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Brain metastases: Presentation, evaluation, and management

ABSTRACT

Brain metastases are a common and devastating consequence of cancer and carry a poor prognosis. Nevertheless, physicians can serve their patients well by suspecting, detecting, and treating them appropriately.

KEY POINTS

A patient with a history of cancer who presents with symptoms suggestive of an intracranial mass should undergo a contrast-enhanced computed tomographic scan or, preferably, a high-dose contrast-enhanced magnetic resonance imaging scan.

Corticosteroids should be given to all symptomatic patients once the diagnosis is confirmed, and can be tapered after definitive therapy is completed.

For most patients, whole-brain irradiation over 2 to 3 weeks relieves symptoms well. In some patients, the addition of either craniotomy or stereotactic radiosurgery can prolong survival and functional independence.

IN A PATIENT WITH CANCER, the new onset of headache or neurologic symptoms may represent a brain metastasis. Although the prognosis is poor, prompt diagnosis and treatment can prolong the patient's life and improve the quality of his or her remaining days.

In this article we briefly review the key diagnostic features of brain metastases, discuss the current role of contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) in the diagnosis, and compare the effectiveness and prognostic implications of current therapies.

BRAIN METASTASES ARE COMMON

Experts estimate that 20% to 40% of patients with cancer develop brain metastasis during the course of their illness,[1,2] resulting in more than 170,000 cases annually.[2] These figures have been increasing over the past 40 years as treatment of malignant diseases has improved and survival times have increased: previously, many patients would die before foci of microscopic brain metastases could proliferate into clinically detectable tumors.

ORIGIN OF BRAIN METASTASES

Malignancies arising from any organ may metastasize to the brain. Some tumor types, however, are more likely to metastasize to the brain.[3–8] In adults, melanoma has the highest frequency of brain metastases, followed by cancers of the lung, breast, and kidneys. However, lung cancer and breast cancer are more common than melanoma, and therefore cause more cases of brain

metastasis (FIGURE 1). Similarly, although cancers of the prostate and the gastrointestinal tract do not commonly metastasize to the brain, they are so common that they cause a considerable number of brain metastases per year.

In children, osteogenic sarcoma, rhabdomyosarcoma, and testicular germ cell tumors are the most common sources of brain metastases.[9]

CANCER CELLS SPREAD HEMATOGENOUSLY

In most cases of brain metastasis, cancer cells make their way to the brain via the blood vessels, as they do to visceral organs. Usually, these cells come from a primary or metastatic tumor in the lung.[10] However, brain metastases can occur without lung involvement, a fact that lends support to the theory that certain tumor cells spread preferentially to specific organs (eg, melanoma and small cell lung cancer spreading preferentially to the brain).[11]

Tumors usually gain access to the brain via the arterial blood supply; however, dissemination via the vertebral venous system (Batson's plexus) may also occur.

SITES OF BRAIN METASTASES

The distribution of brain metastases correlates strongly with cerebral blood flow (FIGURE 2).[6,12] The cerebral hemispheres receive the majority of blood flow and are the site of approximately 80% of brain metastases. The cerebellum is the site of 15% of cases, and the brainstem is the site of 5%.[12]

Within these areas, metastases tend to occur at sites where the blood vessels rapidly diminish in caliber and in the distal reaches of the arterial tree.[12,13] Blood vessels in these regions branch rapidly into end capillaries, and the resulting "filter" may act as a trap for metastasizing cells. The gray matter-white matter interface is one such location, and there is a high frequency of metastasis within this region. Another common location for metastases is within the vascular border or "watershed" zones, which account for only one third of the total brain volume but two thirds of brain metastases.[13,14]

