38%)	6.3 m	hemat
SCLC	yes	As above*	16		-	hemat
SCLC	yes	As above	7		-	hemat
SCLC	yes	As above	9	5 (56%)	-	
***22 SCLC + 2 NSCLC	yes	1.3-1.5 mg/m ² d1-d5 q 4 wks*	24	12 (50%)	6.3 m	UK
SCLC****	yes	1.25-1.5 mg/m ² /day d1-d5 q 21 days	30	33%	-	UK

*2 patients received 0.4 mg/m²/day as CIV over 21 days q 28 days; ** 1 PD in CNS; *** Retrospective analysis of various studies; **** Half the patients had received platinum based CT and 8 pts received WBRT UK- unknown

studied in phase I and II studies. The phase I study^[79] included topotecan in a dose of 1.5 mg/m² on days 1-5 of a 21 day cycle and WBRT in a dose of 60 Gy in 30 fractions over 6 weeks and the phase II study^[80] had a continuous IV infusion of topotecan in dose of 0.4-0.6 mg/m²/day for 21 days in combination with WBRT. Although there was no statistically significant survival advantage over other therapies, the combination was well tolerated.

c) Combination Chemotherapy

The combination of a topoisomerase 1 inhibitor with an alkylating agent has demonstrated synergy in preclinical studies. Following this it was hypothesized that the combination of topotecan with temozolamide may enhance the cytotoxic activity of these two agents. A phase I study^[81] using this combination demonstrated partial responses (PR) in 3 pretreated patients and stable disease (SD) in 7 of the 25 patients treated with various dosage schedules of the two drugs. In view of dose-limiting febrile neutropenia, this study recommended topotecan in a dose of 1.5 mg/m²/day along with temozolamide in a dose of 150 mg/m² daily for 5 days for future phase II trials.

d) Paclitaxel

The role of paclitaxel was reported in a phase III study^[82] in which 86 patients were randomly assigned to receive paclitaxel or WBRT alone. 52 Grade 3/4 toxicity was higher in the paclitaxel group, but median survival was not improved.

Chemotherapy may be useful in the setting of recurrent brain metastases. At recurrence, most patients have multiple lesions that are not amenable to radiotherapy or focal therapy. The majority have active and often symptomatic systemic tumor. The clinical scenario makes palliative chemotherapy an appropriate intervention. Chemotherapy currently has a limited but increasing role in the treatment of brain metastases. Though WBRT is still the standard of care, immediate (first-line) chemotherapy may be considered in patients with a chemo-sensitive primary tumour, with



clinically asymptomatic brain metastases, or with only minor neurological signs and symptoms and in whom there is an indication for systemic chemotherapy for metastases elsewhere in the body.

6. Chemoradiation

In-vitro studies have suggested an increased cell kill using topotecan in combination with irradiation.^[83] The use of cisplatin, carmustine and etoposide with WBRT was studied in a phase II trial^[84] in patients with NSCLC and SCLC. Of the 60 patients there were 35 (58%) CNS responses, of which 25 (42%) had a CR. The median survival was 7.4 months; at 18 months the survival rate was 19%. A phase III study^[85] with cisplatin and vinorelbine and WBRT either sequentially or concurrently showed no difference in the overall response rates (27% in both treatment arms) or median survival time (14 weeks versus 8 weeks). The study however suggested that chemoradiation is feasible, myelosuppression being the only important toxicity.

7. Gefitinib

Gefitinib, an inhibitor of the epidermal growth factor receptor-associated tyrosine kinase is an orally active drug. It enhances the antitumor activity of radiation. The activity of gefitinib in brain metastases patients has also been suggested in several case reports.^[86-88] On the basis of these reports, a phase II study^[88] was conducted. Gefitinib was administered orally at a dose of 250 mg daily to 27 patients. Twenty patients (74%) had received previous first-line platinum-based chemotherapy and 11 patients (41%) had received previous WBRT. At the time of the study report, efficacy results were available for the first 20 patients. Gefitinib produced partial response in six patients (30%) and SD in five other patients (25%). In terms of brain metastases, two patients (10%) had responses, including one with complete remission. Both of these patients had been treated with WBRT for more than 3 months before starting gefitinib. Toxicity consisted of grade 1/2 skin toxicity (20%) and grade 2 diarrhea (10%).

