Clinical Review

Brain Metastasis

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Changes in technology and advancements in patient selection and treatment modalities led the authors to conduct a review of the clinical presentation, diagnosis, therapeutic treatments and strategies, prognosis, and outcomes of patients with cancer and accompanying brain metastasis.

Brain metastasis constitutes more than half of all brain tumors and develops in 15% to 30% of adult patients with cancer, resulting in considerable morbidity and mortality. About 98,000 to 170,000 new cases of brain metastasis occur annually. The development of sensitive neuroimaging techniques and improved survival of patients with cancer have resulted in an apparent increase of incidences.

EPIDEMIOLOGY

Although brain metastasis may be present at the initial diagnosis of malignancy, it is more commonly detected later in the course of the disease. Carcinomas of the lung, breast, colorectum, and melanoma are the most common cancers metastasizing to the brain. Two large studies from the U.S. and Europe have reported a similar incidence rate of brain metastases (Table 1).[1,2] Lung cancer is the most common primary cancer associated with brain metastasis, although breast cancer in women is the most common primary cancer.

PATHOPHYSIOLOGY

Metastasis most commonly reaches the brain by a hematogenous route.[3,4] Roughly 80% to 85% of metastases are found in the cerebral hemispheres (Figure 1).[5,6] There are differences among primary tumor types in terms of a preferred metastatic site within the brain, perhaps related with the similar embryologic origin of the cells. Primary cancers in the abdominal and pelvic cavities have a predilection to metastasize to the posterior fossa, and small-cell lung cancers may metastasize to any part of the brain.[4] Lately, clinicians are finding more breast cancers metastasizing to the brain, particularly in hormone receptor-negative breast cancers.[7]

Table 1. Incidence of brain metastases reported in the literature (%)[1,2]

Reference	Lung	Breast	Colorectal
U.S. study	19.9	5.1	1.8
European study	16.3	5.0	1.2

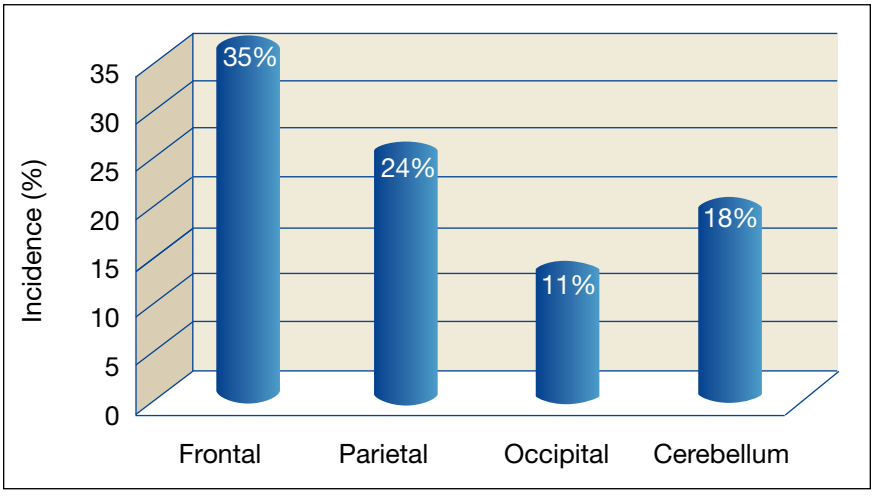

Figure 1. Distribution of brain metastasis (%).[6]

CLINICAL PRESENTATIONS

Historically, common clinical presentations of brain metastasis were headaches, seizures, and neurologic