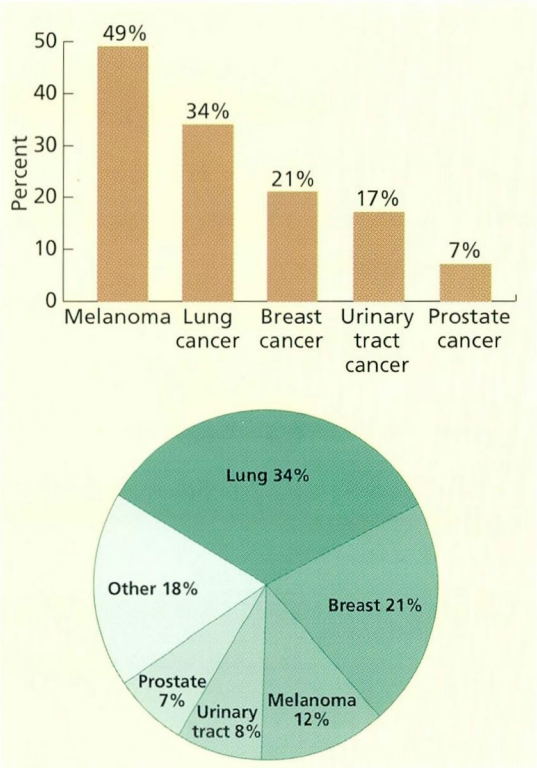

FIGURE 1. Top. frequency of brain metastases in various malignant diseases. **Bottom,** distribution of primary tumors among patients with brain metastases.

Suspect brain metastasis in any cancer patient with a new headache

SYMPTOMS CAN VARY

Symptoms of brain metastasis generally arise when a disruption of the blood-brain barrier results in vasogenic edema. The surrounding brain tissue becomes compressed, and the increasing edema may increase the intracranial pressure. The sensation of pain results from disturbance of pain-sensitive structures such as the dura, dural sinuses, cranial nerves, and blood vessels.

The symptoms can vary greatly in severity and rapidity of onset. The brain accounts for 70% of the intracranial volume; the other 30% consists of cerebrospinal fluid and blood vessels. A slowly growing mass within the brain first displaces cerebrospinal fluid as it compresses the ventricular system, and the intracranial pressure may remain

