The Management of Metastatic Brain Tumors

Dryander J. *Anatomiae, Hoc Est, Corporis Humani Dissectionis* . . . . Marpurgi, E Cervicornus, 1537. First illustrated work devoted to the anatomy of the brain. An early illustration of the cerebral ventricles.

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Interests include clinical research in a variety of solid tumors including melanoma, renal cell carcinoma, and gastrointestinal malignancies.

INTRODUCTION

It is estimated that 10% to 30% of adult cancer patients will develop brain metastases during the course of their disease[3]. This represents greater than 130,000 new cases a year in the United States and exceeds the number of new primary brain tumor patients.[58] Brain tumors are particularly dreaded because the complications include not only death, but also progressive neurologic deterioration with consequent loss of function, loss of independence, and change in personality. The impact on overall quality of life is profound.

Cancer patients are living longer and responding to primary and systemic therapies. Many are surviving and developing brain metastases. The development of such lesions in patients with metastatic cancer is often associated with an exceedingly poor prognosis. Alleviation of symptoms or palliation is the primary goal in most patients. There is, however, a subset of selected patients who enjoy a more favorable outcome when treated aggressively, therefore patients need to be evaluated carefully in order to determine the best course of action and to identify potential long-term survivors.

The incidence of brain metastases varies depending upon the underlying primary tumor. One recent study evaluated 252[76] patients with metastatic disease to the brain or spinal cord who underwent surgery and found the following. Out of 113 women and 139 men with a mean age of 58 (range 14-80 years) the histology of resected tumors were: lung (54), breast (33), melanoma (27), kidney (23), prostate cancer (19) and other tumors (96). Median survival time was 13 months with an overall one-year survival of 63%. The frequency of specific primary tumor sites varies slightly among different studies as shown below in Table 1.[25]

There are three general types of presentation of brain metastases:[132]
De novo brain metastasis, in which surgery is required for both diagnostic and therapeutic purposes. In this case detecting the primary tumor is of limited value,
Simultaneous presentation of both brain metastasis and primary tumors. In this case both craniotomy and primary tumor resection may provide long term survival,
Sequential presentation in someone with a known primary tumor. In this case age, performance status and extent of metastatic disease are important prognostic factors.

A recent review of over 1200 patients with brain metastases by Lagerwaard[72] in Rotterdam provides valuable clinical data regarding patient presentation:

Table 1. PRIMARY SITES OF CANCER IN PATIENTS WITH BRAIN METASTASES

	Authors (year)					
	Simionescu (1960)	Zimm (1981)	Le Chevalier (1985)	Delattre (1988)	Posner (1995)	
Site	Numbers of Cases (%)					Total
Lung	75(38.1)	122(64)	28(45.2)	144(50)	85(40.5)	454(48)
Small cell		28(15)			73(34.8)	101(11)
Nonsmall cell					12(5.7)	12(1.3)
Squamous cell		58(30)				58(6.1)
Adenocarcinoma		33(17)				33(3.5)
Large cell		3(2)				3(.3)
Breast	44(22.6)	26(12)	3(4.8)	43(15)	39(18.6)	155(16)
Skin	12(6.2)					12(1.3)
Melanoma		8(4)	5(8.1)	30(10.5)	20(9.5)	63(6.7)
Salivary glands			2(3.7)			2(.2)
Pelvis-abdomen				27(9.5)		27(2.9)
Gastrointestinal tract	7(3.6)		3(4.8)		14(6.6)	24(2.5)
Colorectal		6(3)	2(3.7)		8(3.8)	16(1.7)
Esophagus		1(.5)			4(1.9)	5(.5)
Gastric		1(.5)			1(.95)	2(.2)
Hepatoma			1(1.6)			1(.1)
Pancreas		1(.5)	5(8.1)		1(.95)	7(.7)
Gynecologic					10(4.8)	10(1)
Ovary	4(2.1)		4(6.5)		3(1.4)	11(1.2)
Uterus	3(1.6)	3(2)	1(1.6)		1(.95)	8(.8)
Cervix					3(1.4)	3(.3)
Choriocarcinoma					3(1.4)	3(.3)
Head and neck		2(1)			4(1.9)	6(.6)
Thyroid gland	4(2.1)		3(4.8)		4(1.9)	11(1.2)
Lymphatic system/lymphoma	2(1.1)				2(.95)	4(.4)
Sarcoma					7(3.3)	7(.7)
Muscles	1(0.55)					1(.1)
Skeleton	2(1.1)					2(.2)
Neuroendocrine					2(.95)	2(.2)
Adrenals	1(0.55)		1(1.6)		1(.5)	3(.3)
Thymoma					1(.5)	1(.1)
Mediastinal germ cell					1(.5)	1(.1)
Genitourinary					15(7)	15(1.6)
Renal	16(8.2)	4(2)	3(4.8)		7(3.3)	30(3.2)
Testis					4(1.9)	4(.4)
Bladder			1(1.6)		2(.95)	3(.3)
Prostate	1(0.55)	1(.5)			2(.95)	4(.4)
Unknown	23(11.8)	16(8)*		32(11)	5(2.4)	76(8)
Other				12(4)		12(1.2)
Total	195	191	62	288	210	946

* There were 16 patients who had an unknown primary metastatic to the brain. The histology of the brain metastasis was adenocarcinoma in 14 cases and squamous cell carcinoma in 2 cases.

Data from Delattre JY, Krol G, Thaler HT, et al: Distribution of brain metastases. Arch Neurol 45:741–744, 1988; Le Chevalier T, Smith FP, Caille P, et al: Sites of primary malignancies in patients presenting with cerebral metastases: A review of 120 cases. Cancer 56:880–882, 1985; Posner JB: Neurologic Complications of Cancer. Philadelphia, Davis, 1995; Simionescu MD: Metastatic tumors of the brain: A follow-up study of 195 patients with neurosurgical considerations. J Neurosurg 17:361–373, 1960; Zimm S, Wampler GL, Stablein D, et al: Intracerebral metastases in solid-tumor patients: Natural history and results of treatment. Cancer 48:384–394, 1981.

PRESENTING SIGNS AND SYMPTOMS

Headache	53%
Motor weakness	38%
Cerebellar dysfunction	26%
Seizures	22%
Dysphasia	14%

Of the16% of patients presenting with signs and symptoms of a brain lesion without prior history of malignancy, 93% of those had lung cancer. Of all patients, 46 % had a single brain metastasis and 54 % had multiple lesions. Of patients having asymptomatic brain metastases detected in routine screening, almost all had either melanoma or renal cell cancer. 40 % of patients with brain metastases with melanoma had seizures.[72]

Seizures are a common presentation of brain tumors. Clearly patients who present with seizures should be placed on anticonvulsants. Phenytoin is most commonly prescribed. The question of prophylactic anticonvulsant use is unanswered although data suggests it is not beneficial.[20] The high frequency of seizures in melanoma patients may suggest greater considerations of prophylaxis in that population.

Historically, steroids were the first intervention to provide some symptomatic relief for patients with brain metastases. The mean survival was less than two months. The main effect is the reduction of vasogenic peri-tumoral edema, although the exact mechanism is not known.[6] Dexamethasone may decrease vascular permeability by reducing the response to vascular permeability factor and decrease the production of this factor by tumor cells.[53] A commonly prescribed dose is 4 mg. QID, and the dose can be reduced as symptoms are controlled, to minimize toxicity. There is evidence that lower doses may be equally effective. It is difficult to distinguish the independent effect of corticosteroids from chemotherapy.[7] The regression of edema, which is the earliest and most dramatic effect of corticosteroid treatment, is not always indicative of a tumor response.

Subsequently radiation therapy was used to alleviate symptoms. This also improved the mean survival to three to four months. Neurosurgery has been used for many decades with variable results. With improved surgical techniques and reduction in perioperative morbidity and mortality, as well as shorter hospital stays for such procedures, this approach has become acceptable and the treatment of choice for many select patients. Radiosurgery, a technique used to deliver a very focused beam of high energy directly to brain tumors, has also been used successfully in the management of these lesions. Combined modality therapy utilizing all of the aforementioned treatments can be the most effective approach in many patients with brain metastases.

PATHOPHYSIOLOGY

Brain metastases are spread from the primary tumor hematogenously. The distribution of lesions within the brain parallels the distribution of blood flow of the brain. 80% of all brain metastases are located in the cerebellar hemispheres, with 15% in the cerebellum , and 5% in the brainstem. Often the lesions are seen at the junction of white matter and gray matter where the blood vessels decrease in size and clusters of tumor cells may become trapped. The lesions tend to develop in the "watershed areas," which are the zones of marginal arteriolar supply from major intracranial arteries. There is some indication that small cell lung cancer, germ cell tumors, and colorectal cancers may have a

propensity to spread to the cerebellum. Tumors from the pelvis or retroperitoneum may metastasize to the brain via Batson's plexus, the vertebral venous circulation.[126]

The role of trophic factors and immunologic factors in the development of brain metastases is not well understood. Both animal models and cell culture studies have been undertaken in an effort to better understand the mechanisms for invasion and adhesion of circulating metastatic cells into the CNS and the establishment of metastatic brain tumors, as well as the etiology of specific metastatic propensities of cancer calls. The following are summaries of some recent relevant studies.

Adhesion Molecules

Investigators are currently examining the role that adhesion molecules, matrix metalloproteinases and their inhibitors, and tumor suppressor genes and loss of heterozygosity play in the development of brain metastases. This research may provide insight into the mechanism of malignant transformation. Eventually these studies may provide information regarding prognosis in patients with metastatic brain tumors.
Neural cell adhesion molecule (NCAM) is down-regulated during periods of embryological cell migration and may be important in local tumor migration or metastasis. Most gliomas, metastatic melanoma and lung carcinoma show a higher percentage of cells positive for NCAM.[66] Metastatic melanoma cell cultures established from patients who underwent resection of CNS lesions were compared with cell cultures established from metastatic lesions in non-CNS locations in the same patients. Constitutive expression of the neuronal cell adhesion molecule (NCAM) was found in all CNS derived specimens and in fewer than 50% of non-CNS derived specimens. IFN gamma was found to have a weak up-regulatory effect in all non-CNS derived cultures, except normal melanocytes. However in CNS derived cultures, INF gamma was associated with reduced expression of NCAM. Thus NCAM may be immune regulatory in the formation of CNS lesions in metastatic melanoma.[38]

Adhesion molecule CD 44 was found in 48% of 48 metastatic brain tumors, with the most constant expression from thyroid, skin and breast. The most pronounced expression was seen in individual neoplastic cells embedded in abundant stroma[31] and in the vicinity of preserved neural tissue, supporting its role in the interaction of cancer cells with extracellular matrix components of tumor stroma. Annexin II is a calcium and phospholipid binding protein and a substrate for the protein tyrosine kinase, which has a possible role in the development of primary and metastatic brain tumors, but its relationship to proliferation, migration or invasion properties is uncertain.[89]

Tumor Suppressor Genes and Loss of Heterozygosity

Loss of heterozygosity (LOH) in specific genetic locations, when found consistently in cancer cells in both primary and metastatic sites, may provide insights into the role of tumor suppressor genes in the development of these malignancies. Several recent studies examining LOH as a marker for malignancy in brain metastases this are summarized below.