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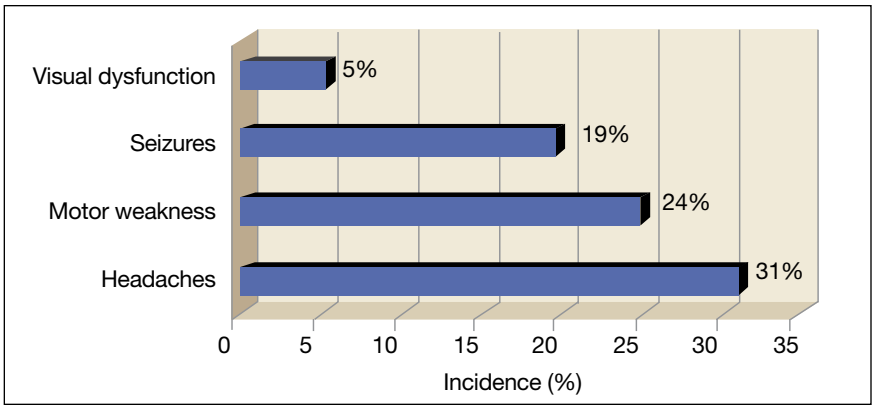

Figure 2. Clinical symptoms.[6]

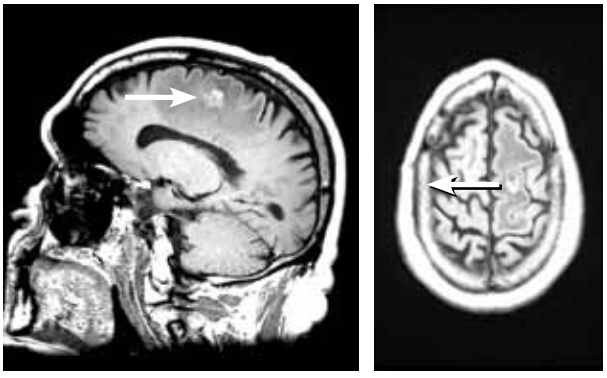

Figure 3. Magnetic resonance imaging showing a mass lesion with a rim and peripheral nodular enhancement (arrow) surrounded by profuse edema within the left cerebral hemisphere.

and cognitive dysfunctions (Figure 2).[8] Headaches were the most common symptom, especially in multiple or posterior fossa tumors. Due to improved imaging studies, brain metastasis is often detected before symptoms manifest or are less severe.[9]

DIAGNOSIS

The diagnosis of brain metastasis is most commonly established by imaging studies. Brain biopsy is not usually necessary if there is an established diagnosis of the primary tumor.

IMAGING STUDIES

Computerized tomographic (CT) scans detect brain metastasis most of the time. However, contrast-enhanced magnetic resonance imaging (MRI) is a more sensitive imaging study, compared with enhanced CT scanning or nonenhanced MRI scanning.[10-13] Magnetic resonance imaging is more sensitive and specific for determining the nature, location, and number of lesions and is more accurate in detection of multiple lesions (up to 20%), compared with contrast-enhanced CT scan. The distinction of single vs multiple brain lesions is critically important when considering surgical therapeutic options. Circumscribed margins surrounded by large amounts of edema (Figure 3) and multiple lesions at the grey-white junction are characteristic features of brain metastasis.

BRAIN BIOPSY

A brain biopsy is not performed most of time. In rare instances, however, a brain biopsy may be necessary to establish or exclude the diagnosis. In one study, roughly 10% of the cases were found to be misdiagnosed as brain metastasis before the lesion was biopsied.[14]

THERAPY

The goals of treatment are relief of symptoms, local control of tumor, and prolongation of survival with acceptable quality of life (QOL).