Distribution of brain metastases

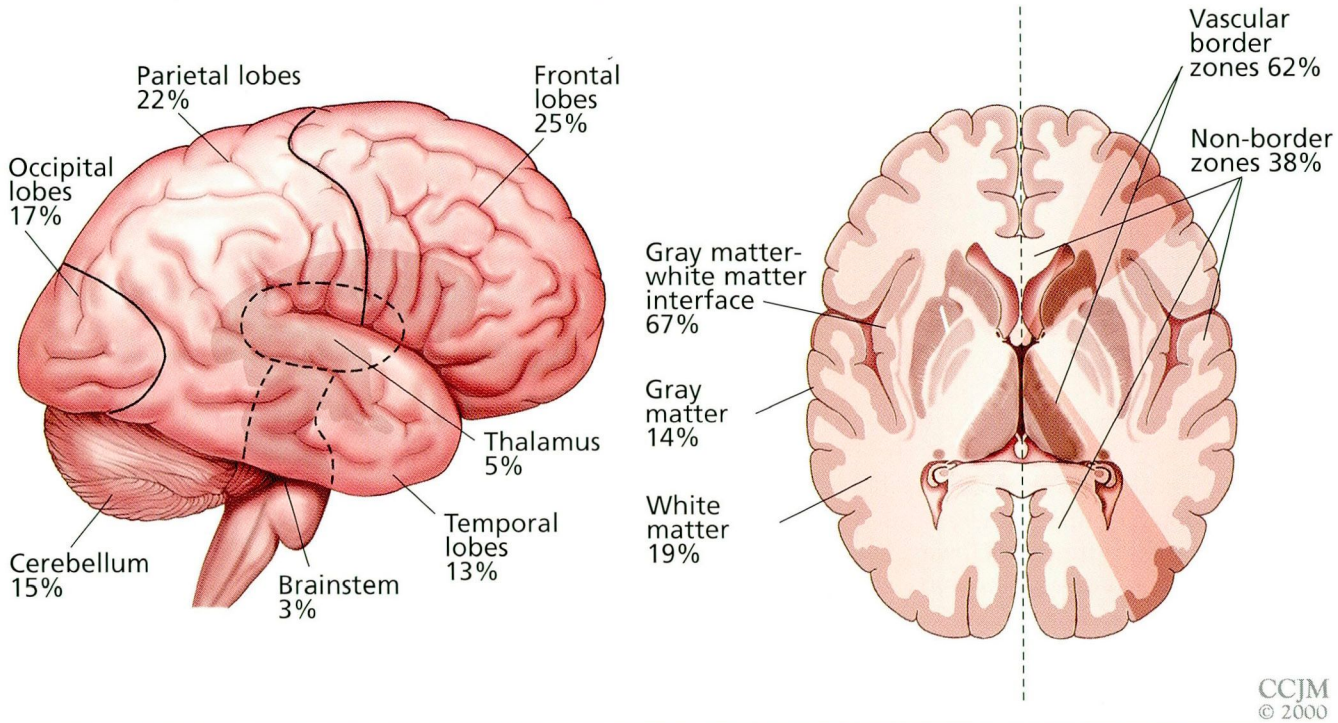

FIGURE 2. Distribution of brain metastases correlates with cerebral blood flow. **Left**, nearly 80% of metastases occur in the central hemispheres.[6,12,41] **Right**, within the substance of the brain, metastases tend to develop in the most distal reaches of the arterial tree, where capillaries may trap metastasizing cells—for example, at the gray matter-white matter interface or at the vascular border zone.[13]

near normal. In this situation, symptoms may be trivial and physical findings absent. Indeed, autopsy studies reveal a surprising number of clinically undetected brain metastases.[9,14,15] On the other hand, metastases often produce a significant amount of surrounding edema, with a rapidly progressive mass effect. In this instance, symptoms can progress rapidly, often prompting an emergency evaluation.

Headache is the most common symptom, occurring in approximately 50% of patients (TABLE 1).[3,6,8,16,17] The headaches usually are worse in the morning, and their duration and severity slowly progress. However, one should suspect brain metastasis in any cancer patient with a new headache, regardless of its characteristics.

Other symptoms include focal weakness, mental status changes, gait disorder, seizures, and visual disturbances.

DIAGNOSIS

A high level of suspicion and a careful history and physical examination are essential. A history of cancer should raise the level of suspicion, since 80% of patients with brain metastasis have a history of cancer.[2,3] However, the brain metastasis itself is the first manifestation of cancer in 10% to 15% of patients with brain metastases, and a thorough evaluation discloses no identifiable primary malignancy in 5% to 10%.

Physical examination

On physical examination, pay special attention to the patient's mental status and to the peripheral neurologic examination. Cognitive deficits can be found in 75% of patients with brain metastases, and hemiparesis in 66%. Unilateral sensory loss, ataxia, aphasia, and papilledema are also common.[3,8,17] With an

adequate history and physical examination and a basic knowledge of neuroanatomy, one can often make an educated guess as to the location of the tumor or tumors.

MRI is more sensitive than CT

In the past, the history and physical examination were the most effective diagnostic tools, but CT and MRI now provide safe, more sensitive methods. Therefore, once brain metastases are suspected, contrast-enhanced CT or MRI is appropriate as an initial examination (FIGURE 3).

In particular, MRI and CT reveal that most patients with brain metastasis have multiple lesions.[10,14,18–20] Lung cancer and melanoma are more often associated with multiple metastases, whereas breast, renal, and colorectal cancer are more often associated with single metastases.[10]

Of the two imaging tests, MRI may be more sensitive, especially when performed with high doses of gadolinium contrast.[18,19,21,22] For example, CT, often the first imaging study obtained, reveals multiple metastases in 50% of patients,[12] but gadolinium-enhanced MRI indicates a prevalence of about 70%.[18,19,21,22]

Differential diagnosis

The etiology of a newly diagnosed intracranial mass must be elucidated before starting therapy. The differential diagnosis includes:

- Primary or metastatic neoplasm
- Infection
- Infarction
- Hemorrhage.

The clinical history and the appearance of the mass on CT or MRI often provide clues as to whether the mass is a neoplasm or one of the other abnormalities. However, no single imaging characteristic can differentiate a primary brain tumor from a metastasis. Features of the mass that increase the suspicion of metastasis are a rounded appearance with peripheral "ring" enhancement, location within the junction between the gray matter and white matter, and a large amount of vasogenic edema.[23] A history of malignancy or the presence of multiple lesions also supports the diagnosis of metastasis rather than a primary brain tumor.