Allelic losses during breast cancer progression in 17 primary breast carcinomas and 22 metastatic lesions (including brain) were studied by analyzing 19 microsatellite sites on seven breast cancer or metastasis-related chromosomal regions and correlating the incidence of combined loss of heterozygosity (LOH) with metastasis-free and post-metastasis survival. In comparison with the corresponding primary tumor, additional LOH events are frequently found in metastases. The incidence of combined LOH in the primary tumor, plus the occurrence of additional LOH events in the distant metastasis correlated significantly with decreased post-metastasis survival. Combined LOH of

the three breast cancer related chromosomal regions alone or in combination with allelic loss at the p53 gene region seems to have a specific influence on the aggressive behavior of metastasis.[50]

Tumor suppressor gene PTEN/MMAC1 was evaluated in 56 brain metastases by loss of heterozygosity (LOH). By direct sequence analysis and differential PCR analysis, the highest LOH rates were detected in metastases from lung (67%) and breast (64%) cancer. PTEN/MMACI alteration may play a role in the progression of these tumors. With the exception of lung carcinoma, PTEN/MMAC genes are involved in only a relatively small subset of brain metastases but the discrepancy of high overall LOH rate (50%) and low frequency of PTEN/MMAC1 mutation detection rate (14%) suggests the presence of one or more additional tumor suppressor genes on chromosome 10q.[47]

Cytokines and Growth Factors

The occurrence of breast cancer metastasis is preferential to certain organs. Astrocytes may play an important role in the development of brain metastases as these cells have been shown to respond to extracellular stimuli by producing many cytokines and growth factors. These are factors which can modulate further cell proliferation, growth and metastasis. A human breast cancer cell line showed increased adhesion to astrocytes and enhanced growth in vitro in the presence of media from con A stimulated astrocytes. The growth stimulatory effect was partially reversed by anti-IL 6, anti transforming growth factor beta (TGF beta) and anti-IGF-1 antibodies indicating that these metastatic cells use exogenous cytokines as paracrine growth factors. These results suggest that cytokines produced by glial cells in vivo may contribute in a paracrine manner to the development of brain metastases by breast cancer cells.[119]

Matrix Metalloproteinases and Their Inhibitors

Within the tumor-stromal microenvironment, a disrupted balance between matrix metalloproteinases (MMP's) and their inhibitors compromises the integrity of the extracellular matrix and promotes malignancy. Tissue inhibition of MMP's have been linked to tumor suppression in studies of genetically altered tissue culture cells and in analysis of clinical specimens in situ. Ectopically overexpressed TIMP-1 in the brains of transgenic mice resulted in a tissue microenvironment with elevated protein levels of this natural MMP inhibitor. Elevated host TIMP-1 imposed resistance to experimental metastases of fibrosarcoma. In TIMP-1 overexpressing mice, brain metastases were significantly reduced by 75% compared to wild - type littermates. Ectopic TIMP-1 expression efficiently exerts a suppressive effect on metastasizing tumor cells.[71]

Brain tumors including lung and melanoma metastases were analyzed by Beliveau for expression of four matrix metalloproteinases, two tissue inhibitors of MMP's (TIMP), and MMP activity. The balance between MMP-2 and TIMP-2 is important in human brain tumors and TIMP expression may be a valuable marker for tumor malignancy.[8]
Another study found that CSF from patients with brain metastases contained precursor gelatinase A, a matrix metalloproteinase (pMMP2), and precursor gelatinase B (pMMP9), whereas negative control CSF contained only pMMP2, thus it is possible that the distribution of gelatinase activity in CSF may provide indication of disease spread.[36]

A study was undertaken[4] to characterize and assess the prognostic value of the immunohistochemical expression of p53, bcl-2, E-cadherin (EC), matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) in brain metastases compared to the expression of these in primary tumors. Results are shown in the following table.

	Brain Metastasis (35)	Primary Tumors (17)
p 53	91% +, 9% intermediate	100% +
MMP9	100% +	100% +
TIMP-1	6% intermediate, 94% --	3% intermediate, 97% --
EC	86% +, 14% intermediate	65% +, 35% intermediate
Bcl-2	Variable	Variable

Neither p53, bc1-2, TIMP-1, or EC staining correlated with overall survival or survival with brain metastases. No assessment of survival difference could be made for MMP-9 because of its overexpression in all tissues. This study suggests that the functional balance between MMP-9 and TIMP-1 is shifted toward extracellular matrix degradation in brain metastases. It further suggests that deregulation of cell cycle control by p53 exists in all brain metastases. The high expression of EC may indicate the importance of adhesion at late stages of metastases.
Tumor development is associated with marked angiogenesis. Vascular endothelial growth factor (VEGF) is a secreted endothelial cell-specific growth factor which is induced by tissue hypoxia and is angiogenic in vivo. Elevated serum VEGF concentrations are found in patients with disseminated cancer including patients with brain metastases. However, the exact role of VEGF in the development of brain metastases has yet to be determined.[108]

Telomerase, an enzyme ribonucleoprotein complex which plays a critical role in cell immortalization and the development of many human cancers, was found in to be expressed in most brain metastases. However, levels of telomerase were not correlated with either tumor subtype or prognosis, but levels may increase with progression of disease.[67]

RADIATION THERAPY

Fractionated whole brain radiation therapy (WBRT) has been a mainstay of therapy for metastatic brain tumors for several decades. WBRT has been shown to palliate 50% to 75% of brain metastases. Survival is often dependent upon the extent of extra-cranial disease. The Radiation Therapy Oncology Group (RTOG) is a cooperative group established to answer important clinical questions regarding the management of radiation therapy patients. Many randomized control trials have been conducted by the RTOG to establish appropriate treatment dosing and schedule guidelines for XRT. Since the RTOG I study in 1971, hundreds of patients with metastatic brain tumors have been entered on protocols.

Different radiation fractionation schedules have been studied since RTOG Trial I which evaluated several schedules (30 Gy over 2 weeks, 30 Gy over 3 weeks, 40 Gy over 3 weeks and 40 Gy over 4 weeks) (n.b. 1 Gray=100 rads). That study showed that almost half the patients achieved significant neurologic improvement with a median survival of 18 weeks, and the improved or stable neurologic status was maintained in 75% to 80% of patients.[133]
The conclusion was that shorter treatment times appeared best for most patients with brain metastases. Subsequent studies to evaluate potential improvement in outcome with higher doses of radiation have failed to show a statistically significant improvement overall. Two recent hyperfractionation trials are described below.

Two novel fractionation schedules for whole brain radiation for patients with brain metastases were evaluated. Twice daily 2.5 Gy to a total dose of 30 Gy, versus twice daily 1.8 Gy to a total dose of 50.4 Gy, compared to an historical patient group treated with one daily fraction of 3 Gy up to 30 Gy. No therapeutic benefit was seen for the 50.4 Gy group. Patients in the accelerated 30 Gy group had a

significantly worse progression free survival and a higher rate of late radiation toxicity. No severe acute toxicity was observed.[86]

A randomized phase III study was conducted examining the potential role of accelerated hyperfractionation radiation versus standard radiation dosing in patients with unresected brain metastases (RTOG 9104). 445 patients who received an accelerated hyperfractionation of 1.6 Gy BID to a total dose of 54.4 Gy were compared to those who received an accelerated fractionation of 30 Gy in 10 daily fractions. No difference in median or one year survival was observed. The conclusion of the trial is that the hyperfractionation regimen is not recommended.[83]

The aforementioned studies have generally shown that underlying histology is not a significant factor in overall outcome. However, response of brain metastases can vary depending on the histology. In a recent study[84] evaluating CT-determined response to external beam radiotherapy, a complete remission was seen in 37% of metastases from small cell lung cancer, 35% of breast cancer, 25% from squamous cell and 14% from non-breast adenocarcinoma. It was also noted that small volume of tumor and absence of necrosis, were the most important factors in achieving a complete remission (CR).

Late effects of radiation such as dementia, ataxia, and progressive mental disturbances are seldom observed because of the poor prognosis[5] of most patients with metastatic brain tumors.To minimize the potential for whole brain radiation toxicity, lower dose fractions of 1.8 to 2.0 Gy can be used in a favorable subset of patients. More protracted schedules of 40 to 50 Gy over 4-5 weeks are associated with more durable responses and less long-term morbidity. At the opposite end of the spectrum, very ill patients with poor performance status may be best served by short hypofractionated schedules such as 29 Gy in 5 fractions, 17 Gy in 2 fractions or possibly 8 to 10 Gy in one fraction. Response rates are good and trips to the treatment facility are minimized. The majority of patients are well served by schedules such as 30 Gy in 10 fractions. The higher long-term toxicity rates associated with larger treatment fractions are of less concern in patients with poor prognosis.

Patient Selection

Careful patient selection is essential in choosing the most appropriate treatment modalities for patients with brain metastases. Evaluation of prognostic factors is also essential in determining if a therapeutic intervention is successful or if results are largely based upon patient selection. Recursive partitioning analysis (RPA), a statistical methodology which creates a regression tree according to prognostic significance, has been used in the retrospective evaluation of hundreds of patients enrolled in RTOG protocols in order to derive prognostic classes for patients with brain metastases. One recent study using this technique[85] evaluated 528 patients treated either with radiotherapy, or with surgery plus radiotherapy. Median survival for all patients was 2.9 months: 2.0 months for patients with Karnofsky performance status (KPS) less than 70%, 3.6 months for KPS greater than 70%. Advanced age, multiple brain metastases, presence of extracranial metastases, and uncontrolled primary tumor each predicted shorter survival in better performance patients. Three subgroups were evaluated as follows: Class 1 patients age 65 or under, KPS equal to or greater than 70; Class 3 KPS less than 70, Class 2 in between Class 1 and Class 3. The median survival time to non-CNS death was 4.1 months: 10.5 months in RPA Class 1, 3.5 months in RPA Class 2, and 2 months in RPA class 3. However, survival was 8.5 months in RPA class 2 patients with controlled primary tumor.

Karnofsky Scale: Criteria of Performance Status (PS)		
Able to perform normal activity; Requires no care.	100	Normal; no complaints or evidence of disease
	90	Able to perform normal activity; minor signs and symptoms of disease
	80	Able to perform normal activity with effort; some signs and symptoms of disease
Unable to work; able to live at home and care for most personal needs; requires varying amount of assistance	70	Cares for self; unable to perform normal activity or to do active work
	60	Requires occasional assistance but is able to care for most of own needs
	50	Requires considerable and frequent medial care
Unable to care for self; requires Equivalent of institutional or Hospital care/ disease may be Progressing rapidly	40	Requires special care and assistance; disabled
	30	Hopitalization indicated, although death not imminent; severely disabled
	20	Hospitalization necessary; active supportive treatment required;
	10	Fatal processes progressing rapidly; moribund
	0	Dead

In a similar analysis of 125 RTOG[42] patients who had surgical resection and XRT, overall survival from the time of diagnosis of brain metastases was 9.5 months. Utilizing the same three RPA derived subgroups as in the previous study, overall survival was 14.8 months in Class 1, 9.9 months in Class 2, and 6.0 months in class 3. Complete surgical resection of the brain lesion was found to be a positive prognostic factor.