SYMPTOM TREATMENT

Corticosteroids

Corticosteroids are used to decrease cerebral edema. Dexamethasone is the preferred steroid because of its low mineralocorticoid activity and lesser risk of infection or cognitive impairment.[15] Symptoms generally improve within 1 to 3 days. Neuroimaging improvement generally takes a week or more. Headaches tend to respond earlier than other symptoms, such as neurologic deficits. The usual dosing is 4 mg 4 times a day following an initial loading dose of 10 mg.[16]

Anticonvulsants

Seizures are treated with anticonvulsant therapy. The lowest effective doses are recommended to minimize possible drug toxicities. However, prophylactic anticonvulsants are not recommended, because some patients may never have seizures. Also, inadequate evidence exists for efficacy of prophylactic treatment.[17,18]

CANCER TREATMENT

The most important factor in therapeutic planning is to identify the number and location of metastatic lesions: single vs multiple to select optimal therapy and for prognostic purposes. Available treatments include radiation therapy, surgery, and radiosurgery. Although sys-

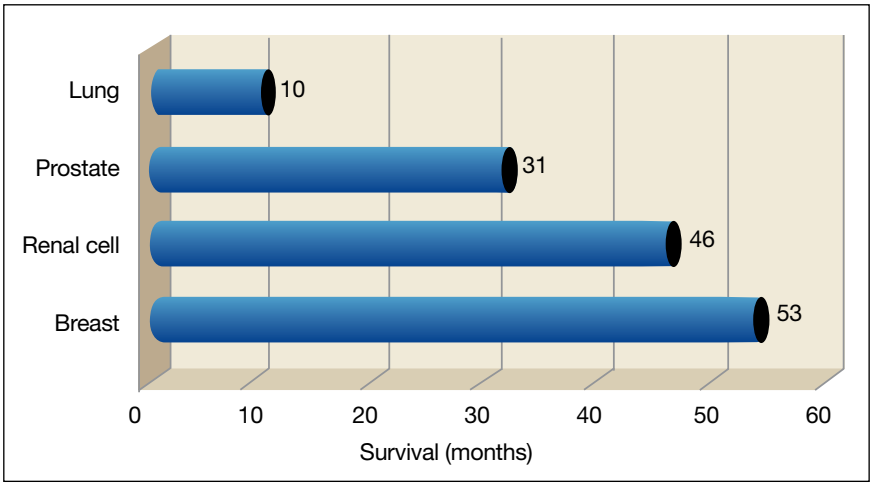

Figure 4. Survival depending on primary tumor site.[6]

temic treatment may be an important part of the treatment of the primary tumor or metastasis outside of the central nervous system (CNS), such treatment has historically been thought to have little impact in the treatment of brain metastasis, because most systemic chemotherapeutic agents do not cross the blood-brain barrier efficiently.

According to a retrospective study by Nussbaum and colleagues, the median survival time was 10 to 53 months, depending on primary tumor of brain metastases (Figure 4).[6]

Surgery

Surgery offers prompt, effective local tumor control, symptomatic improvement, and in selected patients, histologic confirmation of diagnosis. Patients with uncontrolled primary tumors are not candidates for surgical intervention. Other factors in determining surgical candidacy are number and location of brain metastases. Surgery should be considered for patients who have controlled primary cancer and an expected survival time of at least 3 to 4 months. Patients with tumors in vital structures (brain stem, motor cortex, etc) or multiple metastases are not good surgical candidates. Surgical mortality is currently < 3% due to improved patient selection and advances in neurosurgical techniques. Surgical therapy results in local control in 80% of patients compared with 48% following radiotherapy. Overall median survival is also improved (40 weeks vs 15 weeks) in patients who receive postoperative whole brain radiation compared with those who have only whole brain radiation without surgery.

Radiation Therapy

Radiation therapy has been the foundation of treatment for brain metastasis for decades. The primary goal of radiation therapy is local control of the tumor, symptomatic relief, and possible prolongation of life. However, overall survival (OS) is also dependent on other factors, such as the extent of uncontrolled extracranial disease, performance status, and histologic type of primary tumor.[19,20] Early treatment generally produces a better outcome. The overall response rate (RR) is 36% to 74%.[21,22] Neurologic symptoms improve in about 40% of patients.

However, there is no established optimal radiation therapy regimen for brain metastasis. Various dose fraction schedules were studied for the optimum therapy, but no differences were found among several fractionation regimens, such as 4,000 cGy in 3 or 4 weeks, 3,000 cGy in 2 or 3 weeks, or 2,000 cGy in 1 week.[21,24,25] At present, 3,000 cGy in 2 weeks, using a daily dose of 300 cGy, is the most popular mode of radiation therapy.