TABLE 1

Signs and symptoms of brain metastases

SIGN OR SYMPTOM	PREVALENCE
Headache	49%
Weakness	43%
Mental status changes	37%
Cerebellar dysfunction	23%
Papilledema	19%
Sensory disturbance	18%
Seizures	16%

ADAPTED FROM BORGELT ET AL (REFERENCE 41), HOSKIN ET AL (REFERENCE 15), AND POSNER (REFERENCE 8).

In the absence of a known malignancy

If the patient has no known malignancy, the discovery of a single lesion or multiple lesions in the brain should prompt a search for other sites of disease. Chest radiography, urinalysis, a complete blood count, and routine blood chemistries, including liver function tests, should be obtained in all patients. Prostate-specific antigen levels should be tested in all men, and bilateral mammograms should be obtained in all women.

Further study with colonoscopy or CT of the chest, abdomen, and pelvis should not delay the procurement of tissue for diagnosis, and biopsy of a brain mass is indicated if no other sites of disease are identified. Other indications for surgical intervention are discussed later.

Corticosteroids improve symptoms and can double survival time compared with no treatment

PROGNOSIS

The prognosis is uniformly poor. Untreated, patients with brain metastases have a progressively deteriorating course until death about 1 month later, with most deaths resulting directly from the brain metastases.[24–26] In general, management is strictly palliative, but aggressive therapy in carefully selected patients extends the median survival to nearly 1 year.[27–33]

Several factors affect the prognosis.

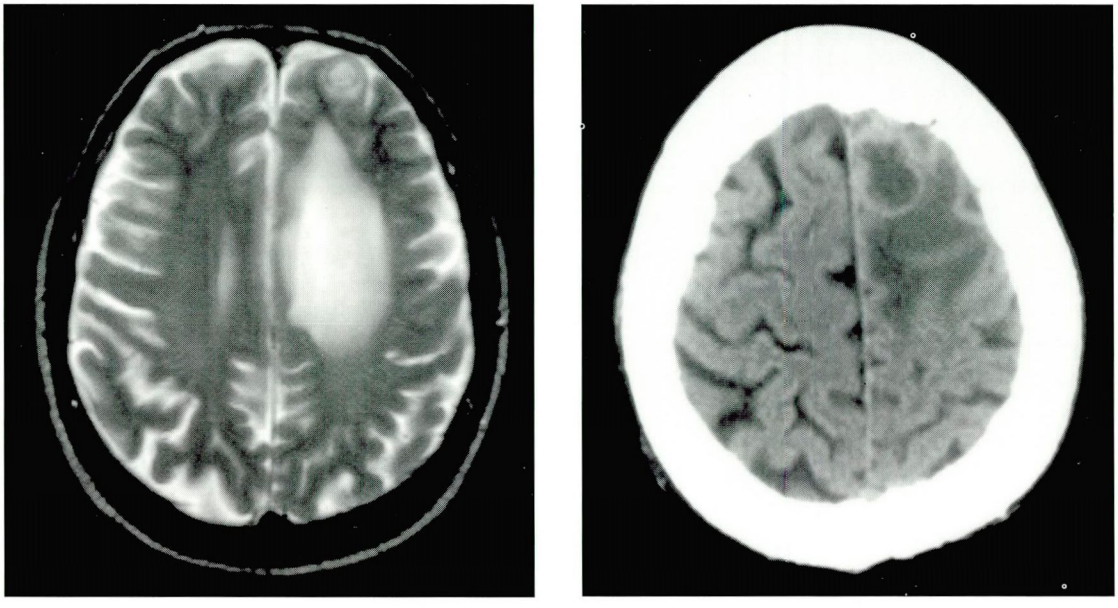

FIGURE 3. MRI (**left**) and CT (**right**) of a typical patient with brain metastases.

Radiotherapy plays a key role in palliation of symptoms of brain metastases

Karnofsky performance status

Recently, the Radiation Therapy Oncology Group[34] divided 1,200 patients treated with whole-brain radiotherapy into three prognostic groups on the basis of their Karnofsky performance status scores (0 indicates no function, 100 indicates completely normal function):

- Patients of any age with a Karnofsky score below 70 (indicating the inability to perform normal activities of daily living) had the worst prognosis (median survival 2.3 months)
- Patients with a Karnofsky score of 70 or higher who were age 65 or older with an uncontrolled primary tumor or evidence of other systemic metastases had a median survival of 4.2 months.
- Patients younger than age 65 with a Karnofsky score of 70 or higher, a controlled primary tumor, and no evidence of other metastases had the best prognosis (median survival 7.1 months).