Prognosis

Once brain metastases have developed, the patient's overall prognosis is poor, with a median survival of 4–5 months and a 1-year survival of approximately 10%.^[89] Important prognostic factors [Table 10] for a better survival are a good performance status, absence of extracranial metastases, controlled primary tumor and age less than 65 years. When all these factors were present, the median survival time was more than 7 months, but if one of them was absent the median survival fell to around 4 months. The treatment options and related outcome has been presented in Table 11.

CONCLUSION

Improvement in therapy for systemic cancer has resulted in an increase in a number of patients living long enough to

Table 10: Prognosis

Prognostic factors	
Performance status	
Mental status	
Response to steroids	
Activity of systemic tumor	
Treatment modality	
Others	
Age	
Site of primary tumor	
Number of brain mets	

Table 11: Options and outcome^[89]

Therapeutic options and expected outcomes (m)	
Untreated	1–2
Corticosteroids	2–3
WBRT	3–6
Surgery with adjuvant WBRT	10–16
SRS and WBRT	6–15
Chemotherapy	8–12

develop brain metastases. Clearly, they pose a major threat to the patient's well being and quality of life with an increased risk of developing neurological and cognitive deficits. In most patients, such metastases are diagnosed late in the disease course. Although the average prognosis for an individual with brain metastases is poor, selected patients will benefit significantly from aggressive local therapy or judicious use of chemotherapy.

REFERENCES

1. Posner JB. Neurologic Complications of Cancer. F.A. Davis Company: Philadelphia; 1995.
2. Davey P. Brain metastases: Treatment options to improve outcomes. *CNS Drugs* 2002;16:325–38.
3. Ewend MG, Carey LA, Morris DE, Harvey RD, Hensing TA. Brain metastases. *Curr Treat Options Oncol* 2001;2:537–47.
4. Lassman AB, DeAngelis LM. Brain metastases. *Neurol Clin N Am* 2003 21:1–23.
5. Delattre JY, Krol G, Thaler HT, Posner JB. Distribution of brain metastases. *Arch Neurol* 1998;45:741–4.
6. Subramanian A, Harris A, Piggott K, Shieff C, Bradford R. Metastasis to and from the central nervous system—the 'relatively protected site'. *Lancet Oncol* 2002;3:498–507.
7. Tsukada Y, Fouad A, Pickren JW, Lane WW. Central nervous system metastasis from breast carcinoma. Autopsy study. *Cancer* 1983;52:2349–54.
8. DeAngelis LM, Posner JB. Brain Metastasis. *Cancer Medicine* 6th edn. 2004. p. 1227–31.
9. Wen PY, Shafman TD. Site-specific therapy of metastatic breast cancer. *In: Harris JR, editor. Disease of the Breast. Philadelphia: Lippincott Williams and Wilkins; 2000. p. 841–53.*
10. DeAngelis LM, Loeffler JS, Mamelak AN. Metastatic brain tumors. *Cancer management: a multidisciplinary approach.* 607–14.
11. Mehta MP, Tremont I. Brain metastases. *In: Furie B, Cassileth P, Atkins MB, Mayer RJ editors): Clinical Hematology and Oncology: Presentation, Diagnosis and Treatment. Philadelphia, PA: Churchill Livingstone; 2003. p. 1062–76.*
12. Levin VA, Prados MR, Wara WM, Davis RL, Gutin PH, Phillips TL, et al. Radiation therapy and bromodeoxyuridine chemotherapy followed by procarbazine, lomustine and vincristine for the treatment of anaplastic gliomas. *Int J Radiat Oncol Biol Phys* 1995;32:75–83.