Two randomized trials in patients with single metastases to brain and limited systemic disease, reveal surgical resection combined with post-operative WBRT superior to WBRT alone[88, 94]. The implication is that WBRT is effective in destroying residual tumor and eliminating undetected micrometastases. In the most recently reported trial[93] evaluating the benefit of post-surgical WBRT, a dose of 1.8 Gy over 28 fractions for a total dose of 50.4 Gy of WBRT over 5 1/2 weeks was used. The addition of post-operative radiation therapy resulted in substantially better control of tumor in the brain than did treatment with surgery alone. Recurrence in the brain was seen in 9/49 patients (18%) who underwent WBRT versus 32/46 patients (70%) in the observation group. WBRT was associated with reduction of recurrence at the original site, and reduction in occurrence of additional brain metastases. The time from treatment to brain metastasis was greater than 52 weeks in the WBRT group and 27 weeks in the observation group. Overall survival was not significantly different: 48 weeks in the WBRT group versus 43 weeks in the observation group. A greater length of time between diagnosis of primary tumor and brain metastases development was associated with increased survival. The WBRT arm had a decrease or delay in death due to neurologic causes, however there was no difference in how long patients maintained functional independence.

Another study evaluated the pattern of relapse for solitary brain metastases treated with surgery and WBRT in 66 patients. The actuarial probability of relapse was 27% and 55% respectively after one and two years. Local relapse rate was high for melanoma, non-breast adenocarcinoma, and squamous cell carcinoma. No local relapse occurred in breast cancer and small cell carcinoma. Symptoms of late radiation toxicity were seen in 11/66 patients.[87] In patients who have relapsed after undergoing WBRT, re-irradiation can be associated with improved duration of survival and improved quality of life. Use of a limited retreatment volume makes it a well tolerated low morbidity procedure that leads to clinical benefit and, in a few patients, enhanced survival with some patients surviving greater than 9 months.[1]

NEUROSURGERY

Patient selection is most important in determining appropriate candidates for resection of metastatic brain tumors. Factors such as the patient's clinical status, the histology of the primary tumor, and the number and location of metastases must all be considered. Tumors which are sensitive to chemotherapy such as lymphoma, germ cell tumor, and small cell lung cancer are optimally treated with modalities other than surgery. Patients selected for surgery must have lesions which are resectable with minimal morbidity.[111] This can be determined by the depth of the lesion within the brain and its juxtaposition to eloquent (functionally critical) brain regions such as the motor cortex or speech centers. Tumors in the thalamus, basal ganglia and brain stem are only rarely considered for surgery due to the high morbidity potential for surgery in those regions.[73]

The M.D. Anderson group reviewed[112] complications from craniotomies performed for excision of intraaxial brain tumors, to assess factors relative to complication rates and predict the risk of surgical morbidity, particularly for surgery in eloquent brain regions. Of 327 neurosurgery patients, 194 had metastatic tumors. The major complication rate was 13%: operative mortality was 1.7% and post-surgical neurologic morbidity was 8.5%. As a consequence of surgery, 32% of patients improved, 9% of these patients deteriorated neurologically, and 58% showed no change. The median post-operative hospital stay was 5 days. Tumors were defined based on their location relative to brain function and this was the most important variable affecting the incidence of any post-surgical neurological deficit. Patients with tumor in eloquent (grade III) or near eloquent (grade II) brain areas incurred more neurologic deficits than did patients with tumor in non-eloquent areas. Neither repeat resections or extent of surgical resection affected the outcome. Regional and systemic complications were more prevalent among older patients (over 60 years) with lower preoperative performance scale scores and posterior fossa masses.

RADIOSURGERY

Radiosurgery was developed by Leksell in Sweden in the 1950's. Stereotactic radiosurgery is an external irradiation technique in which multiple collimated beams of radiation are stereotactically aimed at a radiographically discrete target volume to deliver a single high dose of radiation to a small volume of tissue. [37] The goal is to define a small target volume and to deliver a clinically significant dose to that area while avoiding delivery of such a significant dose to the surrounding tissue. A coordinate system and stereotactic frame affixed to the skull is employed to pinpoint the target for maximum dose delivery. There is a rapid drop in the radiation dose beyond the target's perimeter. The radiobiologic effects of the focal dose distribution may include thrombosis of small blood vessels, reproductive cell death , or both.

There are three forms of high energy radiation which are used for radiosurgery: high energy x-rays generated by a linear accelerator (LINAC), gamma ray radiosurgery with the gamma knife, and radiosurgery with charged particles generated by a cyclotron , which may be most suitable for large targets. The type of radiosurgery equipment used does not appear to have a strong influence on therapeutic outcome or complication rate.[26]

Metastatic brain tumors present some characteristics suitable for treatment using radiosurgery. The lesions are relatively spherical and have low infiltration of surrounding tissue compared to primary brain tumors. This is advantageous because the margin of tumor is relatively easily identified on CT or MRI.[80] Possible advantages of radiosurgery over neurosurgery are that the treatment is less invasive; it can be performed on outpatient basis; and it is applicable to multiple brain lesions. If the

volume of tumor is greater than 15 cc. it is difficult to control with radiosurgery alone and therefore surgical removal should be considered first.

One study reviewed[19] the outcomes of 62 patients to establish criteria for treatment of brain metastases with radiosurgery and to predict local (tumor site) and regional (brain) control of the tumor and patient survival. Only 6/62 failed locally. Variables predicting a higher risk for local or regional recurrences were larger tumor size, increased number of metastases, and infratentorial location. Absence of extracranial disease, KPS>70 and single intracranial metastasis were significant predictors of longer survival. Patients who fulfilled all three criteria had a mean survival of 7.7 months. Those who did not meet any of those criteria had a mean survival of 1.5 months.

Metastases from melanoma or renal cell carcinoma, which are considered radioresistant, can achieve remission with a single dose of 15 to 25 Gy from a stereotactic modified linear accelerator. In large studies, local tumor control rates from 85% to 95%, recurrence rates from 6% to 15% and side effects between 3% and 15% have been reported. Prognostic factors such as volume of metastasis <10 ml., applied dose > 18 Gy, one or two metastases, absence of extracranial metastases, good patient performance, primary treatment, and more than one year between primary diagnosis and brain metastasis showed a trend toward improved survival. The median survival after radiosurgery ranged from 6 to 12 months.

The value of WBRT in addition to radiosurgery (RS) was studied in 43 patients. Survival and local freedom from progression were the same for RS alone and RS/WBRT (median survival 11.3 vs. 11.1 months and one-year freedom from progression (FFP) 71% vs. 79%. Brain FFP was considerably worse (new metastases or local failure) for RS vs RS/ WBRT (28% vs. 69% at one year). However, brain control allowing for successful salvage of a first failure was not significantly different for RS vs. RS/WBRT (62 vs. 73% at one year). Omission of WBRT in initial management of patients with fewer than 4 metastases does not appear to compromise survival or intracranial control allowing for salvage therapy.[121]

In an effort to answer the question of whether post-radiosurgical whole brain radiation therapy improves survival, a group from Heidelberg reviewed their experience[97] with 236 patients who were treated with radiosurgery, 78 of which received radiosurgery followed by WBRT. Overall survival was 5.5 months[7] with control of CNS metastases in 92% of patients. These results were not significantly different in the two groups. However, in patients who had no evidence of extracranial disease, the median survival was increased for those who received WBRT, 15.4 months vs. 8.3 months, demonstrating a trend for superior survival in patients without extracranial metastasis who received WBRT after RS.

The prognostic significance of multiple brain lesions in patients treated with LINAC-based stereotactic surgery at Stanford University was evaluated in a study including 120 patients. 70 patients were treated for one brain metastasis, and 30 patients were treated for two. The two groups had similar survival times, 33 and 38 weeks respectively, demonstrating that patients treated with stereotactic radiation therapy to two brain metastases have a median survival time identical to that of patients with a solitary lesion. Patients with three and four metastases did not do as well, with a mean survival of 14 weeks.[59]

Another study looked at 97 patients who were treated with gamma knife radiosurgery for multiple (2 to 4) brain metastases. Underlying tumors were as follows: lung (44%), breast (21%), renal cell (10%), colorectal (8%), melanoma (7%). The median tumor volume was 3900 cmm. The median

survival time was 6 months, actual one year survival was 26%. A higher Karnofsky Performance rating and absence of extracranial metastasis had a positive effect on survival. A better performance group without extracranial metastases had a median survival of 9 months.[114]

A study was undertaken at the University of Pittsburgh in an effort to determine the value of radiosurgery in combination with WBRT for patients with multiple brain metastases (2, 3 or 4), good performance status, and limited size of tumor (less than 25 mm. in maximum diameter on imaging). 27 patients were randomized: 14 to WBRT as initial management, 13 to WBRT plus stereotactic radiosurgery. The trial was stopped following an initial analysis. There was a significant benefit in the rate of local tumor control after radiosurgery plus WBRT in comparison to WBRT alone.[70]

To determine if results from new techniques such as radiosurgery and stereotactic surgery of brain metastasis are due to therapy alone or attributable in part to patient selection, an RTOG analysis of tumor/patient characteristics and treatment variables was conducted. 1200 patients from 3 consecutive trials were analyzed. Using RPA, the best survival (median 7.1 months) was observed in patients less than 65 years of age with a KPS of at least 70 and a controlled primary tumor, with the brain as the only site of metastasis. The worst survival (median 2-3 months) was seen in patients with KPS less than 70. All other patients had a median survival of 4.2 months. Well selected patients with single brain metastasis treated with WBRT and resection or WBRT and radiosurgery appear to have a comparable outcome although a randomized trial of these two modalities had not been performed. Both resection and radiosurgery yielded superior survival and functional independence compared to WBRT alone.[42]

CHEMOTHERAPY

Chemotherapy is a valuable therapy for patients with metastatic brain tumors from primary tumors which are known to be sensitive to chemotherapy, such as lymphomas, testicular cancer, and small cell lung cancer. The problems associated with chemotherapy for metastatic brain tumors are (1) issues of drug deliver (crossing of the blood-brain barrier), (2) issues of drug sensitivity of the tumors to chemotherapy, and (3) growth of brain tumors in patients with advanced disease who may have already developed resistance to chemotherapy drugs to which they have been exposed.

The blood-brain barrier (BBB) separates the systemic circulation from the central nervous system (CNS) and consists of the specialized endothelium of blood vessels supplying the CNS surrounded by perivascular astrocytes. The barrier normally impedes the entry of water-soluble but not lipid-soluble agents. Disruption of the BBB by a cerebral metastasis results in increased entry of water-soluble substance and macro-molecules.When metastatic brain tumors grow, they promote formation of new blood vessels that lack a normal blood-brain barrier and promote increased permeablility. This begins when tumors exceed 0.2 cmm. in size.[6]

Brain metastases are a major clinical problem for patients with breast carcinoma. They occur in 10% to 20% of such patients and are associated with a poor prognosis. Non small cell lung cancer is complicated by brain metastases in 16% to 65% of patients. Malignant melanoma metastasizes to the brain in 12% to 20% of clinical cases and 36% to 54% in autopsy series, with a very short survival. For a long time, the idea that systemic chemotherapy could not be effective against central nervous system tumors because the BBB would preclude the non-lipid-soluble anti-neoplastic drugs from reaching the CNS. However, it is currently accepted that the integrity of the BBB is impaired in large areas of the tumor vasculature. A group from Italy[34] tested the efficiency of platinum/etoposide in combination to treat brain metastases from breast, non-small cell lung cancer and melanoma. In the 56

breast cancer patients, 7 (13%) achieved a CR and 21 (38%) achieved a CR or partial remission (PR) . Among the 43 patients with non-small cell lung cancer, three (7%) achieved CR and 13 (30%) either CR or PR. There was no response in the 8 patients with metastatic melanoma.