Number of brain lesions

A crucial drawback of the Radiation Therapy Oncology Group study was that it did not elicit the number of brain metastases as a prognostic factor. In general, patients with only one brain metastasis are felt to have a better prognosis than those with more than one, and in particular, those with a "solitary" brain metastasis (ie, one brain lesion without evidence of cancer elsewhere in the body) tend to fare better than those with multiple lesions or a "single" lesion (ie, one brain lesion with uncontrolled cancer elsewhere in the body).

Other factors

Other factors that correlate with longer survival include surgical accessibility of the lesion, and a long disease-free interval following the original diagnosis.[27–33]

MEDICAL MANAGEMENT

The diagnosis of brain metastasis is devastating for patients and their families. Despite this, appropriate management can relieve symptoms and prolong survival, and drug therapy can play a key role.

Corticosteroids

Once the diagnosis has been confirmed, all symptomatic patients should receive corticosteroids, which can be tapered after definitive therapy is completed. This treatment produces clinical improvement in 70% of patients and doubles the expected survival time.[24–26,35,36] Response to treatment is often noticeable within several hours, with maximal effect within 1 week.[10]

The mechanism by which steroids exert their effect is not completely understood, but

they seem to alleviate symptoms by reducing vasogenic edema. Evidence for this theory comes from the observation that symptoms of global cognitive dysfunction respond readily to steroids, whereas focal neurologic deficits tend to be more resistant.

Cautions. Although corticosteroids are safe and effective, care should be taken in patients with an intracranial lesion or lesions and no known history of malignancy. Both lymphoma and infection are among the differential diagnoses of intracranial mass lesions, and the signs and symptoms may be identical to those of metastases. In the absence of a known malignancy, the accurate diagnosis of an intracranial mass depends solely on the biopsy specimen. Unfortunately, lymphomas often respond dramatically to corticosteroids, and if corticosteroids are given before biopsy, the biopsy result may be falsely negative, ultimately delaying appropriate diagnosis and therapy. Conversely, giving a corticosteroid in the presence of infection may limit the host immune response and accelerate the infectious process, with disastrous results.

Anticonvulsants

Anticonvulsant therapy is indicated for patients who present with seizures. A single agent can usually control the seizures.

For patients presenting without seizures, prophylactic anticonvulsant therapy has not been shown to reduce the incidence of subsequent seizures. The routine use of anticonvulsant therapy for patients without seizures is therefore not recommended.[37]

WHOLE-BRAIN IRRADIATION

Radiotherapy plays a central role in the palliation of brain metastases. Treatment of the whole brain is the standard approach, and symptoms improve in more than 80% of patients within 3 weeks of treatment.[16] Median survival is increased to 4 to 5 months after whole-brain irradiation, and the subsequent death rate from neurologic disease is equal to that from systemic disease.[34,38]

The dose and schedule of whole-brain irradiation have long been controversial.[38–41] The standard duration is 2 to 3 weeks,[41] and for most patients, this regimen results in excellent palliation of symptoms. However, a longer course may result in fewer long-term side effects and may be considered for patients with a better prognosis.

Prophylactic cranial irradiation is controversial and reserved for newly diagnosed cancer patients at high risk for developing brain metastasis: eg, patients with small cell lung cancer or advanced stage non-small cell lung cancer. Although many studies have demonstrated a significant reduction in central nervous system dissemination, there has been no consistent evidence of a survival benefit.[42–44]

SURGICAL OPTIONS

Indications for surgical resection for brain metastasis include the absence of a known malignancy, a solitary brain metastasis, and recurrent symptoms or life-threatening edema despite conservative management. The complications of craniotomy have been decreasing thanks to improvements in anesthesia, the routine use of corticosteroids, and the development of stereotactic guidance; therefore, a previous reluctance to perform craniotomy in patients with known malignancy is decreasing as more aggressive therapy is pursued.