13. DeAngelis LM, Gutin PH, Leibel SA, et al, editors. Intracranial tumors: diagnoses and treatment. London: Martin Dunitz; 2002. p. 367–94.
14. Chao JH, Phillips R, Nickson JJ. Roentgenray therapy for cerebral metastases. *Cancer* 1954;7:682–9.
15. Borgelt B, Gelber R, Kramer S, Brady LW, Chang CH, Davis LW, et al. The palliation of brain metastases: final results of two studies by the radiation therapy oncology group. *Int J Radiat Oncol Biol Phys* 1980;6:1–9.
16. Kurtz JM, Gelber R, Brady LW, Carella RJ, Cooper JS. The palliation of brain metastases in a favorable patient population: a randomized clinical trial by the radiation therapy oncology group. *Int J Radiat Oncol Biol Phys* 1981;7:891–5.
17. Sause WT, Scott C, Krisch R, Rotman M, Sneed PK, Janjan N, et al. Phase I/II trial of accelerated fractionation in brain metastases RTOG 85–28. *Int J Radiat Oncol Biol Phys* 1993;26:653–7.
18. Murray KJ, Scott C, Greenberg HM, Emami B, Seider M, Vora NL, et al. A randomized phase III study of accelerated hyperfractionation versus standard in patients with unresected brain metastases: A report of the Radiation Therapy Oncology Group (RTOG) 9104. *Int J Radiat Oncol Biol Phys* 1997;39:571–4.
19. Taimur S, Edelman MJ. Treatment options for brain metastases in patients with non-small cell lung cancer. *Curr Treat Options Oncol* 2003;4:89–95.
20. Regine WF, Scott C, Murray K, Curran W. Neurocognitive outcome in brain metastases patients treated with accelerated-fractionation vs. accelerated-hyperfractionated radiotherapy: An analysis from Radiation Therapy Oncology Group study 91–04. *Int J Radiat Oncol Biol Phys* 2001;51:711–7.
21. Chang SD, Adler JR. Current treatment of patients with multiple brain metastases. *Neurosurg Focus* 2000;9.
22. DeAngelis LM, Mandell LR, Thaler HT, Kimmel DW, Galicich JH, Fuks Z, et al. The role of postoperative radiotherapy after resection of single brain metastases. *Neurosurgery* 1989;24:798–805.
23. DeAngelis LM, Mandell LR, Thaler HT, Kimmel DW, Galicich JH, Fuks Z, et al. The role of postoperative radiotherapy after resection of single brain metastases. *Neurosurgery* 1989;24:798–805.
24. Asai A, Matsutani M, Kohno T, Nakamura O, Tanaka H, Fujimaki T, et al. Subacute brain atrophy after radiation therapy for malignant brain tumor. *Cancer* 1989;63:1962–74.
25. Amorino GP, Lee H, Holburn GE, Paschal CB, Hercules SK, Shyr Y, et al. Enhancement of tumor oxygenation and radiation response by the allosteric effectors of hemoglobin, RSR13. *Radiat Res* 2001;156:294–300.
26. Suh JH. A phase 3, randomized, open-label, comparative study of standard whole brain radiation therapy (WBRT) with supplemental oxygen (O₂), with or without RSR13, in patients with brain metastases. *Neurooncol* 2003;5:345–6.
27. Magda D, Lepp C, Gerasimchuk N, Lee I, Sessler JL, Lin A, 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;51:1025–36.
28. Carde P, Timmerman R, Mehta MP, Koprowski CD, Ford J, Tishler RB, et al. Multicenter phase Ib/II trial of the radiation enhancer motexafin gadolinium in patients with brain metastases. *J Clin Oncol* 2001;19:2074–83.
29. Mehta MP, Shapiro WR, Glantz MJ, Patchell RA, Weitzner MA, Meyers CA, et al. Lead-in phase to randomized trial of motexafin gadolinium and whole-brain radiation for patients with brain metastases: Centralized assessment of magnetic resonance imaging, neurocognitive and neurologic end points. *J Clin Oncol* 2002;20:3445–53.