However, various treatment schedules can be used, depending on patient performance status and the histologic type of primary tumor. Some clinicians recommend a relatively short course therapy of 3,000 cGy in 10 fractions for patients with an unfavorable prognosis and a more aggressive approach with 4,000 cGy in 20 fractions for patients with a favorable prognosis who have more radiosensitive tumors and good performance status with longer survival expectation (at least 1 year or more). The patients with a favorable prognosis have a good prognosis, such as a single and small brain metastasis; controlled or no extracranial disease good performance status, and younger age.

Surgery and Radiotherapy

Surgery followed by adjuvant radiation therapy is superior to whole brain radiotherapy alone for single brain metastasis and controlled primary tumor disease.[26] Patients live longer and have a decreased risk of recurrence. In addition, patients have a better QOL compared with radiotherapy alone.[26-29] One study reported 82% local control rate using postoperative radiation therapy following surgery, compared with 30% with radiation alone.[29] Many patients die of extracranial uncontrolled disease.[30] Nieder and colleagues re-

ported 27% and 55% failure rates in the brain at 1 and 2 years after brain surgery and whole brain radiation therapy.[31]

STEREOTACTIC RADIOSURGERY

Radiosurgery is an alternative to brain surgery. Radiosurgery is not actually surgery but an intensified, highly precise form of radiation therapy, focused on the tumor and on protecting as much surrounding normal brain tissue as possible. Patients with a Karnofsky Performance Status (KPS) ≥ 70 and < 4 metastatic tumors are eligible candidates for radiosurgery.

Patients can return to their activities the next day or within a few days after the procedure. The ideal candidate for radiosurgery should have a small tumor with a well-defined margin. Several studies demonstrated that radiosurgery provides local tumor control comparable to surgical management. Additional benefits of radiosurgery include low morbidity and mortality. In addition, radiosurgery can be applied to tumors in important vital structures that are surgically inaccessible. The addition of radiosurgery to external radiotherapy resulted in a lower risk of local failure and a prolonged time to failure. Unfortunately, there was no improvement in median survival of patients. Local tumor control rate at 6 months was 92% in radiation and radiosurgery patients, compared with 75% with radiosurgery alone.[32]

The Radiation Therapy Oncology Group (RTOG) study also demonstrated improved likelihood of stable or improved performance status at 6 months after radiosurgery combined with whole brain radiotherapy.[33,34] Other studies found similar results after surgery and postoperative radiation group (S+R) compared with radiosurgery followed by whole brain radiation (RS+R). Median survival and 1-year survival rates were 15 months and 56% in S+R patients vs 19 months and 62% in the RS+R group.[35]

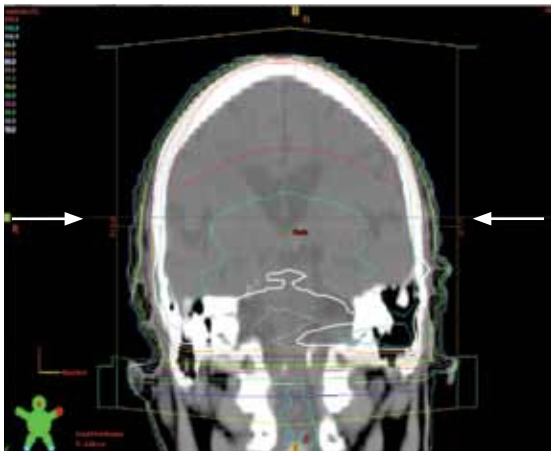

Figure 5. Digitally reconstructed radiographs of coronal view of the conventional bilateral-port radiation technique used for brain metastases radiotherapy of whole brain treatment (arrows indicate beam direction of right and left lateral radiation ports).