Resection or radiosurgery plus whole-brain radiation may inprove survival and function

Contraindications to surgery are based mainly on the extent of systemic disease and the location and number of brain metastases. Resection of masses in critical areas, such as the motor strip or language centers, can cause incapacitating neurologic deficits, which are unacceptable, especially in the palliative setting. Even when technically feasible, surgical resection is not an option for most patients because of the presence of multiple metastases or widespread systemic disease.[10]

Survival after surgical resection for a single brain metastasis appears better than after radiotherapy alone; however, metastases recur in 70% to 85% of patients without the addition of cranial irradiation.[30,45]

Combined resection and radiation

As previously stated, patients with a single brain metastasis, controlled or absent systemic disease (solitary brain metastasis), and a good performance status may be expected to survive longer. If these relatively healthy patients undergo surgical extirpation of the mass fol-

lowed by whole-brain irradiation, they survive for a median of nearly 1 year.[27,30,32,45] Compared with less aggressive management, this combined approach provides significant improvements in median survival, disease-free survival, the death rate from brain metastasis, and functional independence.[27,45] Pending further research, combined surgical resection and brain irradiation should be considered for any patient with a solitary brain metastasis and good functional status.

Stereotactic radiosurgery

Designed to deliver a very high dose of radiation to a small target, stereotactic radiosurgery is very well suited for treating brain metastasis. The features of a brain metastasis that make it amenable to treatment with stereotactic radiosurgery include the following:

- Small size, generally less than 4 cm
- Spherical shape
- Easy identification on contrast-enhanced MRI
- Lack of invasion deep into brain tissue.

The chief advantages of stereotactic radiosurgery are that it is minimally invasive and, unlike whole-brain irradiation, it targets only the lesion. Normal surrounding brain tissue is spared from unnecessary irradiation. Because stereotactic radiosurgery is considered a localized treatment, whole-brain irradiation is often given adjunctively to prevent recurrence of metastases in other parts of the brain. Several reviews of this treatment method have shown survival and local control comparable to that of combined surgical resection and whole-brain irradiation.[28,29,31,33]

Obtain a contrast CT or MRI for signs of an intracranial mass

As an alternative to resection. Although the precise role of stereotactic radiosurgery is still under evaluation, it provides a good alternative for patients who are not surgical candidates or who are opposed to craniotomy. Frequently, tumors regress dramatically after stereotactic radiosurgery, and its advocates propose that it replace resection as the treatment of choice for solitary brain metastases, pointing out that stereotactic radiosurgery offers a noninvasive outpatient procedure requiring no general anesthetic. The Radiation Therapy Oncology Group 95-08 is a prospective randomized trial currently underway to evaluate the use of whole-brain irradiation with and without stereotactic radiosurgery for patients with one to three unresected brain metastases. Plans are also underway for future trials that would directly compare stereotactic radiosurgery and resection, with all patients also undergoing whole-brain irradiation.

CHEMOTHERAPY

The use of intravenous chemotherapy in the treatment of brain metastases is limited. Most of the agents do not penetrate the blood-brain barrier in sufficient quantities to act effectively.

Intrathecal chemotherapy may be useful for patients with diffuse studding of the meninges (meningeal carcinomatosis), but due to limited tissue penetration this method is ineffective for parenchymal metastases.

DIAGNOSIS AND TREATMENT TIPS

- In the patient presenting with signs and symptoms suggestive of an intracranial mass, contrast-enhanced CT or MRI is indicated. After a positive imaging study, the suspicion of brain metastasis should be heightened if there are multiple lesions or if the patient has a history of malignancy.
- If the patient has a remote history or no known history of malignancy, the workup should include a thorough history and physical examination, chest radiography, urinalysis, and blood chemistries, and either mammography or prostate-specific antigen assay, depending on the sex of the patient.
- If no accessible lesions are identified after these studies are completed, further workup with CT scans should not delay craniotomy or stereotactic brain biopsy in the establishment of a diagnosis. Corticosteroids should be started in all symptomatic patients after the diagnosis is confirmed and can usually be tapered after therapy is completed. For the majority of patients, whole-brain irradiation over 2 to 3 weeks is appropriate and results in excellent palliation of symptoms. However, in selected patients, the addition of either craniotomy or stereotactic radiosurgery can result in prolonged survival and functional independence.