In another study, 14 patients (8 lung, 4 breast, 1 colon, 1 stomach) with brain metastases treated with cisplatin/etopside had an overall response rate of 14% (1 CR, 1 PR). The regimen was associated with significant hematologic toxicity, and the authors concluded that this would not be a recommended treatment.[134]

Nitrosoureas, lomustine (CCNU), carmustine (BCNU), and fotemustine, are lipid-soluble chemotherapy agents which can readily cross the BBB. These drugs have been used in many trials involving primary and metastatic brain tumors because of this pharmacologic property. The chemotherapy combination of lomustine, carboplatin, vinorelbine, leucovorin and fluorouracil was used to treat 26 patients with brain metastases (20 lung primary, 6 breast primary). Among the patients there were 9 with partial responses, 6 who achieved stable disease, and 11 with progressive disease. The median duration of response was three months. Median time to progression for the whole group was 3.7 months.[21]

The chemotherapy combination of thioguanine, procarbazine, dibromodulcitol, CCNU, fluorouracil and hydroxyurea (TPDC-FuHu) was designed to improve the efficiency of CCNU in the treatment of recurrent metastatic brain tumors. 115 patients failed to respond to surgery and/or radiotherapy of those, 97 patients were evaluated. The primary tumor sites were as follows: 39 NSCLC; 9 SCLC, 28 breast cancer, 9 melanoma; 12 adeno ca (3 colon, 2 kidney; one bladder, one stomach, 5 adeno unknown origin). The overall response, including stable disease, according to primary histology was NSCLC 52%, SCLC 66%, breast 60%, melanoma 22%. The median time to progression was 12 weeks, 26 weeks, 12 weeks and 6 weeks respectively.[60]

A murine model of metastatic breast cancer with brain lesions demonstrated improvement in survival with local delivery of BCNU polymers which were developed to more readily cross the blood brain barrier. This chemotherapy was delivered with or without XRT. This was not true of carboplatin or camptothecin also delivered in polymers.[31] The topoisomerase II inhibitor, lucathone, readily crossed the BBB in experimental murine animals and regression of brain tumors treated with lucathone and XRT was enhanced.[28]

IMAGING

In comparing CT to MRI as an imaging technique for evaluating brain metastases, among 55 patients with solitary brain lesions detected on CT, 17 (31%) had multiple lesions detected on MRI.[113] The two main characteristics which led to lesions being missed on CT were small diameter and a preferential frontal temporal location. Essential reasons for MRI superiority are better soft tissue contrast, fewer partial volume effects, lack of bone artifacts, stronger enhancement with paramagnetic contrast agent (gadolinium), and direct imaging in three planes. A considerable increase in sensitivity (32% to 55%) in contrast-enhanced CT scan can be obtained by reducing the slice thickness and increasing the contrast medium dose.[120]

Triple-dose contrast MRI screening for brain metastases may be helpful in selected cases with solitary metastasis or with equivocal findings on single-dose contrast MRI. In 12 patients who underwent single-dose contrast MRI, triple-dose contrast MRI detected additional metastases in 25% of equivocal scans or those with solitary metastases. The triple dose contrast also increased the false positive reading. In 70 negative single-dose studies, no additional metastases were seen on triple-dose.[124]

MRI response of brain metastases after gamma knife radiosurgery was evaluated in 48 patients with 78 lesions.[95] Local tumor control was achieved in 66 (90%) of 73 lesions at 20 weeks after radiosurgery. 61% maintained local control at two years. A homogeneous baseline enhancement pattern on MRI, initial good response rate, and greater than 50% lesion volume reduction, predicted better local control. On MRI, five metastases demonstrated a transient volume increase after treatment. The median survival time after stereotactic radiosurgery was 53 weeks and correlated with systemic disease burden and primary tumor type.

Another study[117] reviewed 261 lesions treated in 119 patients with gamma knife radiosurgery, The initial patterns of contrast enhancement on CT were homogeneous in 68% of lesions, heterogeneous in 12%, and ring-enhancing in 19%. A homogeneous contrast enhanced pattern on CT was significantly associated with a longer FFP. Other significant factors were a radiosurgery dose of at least 18 Gy and a long interval between primary diagnosis and RS.

A Japanese study[142] designed to compare usefulness of CT and MRI in pre-operative evaluation and post operative follow–up, evaluated 332 patients with operable non-small cell lung cancer. These patients had no neurologic symptoms and potentially operable non-small cell lung cancer. CT scan was used in 155 patients and MRI was used in 177 patients. Of 279 patients followed post-operatively within the first 12 months of evaluation , brain metastases were observed in 11 patients in the CT group (7.1%) and 12 patients in the MRI group (6.8%). MRI detected brain metastases pre-operatively in 6/12 patients. CT detected 1/11 pre-operatively. The mean maximal diameter of brain metastases detected was significantly smaller in the MRI group: 12.8 cmm. vs. 20.3 cmm. in the CT group. The median survival time and two-year survival rate after treatment of detected lesions were 10 months and 27 % in the CT group, and 17 months and 28% in the MRI group, with no statistically significant difference.

LUNG CANCER

Histology may have a bearing on the outcome in brain metastases from lung cancer. In a review of 93 patients[9] with brain metastases from lung cancer, survival difference was noted based on histology as follows: adenocarcinoma - 3.5 months, squamous cell - 1.9 months, small cell - 2.8 months. On autopsy study, one of 22 patients with adenocarcinoma and 7 of 32 patients with small cell lung cancer appeared to have a sustained complete remission in the brain. Additionally, absence of symptoms related to the lung tumor at the time of brain metastasis is one of the factors that can be used to distinguish patients with a favorable outcome.

Non-Small Cell Lung Cancer

In a review of 159 lung cancer patients with brain metastasis,[56] all underwent XRT. 21 had chemotherapy and 10 underwent surgery. The overall median survival was 3.5 months, and one-year survival was 10.6%. Significant factors were determined to be performance status, age, total radiation dose to brain, brain as first site of metastasis, neurosurgery, symptoms of urine/stool incontinence, synchronous brain metastases, and presence of midline shift on cranial CT. There was a 75% overall symptomatic response rate to therapy.

Another series looked at outcome and risk in patients with non-small cell lung cancer with one to four brain metastases.[64] Treatment was as follows: 77 patients underwent radiosurgery. 71 also underwent WBRT. Overall median survival after RS was 10 months. Five factors significantly affected survival: extent of systemic disease, presence of a neurologic deficit, size of the intracranial tumor, initial

imaging appearance of intratumoral necrosis, and initial resection of the primary tumor of the chest. Local tumor control was achieved in 77/91 lesions (85%) and tumoral radiation necrosis developed in 4 lesions (4.4%).

Some patients with brain metastasis after resection of non-small cell lung cancer survive for long periods after surgical resection of the brain metastasis. In one series, none had systemic disease outside of the brain metastasis and the overall survival was 12.5% at three years and 8.3% at five years. The interval between lung and brain surgery, histologic differentiation of primary cancer, size of primary site, location of the brain metastasis, and post-operative radiation therapy significantly affected survival. The best survival was in patients who had solitary brain lesions and no other disease, in whom relapse in the brain occurred more than one year after resection by lobectomy of the primary site.[106]

Chemotherapy trials for non-small cell lung cancer with brain metastases demonstrate some responses, even some CR, and overall CR can be associated with prolongation of survival (See Table below). Some of the regimens have been very toxic. The use of chemotherapy wih the intention of controlling brain metastases is still experimental.[01, 13, 81]

Non-Small Lung Cancer

Chemotherapy Trials for Non-Small Cell Lung Cancer with Brain Metastases

Chemotherapy	Number of Patients	Overall Response	Mean Survival or Duration of Response
Quantin[101] Vinorelbine/Ifosfamide Cisplatin (plus XRT)	23	30% (Brain response 7CR, 6PR)	7 – 6 months
Boogerd[13] Teniposide	13 (6 previously Had XRT or surgery)	23% (1CR, 2PR)	Duration of response 16, 40, 80 mo. (3 responders)
Tumarello[81] Paclitaxel/Carboplatin	5	20% (1 PR)	
Minotti[128] Cisplatin/teniposide	23	3 CR; 5 PR	Duration of response 21 weeks (PR) 45 weeks (CR)

Small Cell Lung Cancer

The outcome of 30 patients with extensive stage small cell lung cancer with only brain metastases at initial diagnosis was reviewed.[69] All patients received cisplatin based chemotherapy and concomitant whole brain radiotherapy. Thirteen had CR; 11 had PR; and three had regression. Three had stable disease with a median survival of 14 months. The median time to progression was 10 months. Only one patient had disease progression in the brain. 22 patients eventually died of the disease. The therapeutic outcome was similar to that of limited stage small cell lung cancer.

WBRT was evaluated as a single treatment modality in patients with brain metastases from small cell lung cancer who did not have extracranial metastatic tumor. Treatment was 30 Gy over 10 fractions.

Of 20 patients, six had CR, five had PR, and the overall response was 50%. Response duration was 5.4 months, and median survival was 4.7 months. In the majority of these patients, the first site of progression after WBRT was in the CNS. Of these patients, 12 had stabilization or improvement of neurologic function.[99] In small cell carcinoma patients with brain metastasis recurrence, whole brain re-irradiation consisting of 20 Gy in 10 fractions was considered safe, and survival was four months after re-treatment.[57]

There has been a case report of an extrapulmonary small cell metastatic to the brain in which the lesions completely regressed with cisplatin/etoposide chemotherapy.[91]

Prophylactic Cranial Irradiation (PCI)

Prophylactic cranial irradiation (PCI) has been a hotly debated issue in oncology. In patients with limited stage small cell lung cancer who have undergone chemotherapy and radiation therapy to the primary tumor, there is a significant percentage of patients who relapse only in the brain. The two goals of PCI are (1) to prevent brain recurrence and its associated neurologic deterioration, and (2) to improve survival. The potential benefits of PCI also need to be evaluated in the face of potential long-term toxicity from radiation to the brain.

Most studies have shown a reduction in the development of brain metastases in the patients who receive PCI. In some studies this reduction has achieved statistical significance.[43] Most studies have also demonstrated an overall survival advantage in the PCI patients, however this advantage has consistently failed to achieve statistical significance.[74] In one study,[130] which included only 39 patients, seven out of 18 PCI patients survived more than two years and none of the non-PCI patients survived as long. The long-term survivors did suffer some cognitive impairment, which was considered non-disabling. They did develop radiographic abnormalities of cortical atrophy and leukoencephalopathy. There may also be a superior reduction in brain relapse when PCI is administered early in the course of treatment.