Table 2. Prognostic classification using recursive partitioning analysis[35]

Prognostic factors	Class 1	Class 2	Class 3
Karnofsky performance score > 70	Yes	Yes	No
Aged < 65 years	Yes	--	No
Solitary metastasis	Yes	--	No
Primary tumor controlled	Yes	--	No
Prognostic status	Favorable	Intermediate	Poor
Median survival	7 months	4 months	2 months

SYSTEMIC CHEMOTHERAPY

Recently, responses to systemic therapy in metastatic brain tumors have been demonstrated in selected cancers, especially when concurrent whole brain radiotherapy is used. The role of chemotherapy is still limited, and chemotherapy is not routinely used in practice. Systemic chemotherapy was thought to be ineffective because the blood-brain barrier prevents the efficient access to the CNS of many chemotherapeutic agents. However, it is now understood that the development of tumor vasculature may disrupt the blood-brain barrier and thus permit some access of chemotherapeutic agents to brain metastasis.

Small-Cell Lung Cancer

Small-cell lung cancers are very sensitive to chemotherapy. An initial chemotherapy regimen for small-cell lung cancer is etoposide and cisplatin, according to the National Comprehensive Cancer Network (NCCN) Practice Guidelines.[36] Alkylator- and anthracycline-based regimens are superior in both efficacy and toxicity.[36,37] Reported RRs of brain metastasis were 27% to 85%.[38,39] A prospective study using first-line chemotherapy (cyclophosphamide, doxorubicin, and etoposide) by Seute and colleagues

Table 3. Karnofsky performance scale status[35]

Scale	Definition
100	Normal; no complaints; no evidence of disease
90	Able to carry out normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry out normal activity or to do active work
60	Requires occasional assistance but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospital admission is indicated although death not imminent
20	Very sick; hospital admission necessary; active supportive treatment necessary
10	Moribund; fatal processes progressing rapidly

showed 27% brain lesion responses and 73% systemic responses.[39]

Breast Cancer

Responses of breast cancer brain metastasis to systemic treatment have been observed. Rosner and colleagues reported 50 responders among 100 patients treated with systemic chemotherapy (10 complete responses and 40 partial responses); median remission period was 10 months for complete responders and 7 months for partial responders.[40] Another nonrandomized study reported 76% objective tumor regression after 2 cycles of chemotherapy, with an overall median survival of 25 weeks.[41-43]

Non–Small-Cell Lung Cancer

Non–small-cell lung cancer is less responsive than small-cell lung cancer to systemic chemotherapy. However, responses of brain metastasis to systemic chemotherapy have been observed in 30% to 45% of patients.[44,45]

ADVERSE EFFECTS OF RADIATION THERAPY

Acute radiation reactions include skin erythema, headache, hair loss, and general weakness. Possible late radiation complications are neurocognitive deterioration, dementia, leukoencephalopathy, atrophy, and rarely radiation necrosis and hypothyroidism.[4,46] The risk factors of late complications include the total radiation dose/fraction, tumor size, and pretreatment neurologic impairment status.[47]

PROGNOSTIC GROUPS (RECURSIVE PARTITIONING ANALYSIS [RPA]) AND SURVIVAL OUTCOMES

The median survival of patients with untreated brain metastasis is about 1 month. Adding steroids increases survival to 2 months, and whole brain radiation therapy further improves survival to 3 to 6 months. Patients with a single brain metastasis and limited extracranial disease who are treated with surgery and whole brain radiation therapy have a longer median survival of about 10 to 16 months.

Prognostic Groups

Based on a database of 1,200 patients from 3 trial studies, the RTOG developed 3 prognostic classes (Tables 2 and 3), which correlated well with median survival, using RPA; that is, class 1: patients with a (KPS) > 70, aged < 65 years with controlled primary and no extracranial metastases; class 3: KPS < 70; and class 2: all others.[48] According to the RPA, the best survival was observed in class 1 patients; the worst survival was in class 3.