REFERENCES

1. **Cairncross JG, Kim JH, Posner JB.** Radiation therapy for brain metastasis. Ann Neurol 1980; 7:529–541.
2. **Posner JB.** Management of brain metastasis. Rev Neurol (Paris), 1992; 148:477–487.
3. **Wright DC, Delaney TF, Buckner JC.** Treatment of metastatic cancer. In: DeVita VT, Hellman S, Rosenberg SA, editors. Cancer: principles and practice of oncology. 4th edition. Philadelphia: Lippincott, 1993:2170–2186.
4. **Landis SH, Murray T, Bolden S, Wingo PA.** Cancer statistics, 1998. CA Cancer J Clin 1997; 49:8–31.
5. **Hildebrand J.** Lesions of the nervous system in cancer patients. Monograph series of the EORTC Vol. 5 New York: Raven Press, 1978.
6. **Takakura K, Sano K, Hoho S, et al.** Metastatic tumors of the central nervous system. Tokyo: Igaku-Shoin, 1982.
7. **Galich JH, Sundaresan N.** Metastatic brain tumors. In Wilkins RH, Rengachary SS, editors. Neurosurgery. New York: McGraw-Hill, 1985:597–610.
8. **Posner JB.** Diagnosis and treatment of metastasis to the brain. Clin Bull 1974; 4:47–57.
9. **Graus F, Walker RW, Allen JC.** Brain metastases in children. J Pediatr 1983; 103:558–561.
10. **Sze G, Milano E, Johnson C, Heier L.** Detection of brain metastases: Comparison of contrast enhanced MR with unenhanced MR and enhanced CT. AJNR: Am J Neuroradiol 1990; 11:785–791.
11. **Nicolson GL, Dulski KM.** Organ specificity of metastatic tumor colonization is related to organ-selective growth properties of malignant cells. Int J Cancer 1986; 38:289–294.
12. **Delattre JY, Krol G, Thaler HT, Posner JB.** The distribution of brain metastases. Arch Neurol 1988; 45:741–744.
13. **Hwang TL, Close TP, Grego JM, Brannon WL, Gonzales F.** Predilection of brain metastasis in the gray and white matter junction and vascular border zones. Cancer 1996; 77:1551–1555.
14. **Patchell RA.** The treatment of brain metastasis. Cancer Invest 1996; 14:169–177.
15. **Sorenson JB, Hansen HH, Hansen M, Dombernowsky P.** Brain metastases in adenocarcinoma of the lung: frequency, risk groups, and prognosis. J Clin Oncol 1988; 6:1474–1480.
16. **Hoskin PJ, Crow J, Ford HT.** The influence of extent and local management on the outcome of radiotherapy for brain metastases. Int J Radiat Oncol Biol Phys 1990; 19:111–115.
17. **Posner JB.** Clinical manifestations of brain metastases. In: Weiss L, Gilbert HA, Posner JB, editors. Brain metastasis. Boston: GK Hall, 1980:189–207.
18. **Tsukada Y, Fouad A, Pickren JW, Lane WW.** Central nervous system metastasis from breast carcinoma: Autopsy study. Cancer 1983; 52:2349–2354.
19. **Runge VM, Kirsch JE, Burke VJ, et al.** High dose gadoteridol in MR imaging of intracranial neoplasms. J Magn Reson Imaging 1992; 2:9–18.
20. **Reider-Groswasser I, Merimsky O, Karminsky N, Chaitchik S.** Computed tomography features of cerebral spread of malignant melanoma. Am J Clin Oncol 1996; 19:49–53.
21. **Akeson P, Larsson EM, Kristofferson DT, Jonsson E, Holtas S.** Brain metastases: comparison of gadodiamide injection-enhanced MR imaging at standard and high dose, contrast-enhanced CT, and non-contrast-enhanced MR imaging. Acta Radiologica 1995; 36:300–306.
22. **Yuh WT, Fisher DJ, Runge VM, et al.** Phase III multicenter trial of high-dose gadoteridol in MR evaluation of brain metastasis. A J Neurorad 1994; 15:1037–1051.
23. **Manzione JV, Pce LB, Kieffer SA.** Intracranial neoplasms. In: Haaga JR, Lanzieri CF, Sartoris DJ, Zerhouni EA, editors. Computed Tomography and Magnetic Resonance Imaging of the Whole Body. 3rd edition. St. Louis: Mosby, 1994:170–238.
24. **Markesbery WR, Brooks WH, Gupta GD, Young AB.** Treatment for patients with cerebral metastases. Arch Neurol 1978; 35:754–756.