A recent trial evaluating PCI in stage IIIA/IIIB non-small cell lung cancer demonstrated a reduction in the rate of the brain as the first site of relapse from 30% to 8% at four years, and a reduction in overall brain relapse from 54% to 13%.[122]

BREAST CANCER

Brain metastases are diagnosed in 15% of patients with metastatic breast carcinoma. Some patients who undergo aggressive intervention can enjoy a prolonged survival. Careful patient selection is important. Four studies reviewed below have examined these patients and their response to various therapies. Significant prognostic indicators have also been derived from these patients. Survival data for the surgical patients is outlined in the table below.

Breast Cancer Patients Undergoing Craniotomy for Metastatic Brain Tumors

Number	**Median Survival After Brain Tumor**	5 Year Survival
Wronski[139] 70	16.2 months (10.9 months cerebellar mets 14.8 months multiple mets) ER/PR	7%
Pieper[96] 63	16 months	17%
Lentzsch[77] 10 Surgery and XRT	82 weeks	-
Boogerd[12] 28	23 months	-

Wronski[139] reviewed 70 breast cancer patients who underwent craniotomy. The median time between diagnosis of breast cancer and brain metastasis was 28 months. The overall median survival was 54 months after diagnosis of primary breast tumor and 16.2 months after diagnosis of brain tumor. Four patients died within one month of craniotomy. Twelve patients had solitary cerebellar metastases and 16 had multiple metastases. Median survival was 10.9 months and 14.8 months respectively. Patients with estrogen receptor/progesterone receptor (ER/PR) positive tumors had a median survival of 21.9 months vs. 12.5 months for ER/PR negative tumors. Patients with brain lesion larger than 4 cm. had a median survival of 11 months vs. 16 months for those with smaller lesions. For patients younger than 50 years median survival was 17.3 months vs. 11.1 months for patients over 50 years. For patients with neurological deficits the median survival was 11.5 months vs. 17.4 months for patients with no neurological deficits. One-year, two-year, three-year and five-year survival rates were, respectively, 53%, 25.67%, 78.6%, and 7%. The administration of adjuvant WBRT after craniotomy and absence of meningeal carcinomatosis are variables which predicted a better survival.

63 patients with surgical treatment for brain metastasis from breast cancer were evaluated.[96] Median length of survival was 16 months; five-year survival was 17%. Brain metastases recurred in 27 patients at a median interval of 15 months. Eleven had local recurrence, 10 had distant recurrence, and seven developed leptomeningeal disease. Significant prognosticators of length of survival were age, menopausal status, postoperative WBRT, pre-operative neurologic status, and extent of pre-operative systemic disease.

In another recent study from Germany reviewing treatment outcomes,[77] 145 out of 162 breast cancer patients in whom brain metastases had been diagnosed received WBRT. The most common schedule was 30 Gy in 15 daily fractions over 3 weeks. Ten patients underwent surgery in addition to WBRT, and 17 received only corticosteroids. In the WBRT group, women under 40 years of age had a shorter survival (median 12 weeks) than those of other groups (median 29 weeks). Overall, median

survival was 82 weeks for the 10 surgical patients, 26 weeks for patients treated with WBRT and five weeks for patients receiving only corticosteriods. Those patients with solitary metastases treated with radiation alone had a survival of 44 weeks versus those with multiple brain metastases, whose survival was 23 weeks. The radiation dose, solitary metastases, and primary tumor size were all significant prognostic factors for survival.

Boogerd[12] reported on 28 patients with breast cancer who presented with a single brain metastasis as a first site of distant disease. The response to surgery with post-operative XRT was 100%, and 89% in non-surgical therapy, with median recurrence-free survival of 23 months and 5 months, respectively. Retreatment of a local relapse by surgery was associated with a seven month median duration of response vs. three months in non-surgical patients. In 20 patients with multiple brain metastases the response to non-surgical therapy was 55% with a median recurrence-free survival of four months.

RENAL CELL CARCINOMA

The percentage of patients with renal cell carcinoma (RCC) who develop brain metastases during the course of their disease is 4% to13%. However, in more than half of RCC patients with cerebral metastases, multiple tumors are present. The majority of these patients have metastasis at other sites as well, most commonly the lung. The prognosis overall is poor with a mean survival of four to five months. RCC is often considered a radioresistant tumor. Renal cell carcinomas metastasize to the frontal, parietal, temporal, and occipital lobes and brain stem/cerebellum in frequencies ranging from 18.4% to 22.4% in each region. There is no preferable site of RCC metastasis to the brain. In 46/50 (92%) of patients, primary tumors or metastases in other organs had already been detected. The appearance of brain metastasis is usually a late manifestation of the advanced stage of disease.[82]

In 68 Renal cell cancer patients treated for brain metastases,[24] the following adverse prognosis factors were determined: no initial nephrectomy, left side and temporal location of brain metastases, presence of fever or weight loss, ESR > 50 mm/hr., and time from initial diagnosis to brain metastases of 18 months or less. Multivariate analysis also revealed the presence of visceral metastases to be an independent prognostic factor. 44 patients (65%) with none or one adverse prognostic factor had a median survival of 8 months and a 26% one-year survival. 24 patients (35%), with two adverse prognostic factors, had a median survival of 3 months and a 9% one-year survival.

Reports suggest that radiosurgery for brain metastasis is effective regardless of the underlying histology. Mori[82] reported on 35 patients with renal cell carcinoma and brain metastases who underwent radiosurgery. 25 patients had single metastases; 10 had two or more brain lesions; 26 (74%) had active systemic disease. The mean period between diagnosis of primary RCC and brain metastases was 33 months. Overall median survival was 11 months after radiosurgery and 14 months from diagnosis of a brain tumor. The one-year survival was 43%; two-year survival was 22%. 18 patients (72%) died of systemic disease progression. Three (12%) patients died of metastatic disease within the CNS. Young age, good performance status, and nephrectomy prior to radiosurgery were good prognostic factors.

Wronski reported on 119 RCC[140] patients with brain metastases who received WBRT only. The overall median survival time was 4.4 months. Multiple brain tumors were seen in 70 patients with a survival time of 3.0 months. Among 117 patients, the cause of death was neurologic in 90 (76%), systemic cancer in 19 (16%), and unknown in 9 (8%). The survival rates at six months, one year, and two years were 33.6%, 16.8%, and 5.9%, respectively. No significant difference in survival in metachronous vs. synchronous metastases was noted. A single brain metastasis, lack of distant metastasis, and tumor diameter less than 2 cm. were statistically significant prognostic factors.

In another study of 23 patients with RCC and brain metastases, 13 had single metastases and 10 had multiple metastases. The median tumor volume was 5500 cmm. 14 patients had gamma knife RS, 9 patients had gamma knife RS boost and WBRT. Rapid neurological improvement after gamma knife RS was seen in 17 patients. Median survival was 11 months with a one-year survival of 48%.[114]

Chemotherapy and immunotherapy are not generally effective in the palliative management of brain metastasis from RCC.

METASTATIC MELANOMA

Melanoma has a great propensity to metastasize to the CNS (up to 70% in autopsy studies) so that although the incidence of melanoma is not as great as other tumors, it is one of the common underlying malignancies seen with brain metastases. In patients undergoing stereotactic radiosurgery for metastatic melanoma the locations of the lesions in the brain were as follows: cerebral hemisphere (72%), cerebellar (14%), and basal ganglion or thalamus (14%).[116]

A review of 702 patients with brain metastases from melanoma provided valuable clinical and therapeutic information helpful in the management of these patients.[109] Factors found to be associated with development of brain metastases included male gender; primary lesions on mucosal surfaces or on the skin of the trunk, or head and neck, or ulcerated primary lesions; and histological findings of acral lentigenous or nodular lesions. The overall median survival time was 113.2 days. Brain metastases contributed to the death of 94.5% of the patients in this group. Patients with primary lesions in the head and neck region had a significantly shorter survival time. Patients with a single brain lesion, without lung or multiple other visceral metastasis, and patients whose initial presentation with melanoma included a brain metastasis had a significantly better prognosis. The small group of patients who survived more than three years was characterized by the presence of a surgically treated single brain metastasis in the absence of other visceral metastasic disease.

A study performed to evaluate effectiveness of radiosurgery without WBRT in the palliative management of melanoma brain metastases retrospectively assessed 35 patients.[45] Of those patients, four had solitary brain metastases, 13 had single brain metastases and metastases elsewhere; 18 had multiple brain metastases. The local control rate was 55/56 at three months. Median survival was 22 months in patients with solitary brain metastases; 7.5 months in single brain metastases and metastases elsewhere; and 4 months in patients with multiple brain metastases. Surgery was required in 2/35 patients.

A French trial assessed the response rate and efficacy of palliative radiation therapy in patients with metastatic melanoma.[65] Of 28 patients, seven had brain metastasis and two had brain and bone or soft tissue metastases. Patients were treated with 30 Gy of radiation in 10 fractions over 2 weeks, or 20 Gy in 5 fractions over 1.5 weeks. Of patients with brain metastases, 57% had amelioration of neurological functional deficits, 29% did not respond and one had disease progression. Short course XRT can provide palliation in metastatic melanoma with good relief of symptoms.

Fotemustine, a nitrosourea which readily crosses the blood-brain barrier, when used in place of carmustine (BCNU) in the "Dartmouth" regimen for metastatic melanoma, revealed no response in brain metastases. Fotemustine and DTIC have been given concomitantly with irradiation in 12 patients with brain metastasis from metastatic melanoma. Results were four complete responses and two partial responses out of 12 patients. The mean survival of responders was 8.2 months.[105]

Bioimmunotherapy (cisplatinum, dacarbazine, IFN and IL-2) can be used in combination with radiation therapy in patients with advanced metastatic melanoma and brain metastasis.[100,110]

COLORECTAL CANCER

The most common sites of metastatic disease in colorectal cancer include liver, lung, and draining lymph nodes. Brain metastases are relatively uncommon and constitute 1.8% to 4.5% of all metastatic lesions to the brain. Of 53 patients reported by Ko,[68] 55% had a solitary lesion, 45% had multiple lesions (original tumor was localized to the rectum in 62%, left colon in 17%, and right colon in 20%). In 12 patients the brain lesions were solitary metastatic sites. 25 (47%) had lung metastases, 10 (19%) had liver metastases, 4 (8%) had both liver and lung and 14 (26%) had other metastatic sites including bone, peritoneum, and adrenal gland. Median interval to develop brain metastasis after initial diagnosis was 33 months. In three patients who underwent craniotomy and resection, and in three patients who underwent gamma knife radiosurgery, the mean survival time was 86 months. For patients who received non-surgical therapy, mean survival was approximately three months.

In most patients the inferior and middle rectal veins drain into the inferior vena cava, and the superior rectal vein continues as the inferior mesenteric vein. The lower rectum drains directly into the systemic venous system bypassing the portal system. It was proposed that tumor cells from rectal tumors may metastasize to the brain through the paravertebral veins.