30. Xu S, Zakian K, Thaler H, Matei C, Alfieri A, Chen Y, et al. Effects of motexafin gadolinium on tumor metabolism and radiation sensitivity. *Int J Radiat Oncol Biol Phys* 2001;49:1381–90.
31. Mehta MP, Rodrigus P, Terhaard CH, Rao A, Suh J, Roa W, 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;1:2529–36.
32. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, 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;37:745–51.
33. Wen PY, Loeffler JS. Management of brain metastases. *Oncology (Huntingt)* 1999;12:941–54,957–61;discussion 961–62,969.
34. Lang FF, Sawaya R. Surgical management of cerebral metastases. *Neurosurg Clin N Am* 1996;7:459–84.
35. Sperduto PW. A review of stereotactic radiosurgery in the management of brain metastases. *Technol Cancer Res Treat* 2003;2:105–10.
36. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* 1990;322:494–500.
37. Noordijk EM, Vecht CJ, Haaxma-Reiche H, Padberg GW, Voormolen JH, Hoekstra FH, 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;29:711–7.
38. Wronski M, Arbit E, McCormick B. Surgical treatment of 70 patients with brain metastases from breast carcinoma. *Cancer* 1997;80:1746–54.
39. Pieper DR, Hess KR, Sawaya RE. Role of surgery in the treatment of brain metastases in patients with breast cancer. *Ann Surg Oncol* 1997;4:481–90.
40. Bindal RK, Sawaya R, Leavens ME, Lee JJ. Surgical treatment of multiple brain metastases. *J Neurosurg* 1993;79:210–6.
41. Loeffler J, Alexander E. Radiosurgery for the treatment of intracranial metastases. *In: Loeffler JS, editor. Stereotactic Radiosurgery*. New York: McGraw-Hill; 1993. p. 197–206.
42. Vecht CJ, Haaxma-Reiche H, Noordijk EM, Padberg GW, Voormolen JH, Hoekstra FH, et al. Treatment of single brain metastasis: Radiotherapy alone or combined with neurosurgery? *Ann Neurol* 1993;3:583–90.
43. Mintz AH, Kestle J, Rathbone MP, Gaspar L, Hugenholtz H, Fisher B, et al. A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. *Cancer* 1996;78:1470–6.
44. Kondziolka D, Patel A, Lunsford LD, Kassam A, Flickinger JC. Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. *Int J Radiat Oncol Biol Phys* 1999;45:427–34.
45. Chougule PB, Burton-Williams M, Saris S. Randomized treatment of brain metastasis with gamma knife radiosurgery, whole brain radiotherapy or both. *Int J Radiat Oncol Biol Phys* 2000;8:114.
46. Andrews DW, Scott C, Sperduto PW. Phase III randomized trial comparing whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: Results of the RTOG 9508 trial. *Lancet* 2004;63:1665–73.
47. Lee JS, Murphy WK, Glisson BS, Dhingra HM, Holoye PY, Hong WK. Primary chemotherapy of brain metastasis in small-cell lung cancer. *J Clin Oncol* 1989;7:916–22.
48. Cocconi G, Lottici R, Bisagni G, Bacchi M, Tonato M, Passalacqua R, et al. Combination therapy with platinum and etoposide of brain metastases from breast carcinoma. *Cancer Invest* 1990;8:327–34.
49. Rosner D, Nemoto T, Lane WW. Chemotherapy induces regression of brain metastases in breast carcinoma. *Cancer* 1986;58:832–9.
50. Boogerd W, Dalesio O, Bais EM, van der Sande JJ. Response of brain metastases from breast cancer to systemic chemotherapy. *Cancer* 1992;69:972–80.
51. Patel M, McCully C, Godwin K, Balis FM. Plasma and cerebrospinal fluid pharmacokinetics of temozolomide. *Proc Am Soc Clin Oncol* 1995;14:461a.
52. Newlands ES, Stevens MF, Wedge SR et al. Temozolomide: a review of its discovery, chemical properties, pre-clinical development and clinical trials. *Cancer Treat Rev* 1997;23:35–61.