25. **Ruderman NB, Hall TC.** The use of corticosteroids in the palliative treatment of metastatic brain tumors. Cancer, 1965; 18:298–306.
26. **Horton J, Baxter DH, Olson KB.** The management of metastases to the brain by irradiation and corticosteroids. Am J Roentgenol Radium Ther Nucl Med 1971; 111:334–336.
27. **Patchell RA, Tibbs PA, Walsh JW, et al.** A randomized trial of surgery in the treatment of single metastasis to the brain. N Engl J Med 1990; 322:494–500.
28. **Flickinger JC, Kondziolka D, Lunsford D, et al.** A multi-institutional experience with stereotactic radiosurgery for solitary brain metastasis. Int J Radiat Oncol Biol Phys 1994; 28:797–802.
29. **Alexander E, Moriarty TM, Davis RB, et al.** Stereotactic radiosurgery for the definitive, noninvasive treatment of brain metastases. J Natl Cancer Inst 1995; 87:34–40.
30. **Smalley SR, Laws ER, O'Fallon JR, Shaw EG, Schray MF.** Resection for solitary brain metastasis. J Neurosurg 1992; 77:531–540.
31. **Fernandez-Vicioso E, Suh JH, Kupelian PA, Sohn JW, Barnett GH.** Analysis of prognostic factors for patients with solitary brain metastasis treated by stereotactic radiosurgery. Radiat Oncol Invest 1997; 5:31–37.
32. **Vecht CJ, Haaxma-Reiche H, Noordjik EM, et al.** Treatment of single brain metastasis: Radiotherapy alone or combined with neurosurgery? Ann Neurol 1993; 33:583–590.
33. **Joseph J Adler JR, Cox RS, Hancock SL.** Linear accelerator based stereotaxic radiosurgery for brain metastases: the influence of number of lesions on survival. J Clin Oncol 1996; 14:1085–1092.
34. **Gaspar L, Scott C, Rotman M, et al.** Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys 1997; 37:745–751.
35. **Ehrenkranz JR, Posner JB.** Adrenocorticosteroid Hormones. In: Weiss L, Gilbert HA, Posner JB, editors. Brain Metastasis. Boston: GK Hall, 1980:340–363.
36. **Chang DB, Yang PC, Luh KT, Kuo SH, Hong RL, Lenn LN.** Late survival of non–small cell lung cancer patients with brain metastases. Chest 1992; 101:1293–1297.
37. **Cohen B, Strauss G, Lew R, Silver D, Recht L.** Should prophylactic anticonvulsants be administered to patients with newly diagnosed cerebral metastases? A retrospective analysis. J Clin Oncol 1988; 6:1621–1624.
38. **Borgelt B, Gelber R, Kramer S, et al.** The palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys 1980; 6:1–9.
39. **Kramer S, Hendrickson F, Zelen M, Scholtz W.** Therapeutic trial in the management of metastatic brain tumors by different time/dose fractionation scheme of radiation therapy. NCI Mono 1977; 46:213–221.
40. **Kurtz JM, Gelber R, Brady LW, et al.** The palliation of brain metastases in a favorable patient population: a randomized clinical trial. IJROBP 1981; 7:891–895.
41. **Egawa S, Tukiyama I, Akine Y.** Radiotherapy of brain metastases. Int J Radiat Oncol Biol Phys 1986; 12:1621–1625.
42. **Abner A.** Prophylactic cranial irradiation in the treatment of small-cell carcinoma of the lung. Chest 1993; 103(4 supp):445s–448s.
43. **Rubenstein JH, Dosoretz DE, Katin MJ, et al.** Low doses of prophylactic cranial irradiation effective in limited stage small-cell carcinoma of the lung. Int J Radiat Oncol Biol Phys 1995; 33:329–337.
44. **Lee JS, Umsawasdi T, Barkley HT Jr, et al.** Timing of elective brain irradiation: a critical factor for brain metastasis-free survival in small cell lung cancer. Int J Radiat Oncol Biol Phys 1987; 13:697–704.
45. **Patchell RA, Tibbs PA, Regine WF, et al.** Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA 1998; 280:1485–1489.

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