Of 709 patients at Sloan Kettering who underwent resection of brain metastases, 73 had underlying colorectal cancer.[138] Median interval from primary diagnosis to the development of brain metastasis was 27.6 months. Median survival from craniotomy was 8.3 months. One-year and two-year survival rates were 31.5% and 6.8%, respectively. Only the presence of cerebellar brain metastases was associated with decreased survival. Patients with infratentorial tumor location had a mean survival of 5.1 months versus 9.1 months in patients with supratentorial lesions. 74% of patients had pulmonary metastases diagnosed before craniotomy.

The frequency of infratentorial location of brain metastasis in colorectal carcinoma is 35% to 55%. It is three times higher than the percentage of cerebellar metastases from lung cancer (15%), renal carcinoma (16 and 19%), breast carcinoma (10.8%), or melanoma (7.3%). The reason for this may include the anatomy of the colon and rectum with access to the vertebral vascular system as well as colorectal cancer's unique capabilities to colonize specific parts of the brain. Survival for those who have cerebellar metastases is only five months, with a one-year survival rate of 15.4%. Cerebellar lesions often present with obstructive hydrocephalus or imminent cerebrospinal fluid obstruction. Surgical resection of the cerebellar lesion may be the most expeditious way to prevent hydrocephalus.[138]

CARCINOMA OF UNKNOWN PRIMARY

In 39 patients who presented with brain metastasis[125] as the only manifestation of an undetected primary tumor, 31 had adenocarcinoma. In 12 patients the primary tumor was eventually found, most commonly lung cancer. Median survival for all patients was 13.4 months. Overall survival at one,

three, and five years was 56%, 19%, and 15%, respectively. Intracranial disease control was 72% at five years. Patients who underwent gross total resection and XRT had better survival than those who had XRT alone. Overall survival was similar to those whose primary lesion was eventually discovered.

Surgery was performed on 211 patients for brain metastases. Of these patients, 140 (66%) male and 71 (34%) female, the average age was 59 years. Lung cancer (47%) and breast cancer (21%) were most frequently seen. In 17% of patients the primary lesion was unknown. Average survival was 14 months and, in 8 patients (4%) it was more than five years. In 36 (17%) cases recurrence appeared 8 months after the first operation. Survival averaged 11 months after discovery of relapse. Prognostically, renal cell behaved more favorably (27 months) and melanoma was worse (7 months). Patients with metastases from an unknown primary had no significantly different outcome from patients with known primary tumors.

In another study, 32/276 patients, or 11.5%, had brain metastases from an unknown primary site. Single lesions were resected followed by XRT. Patients with multiple lesions underwent WBRT. Median survival was 31.5 weeks for patients with single lesions and 19.1 weeks for patients with multiple lesions.

TESTICULAR CANCER

Patients with testicular cancer who develop brain metastases are considered to have a poor prognosis. Bokemeyer reported[11] on 44 patients with testicular tumors and brain metastases. 18 presented with brain metastases (group 1), 4 developed brain metastases at relapse after response to chemotherapy (group 2) and 22 developed brain metastases during or directly after cisplatin based chemotherapy (group 3). Long term survival was seen in 10 patients (23%): 6/18 in group 1, 3/4 in group 2, and 1/23 in group 3. Patients with longest survival received both chemotherapy and whole brain irradiation. The best survival was seen in patients who had a single brain metastasis, and in those who received both chemotherapy and whole brain irradiation.

Mahalati reported on 167 non-seminomatous germ cell tumor patients, 11 of whom had brain metastases.[78] Patients received chemotherapy and intrathecal methotrexate. Of the 11 patients, six had chemotherapy alone, one had chemotherapy plus XRT, and four had all three treatments. Ten patients presented with symptoms relative to intracranial lesions. All patients with brain metastasis had bulky thoracic disease (11/34 or 32% of patients with advanced thoracic disease). Four brain metastases patients were alive at 3, 12, 34, and 47 months. Two of five who developed brain metastasis during the course of chemotherapy were alive. Those with single brain mets had a better prognosis.

Fossa[33] reported on two groups of patients with brain metastases and mixed germ cell tumors. Group I (56 patients) had brain metastases at diagnosis and Group 2 (83 patients) developed brain metastases after cisplatin based chemotherapy. In group 1 all patients received standard chemotherapy and XRT (36) and/or neurosurgery (10). In group 2, metastases were detected 9 months (median) after initiation of chemotherapy. Patients were treated was as follows: 35 with chemotherapy, 59 with XRT, and 25 with neurosurgery. The five-year cause-specific survival in group 1 was 45%. Neurosurgery and absence of extracerebral non-pulmonary visceral disease were independent predictors of good prognosis. The five-year cause-specific survival in group 2 was 12%, but it was 39% among those with an isolated brain recurrence (24 patients). Radiotherapy represented an independent predictor of good response together with brain metastasis at first recurrence and absence of extracerebral disease.

SARCOMA

Musculoskeletal tumors rarely have brain metastases. In 480 sarcoma patients, of 179 patients with distant metastases, 20 had brain metastases (4.2%).[90] Subtypes were as follows: alveolar soft-part sarcoma (3/4), extraskeletal Ewing's sarcoma (2/8), rhabdomyosarcoma (2/13), and osseous Ewing's sarcoma (2/18). All 20 patients had distant or local relapses and 16/20 had pulmonary metastases. Three patients underwent surgical treatment and two survived more than one year. Mean survival after diagnosis of brain metastases was 5.1 months. Surgery is effective in treating selected patients with sarcoma metastases to the brain. The presence of lung metastases is not a contraindication to surgery.[107]

GYNECOLOGIC MALIGNANCIES

Central nervous system involvement by an epithelial ovarian cancer is rare. There has been a case report of a patient with ovarian cancer and multiple brain metastases who achieved a complete response to systemic chemotherapy with carboplatin.[22] A prospective randomized trial has been implemented by the RTOG to evaluate the benefit of radiosurgery in comparison with WBRT for ovarian cancer metastatic to the brain.[23]

Brain metastases in endometrial carcinoma are rare. They tend to follow an unpredictable dissemination pattern. They usually occur in patients with widely disseminated disease but isolated brain metastases have been reported.[79]

THYROID CANCER

In 47 cases of brain metastases from thyroid cancer, once diagnosed , the disease specific mortality was 78% with median survival of 4.7 months. Resection of one or more foci of brain metastases significantly improved survival to 16.7 months for those undergoing excision vs. 3.4 months in those who did not. No responses were noted to radioactive Iodine (RAI), external beam XRT, or chemotherapy.[18]

REFERENCES

1. Abdel-Wahab MM, Wolfson HA, Raub W, et al.: The role of hyperfractionated re-irradiation in metastatic brain disease: a single institutional trial. Am J Clin Oncol 20(2):158-60, 1997.

2. Alexander E 3rd, Loeffler JS: The case for radiosurgery. Clin Neurosurg 45:32-40, 1999.

3. Arbit E, Wronski M: Clinical decision making in brain metastases. Neurosurg Clin North Am 7:447-57, 1996.

4. Arnold SM, Young AB, Munn RK, et al.: Expression of p53, bcl-2, E-cadherin, matrix metalloproteinase-9, and tissue inhibitor of metalloproteinases-1 in paired primary tumors and brain metastasis. Clin Cancer Res 5(12):4028-33, 1999.

5. Baldini EH: Palliative radiation therapy for non-small cell lung cancer. Hematol Oncol Clin North Am 11(2):303-9, 1997.

6. Batchelor T, DeAngelis L: Medical management of cerebral metastases. Neurosurg Clin North Am 7:435-46, 1996.

7. Becker G, Duffner F, Kortmann R, et al.: Radiosurgery for the treatment of brain metastases in renal cell carcinoma. Anticancer Res 19(2C):1611-7, 1999.

8. Beliveau R, Delbecchi L, Beaulieu E, et al.: Expression of matrix metalloproteinases and their inhibitors in human brain tumors. Ann N Y Acad Sci 886:236-9, 1999.

9. Bergqvist M, Brattstrom D, Bennmarker H, et al.: Irradiation of brain metastases from lung cancer: a retrospective study. Lung Cancer 20(1):57-63, 1998.

10. Bogart JA, Ungureanu C, Shihadeh E, et al.: Resection and permanent I-125 brachytherapy without whole brain irradiation for solitary brain metastasis from non-small cell lung carcinoma. J Neurooncol 44(1):53-7, 1999.

11. Bokemeyer C, Nowak P, Haupt A, et al.: Treatment of brain metastases in patients with testicular cancer. J Clin Oncol 15(4):1449-54, 1997.

12. Boogerd W, Hart AA, Tjahja IS: Treatment and outcome of brain metastasis as first site of distant metastasis from breast cancer. J Neurooncol 35(2):161-7, 1997.

13. Boogerd W, van der Sande JJ, van Zandwijk N: Teniposide sometimes effective in brain metastases from non-small cell lung cancer. J Neurooncol 41(3):285-9, 1999.

14. Botturi M, Fariselli L: Clinical results of unconventional fractionation radiotherapy in central nervous system tumors. Tumori 84(2):176-87, 1998.

15. Boyd TS, Mehta MP: Radiosurgery for brain metastases. Neurosurg Clin N Am 10(2):337-50, 1999.

16. Chidel, MA, Suh, JH, Barnett GH: Brain metastases: presentation, evaluation, and management. Cleve Clin J Med 67(2):120-7, 2000.

17. Chidel MA, Suh JH, Greskovich JF, et al.: Treatment outcome for patients with primary nonsmall-cell lung cancer and synchronous brain metastasis. Radiat Oncol Investig 7(5):313-9, 1999.

18. Chiu AC, Delpassand ES, Sherman SI: Prognosis and treatment of brain metastases in thyroid carcinoma. J Clikn Endocrinol Metab 82(11):3637-42, 1997.

19. Cho KH, Hall WA, Gerbi BJ, et al.: Patient selection criteria for the treatment of brain metastases with stereotactic radiosurgery. J Neurooncol 40(1):73-86, 1998.

20. Cohen N, Strauss G, Lew R, et al.: Should prophylactic anticonvulsants be administered to patients with newly diagnosed cerebral metastases? A retrospective analysis. J Clin Oncol 6:1621-1624, 1988.

21. Colleoni M, Graiff C, Nelli P, et al.: Activity of combination chemotherapy in brain metastases from breast and lung adenocarcinoma. Am J Clin Oncol 20(3):303-7, 1997.

22. Cormio G, Gabriele A, Maneo A, et al.: Complete remission of brain metastases from ovarian carcinoma with carboplatin. Eur J Obstet Gynecol Reprod Biol 78(1):91-3, 1998.

23. Corn BW, Mehta MP, Buatti JM, et al.: Stereotactic irradiation: potential new treatment method for brain metastases resulting from ovarian cancer. Am J Clin Oncol 22(2):143-6, 1999.

24. Culine S, Bekradda M, Kramar A, et al.: Prognostic factors for survival in patients with brain metastases from renal cell carcinoma. Cancer 83(12):2548-53, 1998.

25. Das A, Hochberg FH: Clinical presentation of intracranial metastases. Neurosurg Clin North Am 7:377-91, 1996.

26. Davey P: Brain metastases. Curr Probl Cancer 23(2):59-98, 1999.

27. Dhote R, Beuzeboc P, Thiounn N, et al.: High incidence of brain metastases in patients treated with an M-VAC regimen for advanced bladder cancer. Eur Urol 33(4):392-5, 1998.