55. Agarwala SS, Kirkwood JM. Temozolomide, a novel alkylating agent with activity in the central nervous system, may improve the treatment of advanced metastatic melanoma. *Oncologist* 2000;5:144–51.
56. Middleton MR, Grob JJ, Aaronson N, Fierlbeck G, Tilgen W, Seiter S, et al. Randomised phase III study of temozolamide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol* 2003;18:158–66.
57. Dziadziszko R, Ardizzoni A, Postmus PE, Smit EF, Price A, Debruyne C, et al. Temozolamide in patients with advanced non-small-cell lung cancer with and without brain metastasis: a phase II study of the EORTC Lung Cancer Group. *Eur J Cancer* 2003;39:1271–6.
58. Adonizion CS, Babb JS, Maiala C, Huang C, Donahue J, Millenson MM, et al. Temozolamide in non-small-cell lung cancer: preliminary results of a phase II trial in previously treated patients. *Clin Lung Canc* 2002;3:254–8.
59. Friedman HS, Evans B, Reardon D. Phase II trial of temozolamide for patients with progressive brain metastasis. *Proc Am Soc Clin Oncol* 2003;22:408.
60. Siena S, Lanonio G, Baietta E. Multicenter phase II study of temozolamide therapy for brain metastasis in patients with malignant melanoma, breast cancer and non-small cell lung cancer. *Proc Am Soc Clin Oncol* 2003;22:102.
61. Christodoulou C, Bafaloukos D, Kosmidis P, Samantas E, Bamias A, Papakostas P, et al. Phase II study of temozolomide in heavily pretreated cancer patients with brain metastases. *Ann Oncol* 2001;2:249–54.
62. Abrey LE, Olson JD, Raizer JJ, Mack M, Rodavitch A, Boutros DY, et al. A phase II trial of temozolomide for patients with recurrent or progressive brain metastases. *J Neurooncol* 2001;53:259–65.
63. Antonadou D, Paraskevaidis M, Sarris G, Coliarakis N, Economou I, Karageorgis P, et al. Phase II randomized trial of temozolamide and concurrent radiotherapy in patients with brain metastasis. *J Clin Oncol* 2002;20:3644–50.
64. Verger E, Gil M, Yaya R. Concomitant temozolamide and whole brain radiotherapy in patients with brain metastasis: randomized multicentric phase II study. *Proc Am Soc Clin Oncol* 2003;22:101.
65. Dardoufas C, Miliadou A, Skarleas C. 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;0:75b.
66. Agarwala SS, Kirkwood JM, Gore M, Dreno B, Thatcher N, Czarnetski B, et al. Temozolomide for the treatment of Brain Metastases associated with metastatic melanoma: A Phase II Study. *J Clin Oncol* 2004;22:2101–7.
67. Giorgio CG, Giuffrida D, Pappalardo A, Russo A, Santini D, Salice P, et al. Oral Temozolomide in heavily pre-treated brain metastasis from non-small cell lung cancer: Phase II study. *Lung Cancer* 2005 (article in press).
68. Christodoulou C, Bafaloukos D, Linardor H, Aravantinos G, Bamias A, Carina M, et al. Temozolomide combined with cisplatin in patients with brain metastasis from solid tumors: a Hellenic Cooperative Oncology Group (HeCOG) Phase II Study. *J Neuro Oncol* 2005;71:61–5.
69. Bookman MA, Malmstrom H, Bolis G, Gordon A, Lissoni A, Krebs JB, et al. Topotecan for the treatment of advanced epithelial ovarian cancer: an open-label phase II study in patients treated after prior chemotherapy that contained cisplatin or carboplatin and paclitaxel. *J Clin Oncol* 1998;16:3345–52.
70. Rodriguez M, Rose PG. Improved therapeutic index of lower dose topotecan chemotherapy in recurrent ovarian cancer. *Gynecol Oncol* 2001;83:257–62.
71. Blaney SM, Cole DE, Balis FM, Godwin K, Poplack DG. Plasma and cerebrospinal fluid pharmacokinetic study of topotecan in nonhuman primates. *Cancer Res* 1993;53:725–7.