Sperduto and colleagues revised the RPA and proposed a new prognostic classification: graded prognostic assessment (GPA).[49] The GPA is a scoring system using 4 prognostic indexes: age, KPS, and cranial and extracranial metastases. One point was assigned for younger age (< 50 years); good KPS (90-100); single brain lesion; and no evidence of extracranial metastases. A score of 0 was given for older age (> 60 years); poor KPS (< 70); multiple brain lesions (> 3); and the presence of extracranial metastases. Intermediate criteria were scored as 0.5. The authors felt this system was convenient and relatively objective.

Survival Outcomes

The OS was longer when patients received surgical and adjuvant radiotherapy compared with radiation therapy alone (40 weeks vs 15 weeks, respectively).[14] According to Vecht and colleagues, the combi-

nation of surgery and radiation led to longer survival and longer functionally independent survival, compared with radiotherapy alone.[50] Functional improvement occurred quicker and for longer periods after surgery and radiotherapy vs radiotherapy alone. After receiving postsurgical radiation treatment, patients were significantly less likely to develop intracranial recurrences compared with surgery alone (18% vs 70%, respectively) and less likely to die of brain metastases.[29]

CONCLUSION

Brain metastasis is a common complication of cancer, leading to significant morbidity and mortality. Radiotherapy of brain metastasis has been the standard approach to management with the primary goal of symptom palliation. Recent advancements in patient selection and treatment modalities have identified roles for neurosurgery, stereotactic radiosurgery, and possibly systemic chemotherapy. Combination approaches have resulted in improved symptom relief, local control, and even prolonged survival. In general, the optimal therapeutic approach to a single brain metastasis would currently be surgical resection or radiosurgery, followed by whole brain radiation. For patients with multiple metastases, external-beam radiotherapy to the whole brain would be the preferred therapy. ●

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this editorial.