28. Del Rowe JD, Bello J, Mitnick R, et al.: Accelerated regression of brain metastases in patients receiving whole brain radiation and the topoisomerase II inhibitor, lucanthone. Int J Radiat Oncol Biol Phys 43(1):89-93, 1999.

29. Earnest F 4th, Ryu JH, Miller GM, et al.: Suspected non-small cell lung cancer: incidence of occult brain and skeletal metastases and effectiveness of imaging for detection—pilot study. Radiology 211(1):137-45, 1999.

30. Engebraaten O, Fodstad O. Site-specific experimental metastasis patterns of two human breast cancer cell lines in nude rats. Int J Cancer 82(2):219-25, 1999.

31. Ewend MG, Sampath P, Williams JA, et al.: Local delivery of chemotherapy prolongs survival in experimental brain metastases from breast carcinoma. Neurosurgery 43(5):1185-93, 1998.

32. Fidler IJ, Schackert G, Zhang RD, et al.: The biology of melanoma brain metastasis. Cancer Metastasis Rev 18(3):387-400, 1999.

33. Fossa SD, Bokemeyer C, Gerl A, et al.: Treatment outcome of patients with brain metastases from malignant germ cell tumors. Cancer 85(4):988-97, 1999.

34. Franciosi V, Cocconi G, Michiara M, et al.: Front-line chemotherapy with cisplatin and etoposide for patients with brain metastases from breast carcinoma, non small cell lung carcinoma, or malignant melanoma: a prospective study. Cancer 85(7):1599-605, 1999.

35. Frank S, Muller J, Plaschke J, et al.: The putative tumor suppresor gene FHIT at 3p14.2 is rarely affected by loss of heterozygosity in primary human brain tumors. Cancer Res 57(13):2638-41, 1997.

36. Friedberg MH, Glantz MJ, Klempner MS, et al.: Specific matrix metalloproteinase profiles in the cerebrospinal fluid correlated with the presence of malignant astrocytomas, brain metastases, and carcinomatous meningitis. Cancer 82(5):923-30, 1998.

37. Friedman WA, Foote KD: Linear accelerator radiosurgery in the management of brain tumors. Ann Med 32:64-80, 2000.

38. Geertsen R, Zenklusen R, Kamarshev J, et al.: Inverse regulation of neuronal cellular adhesion molecule (NCAM) by IFN-gamma in melanoma cell cultures established from CNS lesions. Int J Cancer 83(1):135-40, 1999.

39. Geiger M, Wu JK, Ling MN, et al.: Response of intracranial melanoma metastases to stereotactic radiosurgery. Radiat Oncol Investig 5(2):72-80, 1997.

40. Glantz MJ, Choy H, Yee L: Prophylactic cranial irradiation in small cell lung cancer: rationale, results, and recommendations. Semin Oncol 24(4):477-83, 1997.

41. Gramaglia A, Loi GF, Mongioj V, Baronzio GF: Increased survival in brain metastatic patients treated with stereotactic radiotherapy, omega three fatty acids and bioflavonoids. Anticancer Res 19(6C):5583-6, 1999.

42. Gregor A: Prophylactic cranial irradiation in small-cell lung cancer: is it ever indicated? Oncology (Huntingt) 12(1 Suppl 2):19-24, 1998.

43. Gaspar L, Scott C, Rotman M, et al: Recursive partitioning analysis (RPA) of prognostic factors in three radiation therapy oncology group (RTOG) brain metastasis trials. INT J RAD Oncol Biol Phys 37(4)745-751, 1997.

44. Gridelli C, Perrone F, Gallo C, et al.: Single-agent gemcitabine as second-line treatment in patients with advanced non small cell lung cancer (NSCLC): a phase II trial. Anticancer Res 19(5C):4535-8, 1999.

45. Grobb JJ, Regis J, Laurans R, et al.: Radiosurgery without whole brain radiotherapy in melanoma brain metastases. Club de Cancerologie Cutanee. Eur J Cancer 34(8):1187-92, 1998.
46. Gupta G, Robertson AG, MacKie RM: Cerebral metastases of cutaneous melanoma. Br J Cancer 76(2):256-9, 1997.

47. Hahn M, Wieland I, Koufaki ON, et al.: Genetic alterations of the tumor suppressor gene PTEN/MMAC1 in human brain metastases. Clin Cancer Res 5(9):2431-7, 1999.

48. Haines SJ: Surgical or radiosurgical treatment for brain metastases? Opportunity lost, responsibility shirked. Clin Neurosurg 45:30-1, 1999.

49. Hamasaki H, Aoyagi M, Kasama T, et al.: GT1b in human metastatic brain tumors: GT1b as a brain metastasis-associated ganglioside. Biochimica et Biophysica Acta 1437(1):93-9, 1999.

50. Hampl M, Hampl JA, Reiss G, et al.: Loss of heterozygosity accumulation in primary breast carcinomas and additionally in corresponding distant metastases is associated with poor outcome. Clin Cancer Res 5(6):1417-25, 1999.

51. Harabin-Slowinska M, Slowinski J, Konecki J, Mrowka R: Expression of adhesion molecule CD44 in metastatic brain tumors. Folia Neuropathol 36(3): 179-84, 1998.

52. Harada Y, Nonomura N, Kondo M, et al.: Clinical study of brain metastasis of renal cell carcinoma. Eur Urol 36(3):230-5, 1999.

53. Heiss JD, Papavassilliou E, Merrill MJ, et al.: Mechanism of dexamethasone suppression of brain tumor–associated vascular permeability in rats. J Clin Invest 98:1400-8, 1996.

54. Hildebrand J, Dewitte O, Dietrich PY, de Tribolet N: Management of malignant brain tumors. Eur Neurol 38(3):238-53, 1997.

55. Hoegler D: Radiotherapy for palliation of symptoms in incurable cancer. Curr Probl Cancer 21(3):129-83, 1997.

56. Hsiung CY, Leung SW, Wang CJ, et al. The prognostic factors of lung cancer patients with brain metastases treated with radiotherapy. J Neurooncol 36(1):71-7, 1998 Jan.

57. Imanaka K, Sugimoto K, Obayashi Y, et al.: Reirradiation therapy for brain metastases from small cell lung cancer. Radiat Med 16(2):153-6, 1998.

58. Johnson JD, Young B: Demographics of brain metastases. Neurosurg Clin North Am 7:337-44, 1996.

59. Joseph J, Adler JR, Cox RS, et al: Linear Acclerator based stereotactic radiosurgery for brain metastases: The influence of number of lesions on survival. J Clin Oncol 14:1085-1092, 1996.

60. Kaba SE, Kyritsis AP, Hess K, et al.: TPDC-FuHu chemotherapy for the treatment of recurrent metastatic brain tumors. J Clin Oncol 15(3):1063-70, 1997.

61. Kawai A,Nagasaka Y, Muraki M, et al.: Brain metastasis in malignant pleural mesothelioma. Intern Med 36(8):591-4, 1997.

62. Kelly K, Bunn PA Jr.: Is it time to reevaluate our approach to the treatment of brain metastases in patients with non-small cell lung cancer? Lung Cancer 20(2):85-91, 1998.

63. Khansur T, Routh A, Hickman B: Brain metastases from unknown primary site. J Miss State Med Assoc 38(7):238-42, 1997.

64. Kim YS, Kondziolka D, Flickinger JC, Lunsford LD: Stereotactic radiosurgery for patients with nonsmall cell lung carcinoma metastatic to the brain. Cancer 80(11):2075-83, 1997.

65. Kirova YM, Chen J, Rabarijaona LI, et al.: Radiotherapy as palliative treatment for metastatic melanoma. Melanoma Res 9(6):611-3, 1999.

66. Kleinschmidt-DeMasters BK, Orr EA, Savelieva E, et al.: Paucity of retinoic acid receptor alpha (RAR alpha) nuclear immunostaining in gliomas and inability of retinoic acid to influence neural cell adhesion molecule (NCAM) expression. J Neurooncol 41(1):31-42, 1999.

67. Kleinschmidt-DeMasters BK, Shroyer AL, Haskizumi TL, et al.: Part I. Telomerase levels in human metastatic brain tumors show four-fold logarithmic variability but no correlation with tumor type or interval to patient demise. J Neurol Sci 161(2):116-23, 1998.

68. Ko FC, Liu JM, Chen WS, et al.: Risk and patterns of brain metastases in colorectal cancer: 27-year experience. Dis Colon Rectum 42(11):1467-71, 1999.

69. Kochhar R, Frytak S, Shaw EG: Survival of patients with extensive small-cell lung cancer who have only brain metastases at initial diagnosis. Am J Clin Oncol 20(2):125-7, 1997.

70. 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 45(2):427-34, 1999.

71. Kruger A, Sanchez-Sweatman OH, Martin DC, et al.: Host TIMP-1 overexpression confers resistance to experimental brain metastasis of fibrosarcoma cell line. Oncogene 16(18):2419-23, 1998.

72. Lagerwaard FJ, Levendag PC, Nowak PJ, et al.: Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. Int J Radiat Oncol Biol Phys 43(4):795-803, 1999.

73. Lang FF, Sawaya R: Surgical treatment of metastatic brain tumors. Semin Surg Oncol 14(1):53-63, 1998.

74. Laplanche A, Monnet I, Santos-Miranda JA, et al.: Controlled clinical trial of prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Lung Cancer 21(3):193-201, 1998.

75. Loeffler JS, Barker FG, Chapman PH: Role of radiosurgery in the management of central nervous system metastases. Cancer Chemother Pharmacol 43 Suppl:S11-4, 1999.

76. Ludwig HC, Behnke J, Markakis E: Brain metastases in neurosurgery: indications, surgical procedures and outcome. Anticancer Res 18(3C):2215-8, 1998 May-Jun.

77. Lentzsch S, ReichardT P, Weber F et al: Brain metastases in breast cancer: Prognostic factors and management. EUR J Cancer 35(4)580-585, 1999.

78. Mahalati K, Bilen CY, Ozen H, etal.: The management of brain metastasis in nonseminomatous germ cell tumours. Bju International 83(4):457-61, 1999 Mar.

79. Martinez-Manas RM, Brell M, Rumia J, Ferrer E: Brain metastases in endometrial carcinoma. Gynecol Oncol 70(2):282-4, 1998.

80. Matsuo T, Shibata T, Yasunaga A, et al.: Dose optimization and indication of Linac radiosurgery for brain metastases. Int J Radiat Oncol Biol Phys 45(4):931-9, 1999.

81. Minotti V, Crino L, Meacci ML, et al.: Chemotherapy with cisplatin and teniposide for cerebral metastases in non-small cell lung cancer. Lunc Cancer 20(2):93-8, 1998.

82. Mori Y, Kondziolka D, Flickinger JC, et al.: Stereotactic radiosurgery for brain metastasis from renal cell carcinoma. Cancer 83(2):344-53, 1998 Jul 15.

83. Murray KJ, Scott C, Greenberg HM, 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 39(3):571-4, 1997.

84. Nieder C, Berberich W, Schnabel K: Tumor-related prognostic factors for remission of brain metastases after radiotherapy. Int J Radiat Oncol Biol Phys 39(1):25-30, 1997.