72. Oberhoff C, Kieback DG, Wurstlein R, Deertz H, Sehouli J, van Soest C, et al. Topotecan chemotherapy in patients with breast cancer and brain metastases: results of a pilot study. *Onkologie* 2001;24:256–60.
73. Manegold C, Pawel JV, Scheithauer W. Response of SCLC brain metastases on topotecan (SK and F 104864) therapy. *Ann Oncol* 1996;7:106–7.
74. Ardizzoni A, Hansen H, Dombernowsky P, Gamucci T, Kaplan S, Postmus P, et al. Topotecan, a new active drug in second-line treatment of small-cell lung cancer: a phase II study in patients with refractory and sensitive disease. *J Clin Oncol* 1997;15:2090–6.
75. Depierre A, von Pawel J, Hans K. Evaluation of topotecan (Hycamtin TM) in relapsed small cell lung cancer (SCLC): a multicentre phase II study. *Lung Cancer* 1997;18:35.
76. Scutte W, Manegold C, von Pawel JV, Lan J, Schafer B, Kaubitzsch S, Staab HJ, et al. Topotecan—a new treatment option in the therapy of brain metastases of lung cancer. *Front Radiat Ther Oncol* 1999;33:354–63.
77. Korfel A, Oehm C, von Pawel J, Keppler U, Deppermann M, Kaubitsch S, et al. Response to topotecan of symptomatic brain metastases of small-cell lung cancer also after whole-brain irradiation: a multicentre phase II study. *Eur J Cancer* 2002;38:1724–9.
78. Schutte W, Manegold C, von Pawel JV, Lan J, Schafer B, Kaubitzsch S, et al. Topotecan in the therapy of brain metastases in lung cancer. *Onkologie* 1998;21:25–7.
79. Fisher BJ, Scott C, Macdonald DR, Coughlin C, Curran WJ. Phase I study of topotecan plus cranial radiation for glioblastoma multiforme: results of Radiation Therapy Oncology Group Trial 9507. *J Clin Oncol* 2001;19:1111–7.
80. Fisher B, Won M, Macdonald D, Johnson DW, Roa W. Phase II study of topotecan plus cranial radiation for glioblastoma multiforme: results of Radiation Therapy Oncology Group 9513. *Int J Radiat Oncol Biol Phys* 2002;53:980–6.
81. Eckardt JR, Martin KA, Schmidt AM. A phase I trial of IV topotecan in combination with oral temozolamide daily times 5 every 28 days. *Proc Am Soc Clin Oncol* 2002;21:83b.
82. Glantz M, Choy H, Chakravarthy A. A randomized phase III trial of concurrent paclitaxel and whole brain radiotherapy (WBRT) vs. WBRT alone for brain metastases. *Proc Am Soc Clin Oncol* 1999;18:140a. (abstr 535) 2001;49:1381–90.
83. Kim JH, Kim SH, Kolozsvary A, Khil MS. Potentiation of radiation response in human carcinoma cells in vitro and murine fibrosarcoma in vivo by topotecan, an inhibitor of DNA topoisomerase 1. *Int J Radiat Oncol Biol Phys* 1992;22:515–8.
84. Reboul F, Vincent P, Brewer Y. Chemoradiation for brain metastasis of lung origin. Results of a phase II study. *Proc Am Soc Clin Oncol* 1996;15:373.
85. Robinet G, Thomas P, Breton JL. Phase III study of early versus delayed whole brain radiotherapy (WBRT) with concurrent cisplatin and vinorelbine combination in brain metastasis (BM) of non small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 1998;17:453a.
86. Fujiwara K, Kiura K, Ueoka H, Tabata M, Hamasaki S, Tanimoto M, et al. Dramatic effect of ZD1839 (“Iressa”) in a patient with advanced non-small-cell lung cancer and poor performance status. *Lung Cancer* 2003;40:73–6.
87. Villano JL, Mauer AM, Vokes EE. A case study documenting the anticancer activity of ZD1839 (Iressa) in the brain. *Ann Oncol* 2003;4:656–8.
88. Ceresoli GL, Cappuzzo F, Gregorc V, Bartolini S, Crino L, Villa E. Gefitinib in patients with brain metastases from non-small-cell lung cancer: A prospective trial. *Ann Oncol* 2004;5:1042–7.
89. Lagerwaard FJ, Levendag PC, Nowak PJ, Eijkenboom WM, Hanssens PE, Schmitz PI. Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. *Int J Radiat Oncol Biol Phys* 1999;43:795–803.