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REFERENCES

1. Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. *J Clin Oncol.* 2004;22(14):2865-2872.
2. Schouten LJ, Rutten J, Huveneers HA, Twijnstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. *Cancer.* 2002;94(10):2698-2705.
3. Hwang TL, Close TP, Grego JM, Brannon WL, Gonzales F. Predilection of brain metastasis in gray and white matter junction and vascular border zones. *Cancer.* 1996;77(8):1551-1555.
4. Delattre JY, Krol G, Thaler HT, Posner JB. Distribution of brain metastases. *Arch Neurol.* 1988;45(7):741-744.
5. Lim LC, Rosenthal MA, Maartens N, Ryan G. Management of brain metastases. *Inter Med J.* 2004;34(5):270-278.
6. Nussbaum ES, Djalilian HR, Cho KH, Hall WA. Brain metastases: Histology, multiplicity, surgery, and survival. *Cancer.* 1996;78(8):1781-1788.
7. Lin NU, Bellon JR, Winer EP. CNS metastases in breast cancer. *J Clin Oncol.* 2004;22(17):3608-3617.
8. Lassman AB, DeAngelis LM. Brain metastases. *Neurol Clin.* 2003;21(1):1-23, vii.
9. Nutt SH, Patchell RA. Intracranial hemorrhage associated with primary and secondary tumors. *Neurosurg Clin N Am.* 1992;3(3):591-599.
10. Sze G, Milano E, Johnson C, Heier L. Detection of brain metastases: Comparison of contrast-enhanced MR with unenhanced MR and enhanced CT. *Am J Neuroradiol.* 1990;11(4):785-791.
11. Davis PC, Hudgins PA, Peterman SB, Hoffman JC Jr. Diagnosis of cerebral metastases: Double-dose delayed CT vs contrast-enhanced MR imaging. *Am J Neuroradiol.* 1991;12(2):293-300.
12. Schaefer PW, Budzik RF Jr, Gonzalez RG. Imaging of cerebral metastases. *Neurosurg Clin N Am.* 1996;7(3):393-423.
13. Muroff LR, Runge VM. The use of MR contrast in neoplastic disease of the brain. *Top Magn Reson Imaging.* 1995;7(3):137-157.
14. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med.* 1990;322(8):494-500.
15. Batchelor T, DeAngelis LM. Medical management of cerebral metastases. *Neurosurg Clin N Am.* 1996;7(3):435-446.
16. Vecht CJ, Hovestadt A, Verbiest HB, et al. Dose-effect relationship of dexamethasone on Karnofsky performance in metastatic brain tumors: A randomized study of doses of 4, 8, and 16 mg per day. *Neurology.* 1994;44(4):675-680.
17. Glantz MJ, Cole BF, Friedberg MH, et al. A randomized, blinded, placebo-controlled trial of divalproex sodium prophylaxis in adults with newly diagnosed brain tumors. *Neurology.* 1996;46(4):985-991.
18. Forsyth PA, Weaver S, Fulton D, et al. Prophylactic anticonvulsants in patients with brain tumour. *Can J Neurol Sci.* 2003;30(2):106-112.
19. Sneed PK, Larson DA, Wara WM. Radiotherapy for cerebral metastases. *Neurosurg Clin N Am.* 1996;7(3):505-515.
20. Lagerwaard FJ, Levendag PC, Nowak PJ, Eijkenboom WM, Hanssens PE, Schmitz PI. Identification of prognostic factors in patients with brain metastases: A review of 1292 patients. *Int J Radiat Oncol Biol Phys.* 1999;43(4):795-803.
21. Tsao MN, Lloyd NS, Wong RK, et al; Supportive Care Guidelines Group of Cancer Care Ontario's Program in Evidence-based Care. Radiotherapeutic management of brain metastases: A systematic review and meta-analysis. *Cancer Treat Rev.* 2005;31(4):256-273.
22. Cairncross JG, Kim JH, Posner JB. Radiation therapy for brain metastases. *Ann Neurol.* 1980;7(6):529-541.
23. Slimane K, Andre F, Delaloge S, et al. Risk factors for brain relapse in patients with metastatic breast cancer. *Ann Oncol.* 2004;15(11):1640-1644.
24. Vermeulen SS. Whole brain radiotherapy in the treatment of metastatic brain tumors. *Semin Surg Oncol.* 1998;14(1):64-69.
25. Berk L. An overview of radiotherapy trials for the treatment of brain metastases. *Oncology (Williston Park).* 1995;9(11):1205-1212.
26. Pfister DG, Johnson DH, Azzoli CG, et al. American society of clinical oncology treatment of unresectable non-small-cell lung cancer guideline: Update 2003. *J Clin Oncol.* 2004;22(2):330-353.
27. Smalley SR, Schray MF, Laws ER Jr, O'Fallon JR. Adjuvant radiation therapy after surgical resection of solitary brain metastasis: Association with pattern of failure and survival. *Int J Radiat Oncol Biol Phys.* 1987;13(11):1611-1616.
28. Skibber JM, Soong SJ, Austin L, Balch CM, Sawaya RE. Cranial irradiation after surgical excision of brain metastases in melanoma patients. *Ann Surg Oncol.* 1996; 3(2):118-123.
29. Patchell RA, Tibbs, PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single brain metastases to the brain. *JAMA.* 1998;280(17):1485-1489.
30. Nieder C, Astner ST, Grosu AL, Andratschke NH, Mollis M. The role of postoperative radiotherapy after resection of a single brain metastasis: Combined analysis of 643 patients. *Strahlenther Onkol.* 2007;183(10):576-580.
31. Nieder C, Schwerdtfeger K, Steudel W-I, Schnabel K. Patterns of relapse and late toxicity after resection and whole-brain radiotherapy for solitary brain metastases. *Strahlenther Onkol.* 1998;174(5):275-278.
32. Rades D, Kueter JD, Hornung D, et al. Comparison of stereotactic radiosurgery (SRS) alone and whole brain radiotherapy (WBRT) plus a stereotactic boost (WBRT + SRS) for one to three brain metastases. *Strahlenther Onkol.* 2008;184(12):655-662.
33. Kondziolka D, Patel A, Lunsford LD, Kassam A, Flickinger JC. Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. *Int J Radiat Oncol Biol Phys.* 1999;45(2):427-434.
34. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: Phase III results of the RTOG 9508 randomised trial. *Lancet.* 2004;363(9422):1665-1672.