85. Nieder C, Nestle U, Motaref B, et al.: Prognostic factors in brain metastases: should patients be selected for aggressive treatment according to recursive partitioning analysis (RPA) classes? Int J Radiat Oncol Biol Phys 46(2):297-302, 2000.

86. Nieder C, Nestle U, Niewald M, Schnabel K: Accelerated radiotherapy for brain metastases. Radiother Oncol 45(1):17-22, 1997.

87. Nieder C, Schwerdtfeger K, Steudel WI, Schnabel K: Patterns of relapse and late toxicity after resection and whole-brain radiotherapy for solitary brain metastases. Strahlenther Onkol 174(5):275-8, 1998.

88. Noordijk EM, Vecht CJ, Haaxma-Reiche H: The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age. Int J Radiation Oncol Biol Phys 29:711-17, 1994.

89. Nygaard SJ, Haugland HK, Kristoffersen EK, et al.: Expression of annexin II in glioma cell lines and in brain tumor biopsies. J Neurooncol 38(1):11-8, 1998.

90. Ogose A, Morita T, Hotta T, et al.: Brain metastases in musculoskeletal sarcomas. Jpn J Clin Oncol 29(5):245-7, 1999.

91. Orhan B, Yalcin S, Evrensel T, et al.: Successful treatment of cranial metastases of extrapulmonary small cell carcinoma with chemotherapy alone. Med Oncol 15(1):66-9, 1998.

92. Palmieri G, Montella L, Martignetti A, Bianco AR: Interferon alpha-2b at low doses as long-term antiangiogenic traetment of a metastatic intracranial hemangioendothelioma: a case report. Oncology Reports 7(1):145-9, 2000.

93. Patchell, RA, Tibbs PA, Regine WF: Postoperative Radiotherpay in the treeatment of single metastases to the brain. JAMA 280:1485-1489, 1998.

94. Patchell RA, Tibbs PA, Walsh JW, et al.: A randomized trial of surgery in the treatment of single metastases to the brain. N Eng J Med 322:494-500, 1990.

95. Peterson AM, Meltzer CC, Evanson EJ, et al.: MR imaging response of brain metastases after gamma knife stereotactic radiosurgery. Radiology 211(3):807-14, 1999.

96. Pieper DR, Hess KR, Sawaya RE: Role of surgery in the treatment of brain metastases in patients with breast cancer. Ann Surg Oncol 4(6):481-90, 1997.

97. Pirzkall A, Debus J, Lohr F, et al.: Radiosurgery alone or in combination with whole-brain radiotherapy for brain metastases. J Clin Oncol 16(11):3563-9, 1998.

98. Postler E, Meyermann R: Brain metastasis in renal cell carcinoma: clinical data and neuropathological defferential diagnoses. Anticancer Res 19(2C):1579-81, 1999.

99. Postmus PE, Haaxma-Reiche H, Gregor A, et al.: Brain-only metastases of small cell lung cancer; efficacy of whole brain radiotherapy. An EORTC phase II study. Radiother Oncol 46(1):29-32, 1998.

100. Proebstle TM, Fuchs T, Scheibenbogen C, et al.: Long-term outcome of treatment with dacarbazine, cisplatin, interferon-alpha and intravenous high dose interleukin-2 in poor risk melanoma patients. Melanoma Res 8(6):557-63, 1998.

101. Quantin X, Khial F, Reme-Saumon M, et al.: Concomitant brain radiotherapy and vinorelbine-ifosfamide-cisplatin chemotherapy in brain metastases of non-small cell lung cancer. Lung Cancer 26(1):35-9, 1999.

102. Quantin X, Pujol JL, Paris A, et al.: Concomitant brain radiotherapy and high-dose ifosfamide in brain relapses of lung cancer. Ann Oncol 8(9):911-3, 1997.

103. Ruan S, Fuller G, Levin V, et al.: Detection of p21 WAFI/Cip1 in brain metastases. J Neurooncol 37(3):223-8 1998.

104. Ricci PE: Imaging of adult brain tumors. Neuroimaging Clin N Am 9(4):651-69, 1999.

105. Richard MA, GrobJJ, Zarrour H, et al.: Combined treatment with dacarbazine, cisplatin, fotemustine and tamoxifen in metastatic malignant melanoma. Melanoma Res 8(2):170-4, 1998.

106. Saitoh Y, Fujosawa T, Shiba M, et al.: Prognostic factors in surgical treatment of solitary brain metastasis after resection of non-small-cell lung cancer. Lung Cancer 24(2):99-106, 1999.

107. Salvati M, Cervoni L, Caruso R, et al.: Sarcoma metastatic to the brain: a series of 15 cases. Surg Neurol 49(4):441-4, 1998.

108. Salven P, Manpaa H, Orpana A, et al.: Serum vascular endothelial growth factor is often elevated in disseminated cancer. Clin Cancer Res 3(5):647-51, 1997.

109. Sampson JH, Carter JH Jr., Friedman AH, Seigler HF: Demographics, prognosis, and therapy in 702 patients with brain metastases from malignant melanoma. J Neurosurg 88(1):11-20, 1998.

110. Savas B, Arslan G, Gelen T, et al.: Multidrug resistant malignant melanoma with intracranial metastasis responding to immunotherapy. Anticancer Res 19(5C):4413-20, 1999.

111. Sawaya R: Surgical treatment of brain metastases. Clin Neurosurg 45:41-7, 1999.

112. Sawaya R, Hammoud M, Schoppa D, et al.: Neurosurgical outcomes in a modern series of 400 craniotomies for treatment of parenchymal tumors. Neurosurgery 42(5):1044-55; discussion 1055-6, 1998.

113. Schellinger PD, Meinck HM, Thron A: Diagnostic accuracy of MRI compared to CCT in patients with brain metastases. J Neurooncol 44(3):275-81, 1999.

114. Schoeggl A, Kitz, k, Ertl A, et al.: Progrnostic factor analysis for multiple brain metastases after gamma knife radiosurgery: results in 97 patients. J Neurooncol 42(2):169-75, 1999.

115. Sen M, Demiral AS, Cetingoz R, et al.: Prognostic factors in lung cancer with brain metastasis. Radiother Oncol 46(1):33-8, 1998.

116. Seung SK, Sneed PK,McDermott MW, et al.: Gamma knife radiosurgery for malignant melanoma brain metastases. Cancer J Sci Am 4(2):103-9, 1998.

117. 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 37(2):375-83, 1997.

118. Shuper A, Cohen IJ, Mor C, et al.: Metastatic brain involvement in Ewing family of tumors in children. Neurology 51(5):1336-8, 1998.

119. Sierra A, Price JE, Garcia-Ramirez M, et al.: Astrocyte-derived cytokines contribute to the metastatic brain specificity of breast cancer cells. Lab Invest 77(4):357-68, 1997.

120. Sighvatsson V, Ericson K, Tomasson H: Optimising contrast-enhanced cranial CT for detection of brain metastases. Acta Radiol 39(6):718-22, 1998.

121. Sneed PK, Lamborn KR, Forstner JM, et al.: Radiosurgery for brain metastases: is whole brain radiotherapy necessary? Int J Radiat Oncol Biol Phys 43(3):549-58, 1999.

122. Stuschke M, Eberhardt W., Pottgen C, et al.:L 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 17(9):2700-9, 1999.

123. Suwinski R, Lee SP, Withers HR: Dose-response relationship for prophylactic cranial irradiation in small cell lung cancer. Int J Radiat Oncol Biol Phys 40(4):797-806, 1998.

124. Sze G, Johnson C, Kawamura Y, et al.: Comparison of single- and triple-dose contrast material in the MR screening of brain metastases. AJNR Am J Neuroradiol 19(5):821-8, 1998.

125. Taddei GL, Moncini D, Raspollini MR, et al.: Metastatic brain tumors. Pathologica 91(1):13-7, 1999.

126. Takahashi JA, Llena JF, Hirano A: Pathology of cerebral metastases. Neurosurg Clin North Am 7:345-67, 1996.

127. Thng CH, Tay KH, Chan LL, et al.: Magnetic resonance imaging of brain metastases: magnetisation transfer or triple dose gadolinium? Ann Acad Med Sigapore 28(4):529-33, 1999.

128. Tummarello D, Lippe P, Bracci R, et al.: First line chemotherapy in patients with brain metastases from non-small cell and small cell lung cancer. Oncol Rep 5(4):8977-900, 1998.

129. Ulrich J, Gademann G, Gollnick H: Management of cerebral metastases from malignant melanoma: results of a combined, simultaneous treatment with fotemustine and irradiation. J Neurooncol 43(2):173-8, 1999.

130. Van de Pol M, ten Velde GP, Wilmink JT, et al.: Efficacy and safety of prophylactic cranial irradiation in patients with small cell lung cancer. J Neurooncol 35(2):153-60, 1997.

131. Van der Ree TC, Dippel DW, Avezaat CJ, et al.: Leptomeningeal metastasis after surgical resection of brain metastases. J Neurol Neurosurg Psychiatry 66(2):225-7, 1999.

132. Vecht, CJ: Clinical management of brain metastases. J Neurol 245:127-31, 1998.

133. Vermeulen SS: Whole brain radiotherapy in the treatment of metastatic brain tumors. Semin Surg Oncology 14(1):64-9, 1998.

134. Vinolas N, Graus F, Mellado B, et al.: Phase II trial of cisplatinum and etoposide in brain metastases of solid tumors. J Neurooncol 35(2):145-8, 1997.

135. Wagner H Jr.: Prophylactic cranial irradiation for patients with small cell lung cancer. An enduring controversy. Chest Surg Clin N Am 7(1):151-66, 1997.

136. Wen PY, Loeffler JS: Management of brain metastases. Oncology (Huntingt) 13(7):941-54, 957-61: disucssion 961-2, 9, 1999.

137. Willner J, Flentje M, Bratengeier K: CT simulation in stereotactic brain radiotherapy—analysis of isocenter reproducibility with mask fixation. Radiother Oncol 45(1):83-8, 1997.

138. Wronski M, Arbit E: Resection of brain metastases from colorectal carcinoma in 73 patients. Cancer 85(8):1677-85, 1999.

139. Wronski M, Arbit E, McCormick B, Wronski M: Surgical treatment of 70 patients with brain metastases from breast carcinoma. Cancer 80(9):1746-54, 1997.

140. Wronski M, Maor MH, Davis BJ, et al.: External radiation of brain metastases from renal carcinoma: a retrospective study of 119 patients from the M.D. Anderson Cancer Center. Int J Radiat Oncol Biol Phys 37(4):753-9, 1997.

141. Yamanaka K, Gohji K, Hara I, et al.: Clinical study of renal cell carcinoma with brain metastasis. Int J Urol 5(2):124-8, 1998.

142. Yokoi K, Kamiya N, Matsuguma H, et al.: Detection of brain metastasis in potentially operable non-small cell lung cancer: a comparison of CT and MRI. Chest 115(3):714-9, 1999.

143. Young RF: Radiosurgery for the treatment of brain metastases. Semin Surg Oncol 14(1):70-8, 1998.