35. D'Agostino GR, Autorino R, Pompucci A, et al. Whole-brain radiotherapy combined with surgery or stereotactic radiotherapy in patients with brain oligometastases: Long-term analysis. *Strahlenther Onkol.* 2011;187(7):421-425.
36. National Comprehensive Cancer Network (NCCN). NCCN Guidelines®. National Comprehensive Cancer Network Website. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#sclc. Accessed March 12, 2013.
37. Sundstrøm S, Bremnes RM, Kaasa S, et al. Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: Results from a randomized phase III trial with 5 years' follow-up. *J Clin Oncol.* 2002;20(24):4665-4672.
38. Kristjansen PE, Soelberg Sørensen P, Skov Hansen M, Hansen HH. Prospective evaluation of the effect on initial brain metastases from small-cell lung cancer of platinum-etoposide based induction chemotherapy followed by an alternating multidrug regimen. *Ann Oncol.* 1993;4(7):579-583.
39. Seute T, Leffers P, Wilmink JT, ten Velde GP, Twijnstra A. Response of asymptomatic brain metastases from small-cell lung cancer to systemic first-line chemotherapy. *J Clin Oncol.* 2006;24(13):2079-2083.
40. Rosner D, Nemoto T, Lane WW. Chemotherapy induces regression of brain metastases in breast carcinoma. *Cancer.* 1986;58(4):832-839.
41. Boogerd W, Dalesio O, Bais EM, van der Sande JJ. Response of brain metastases from breast cancer to systemic chemotherapy. *Cancer.* 1992;69(4):972-980.
42. Christodoulou C, Bafaloukos D, Linardou H, et al. Temozolomide (TMZ) combined with cisplatin (CDDP) in patients with brain metastases from solid tumors: A Hellenic Cooperative Oncology Group (HeCOG) Phase II study. *J Neurooncol.* 2005;71(1):61-65.
43. Rivera E, Meyers C, Groves M, et al. Phase I study of capecitabine in combination with temozolomide in the treatment of patients with brain metastases from breast carcinoma. *Cancer.* 2006;107(6):1348-1354.
44. Bernardo G, Cuzzoni Q, Strada MR, et al. First-line chemotherapy with vinorelbine, gemcitabine, and carboplatin in the treatment of brain metastases from non-small-cell lung cancer: A phase II study. *Cancer Invest.* 2002;20(3):293-302.
45. 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.* 1999;85(7):1599-1605.
46. Heikens J, Michiels EM, Behrendt H, Endert E, Bakker PJ, Fliers E . Long-term neuro-endocrine sequelae after treatment for childhood medulloblastoma. *Eur J Cancer.* 1998;34(10):1592-1597.
47. Schultheiss TE, Kun LE, Ang KK, Stephens LC. Radiation response of the central nervous system. *Int J Radiat Oncol Biol Phys.* 1995;31(5):1093-1112.
48. 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(4):745-751.
49. Sperduto PW, Berkey B, Gaspar L, Mehta M, Curran W. A new prognostic index and comparison to three other indices for patients with brain metastases: An analysis of 1,960 patients in the RTOG database. *Int J Radiat Oncol Biol Phys.* 2008;70(2):510-514.
50. Vecht CJ, Haaxma-Reiche H, Noordijk EM, et al. Treatment of single brain metastasis: Radiotherapy alone or combined with neurosurgery? *Ann Neurol.* 1993;33(6):583-590.