Chapter 50
Brain Metastases

Tiago Costa de Pádua, Adrialdo José Santos, Hakaru Tadokoro, and Ramon Andrade De Mello

Abstract Metastasis to the brain is the most feared complication of systemic cancer, and it is the most common intracranial tumor in adults, being symptomatic in more than two-thirds of patients, with similar manifestations observed in primary brain tumors. Any patients with a cancer diagnosis who present with neurologic symptoms must be examined carefully and imaging studies must be performed to exclude BMs. With treatment, survival improves, but it is still discouraging. The management of BMs is divided in two major goals: symptomatic control and specific cancer treatment. It is essential to have a multidisciplinary team, and the patient should be a part of the decision-making process.

Keywords Brain metastasis · Supportive care · Radiotherapy

50.1 Introduction

Metastasis to the brain is the most feared complication of systemic cancer, and it is the most common intracranial tumor in adults, occurring in 20–40% of patients diagnosed with advanced cancer, which exceeds the frequency of primary tumors.

T. C. de Pádua
Department of Medical Oncology, Federal University of São Paulo, UNIFESP, São Paulo, SP, Brazil

A. J. Santos
Neuro-Oncology, Hospital São Paulo, Universidade Federal de São Paulo, São Paulo, Brazil

H. Tadokoro
Division of Medical Oncology, Escola Paulista de Medicina, Federal University of São Paulo, São Paulo, Brazil

R. A. De Mello (✉)
Division of Medical Oncology, Federal University of São Paulo (UNIFESP) & Hospital Israelita Albert Einstein, São Paulo, Brazil

Department of Biomedical Sciences and Medicine, University of Algarve, Faro, Portugal
e-mail: ramello@ualg.pt; ramondemello@doctors.org.uk

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The true incidence of brain metastases is unknown, but studies from the United States show an approximate incidence of 200,000 new cases annually. Recently, an increase in the incidence of brain metastasis (BM) was observed, which is probably due to an increased overall survival as a result of therapeutic advances and better radiologic examinations [1–4].

Any type of cancer can compromise the central nervous system (CNS), although in adults, lung cancer is the most associated with brain metastases (around 50% of all cases), mainly oat-cell carcinoma. Other neoplasms commonly associated with BM are breast cancer, renal cell carcinoma, colorectal cancer, germ cell tumor, and melanoma [3]. This was demonstrated in a large study by the Metropolitan Detroit Cancer Surveillance System, which estimated the incidence of BMs from 1973 to 2001. The study found a cumulative incidence of BMs of 9.6% for all primary sites combined, with the highest in the lungs (19.9%), followed by melanoma (6.9%), renal (6.5%), breast (5.1%), and colorectal (1.8%) cancers [4].

BMs can be single or multiple, and they are often found in the gray/white matter junction; 80% are found in the cerebral hemispheres, 15% in the cerebellum, and 5% in the brainstem. The mechanisms of metastases include hematogenous spreading or invasion by contiguity. Another possible mechanism is dissemination to the posterior fossa by the venous plexus of Batson, as in pelvic tumors [5, 6].

50.2 Clinical Manifestations

BMs are symptomatic in more than two-thirds of patients, with similar manifestations observed in primary brain tumors. Generally, the onset of symptoms is subacute, and BM has variable clinical features depending on the location, number of lesions, and associated complications (e.g., bleeding or hydrocephalus). In some cases, BMs can occur with intratumoral hemorrhage, and most are associated with melanoma and choriocarcinoma, which lead to an acute onset of symptoms.

The most common symptoms are due to an increase in the intracranial pressure (e.g., headache, nausea, and vomiting). Seizures, memory problems, mood or personality changes, and focal neurological dysfunction (e.g., ataxia, hemiparesis, and language disturbs) are other possible symptoms [7–10]. However, 10% of patients may be asymptomatic, and the BM is discovered after cranial imaging as part of disease staging.

BMs can occur as the first manifestation of cancer (observed in 5–10% of all patients), and they can present synchronously with systemic and intracranial cancer (5–10%). However, it is more common for them to present metachronously after the diagnosis of systemic cancer (>80% of all patients).

50.3 Diagnosis

Any patients with a cancer diagnosis who present with neurologic symptoms must be examined carefully, and imaging studies must be performed to exclude BMs. Usually the first examination is CT of the brain, because it is an easily accessibility

and inexpensive diagnostic tool that shows lesions with circumscribed margins, associated vasogenic edema, and localization at the junction of the grey/white matter. However, there is a great deal of variability in the appearance of these tumors.

MRI with contrast enhancement is the preferred exam, because it has a better sensitivity and specificity than other imaging modalities for determining the presence, location, and number of metastases. The aspect is typically iso- to hypointense on T1- and hyperintense on T2-weighted images. S**pectroscopy shows** intratumoral choline peaks with no choline elevation in the peritumoral edema [11, 12].

Differential diagnosis includes primary brain neoplasm (especially glioblastoma), cerebral abscess, subacute stroke, and demyelinating diseases [9].

In patients with unknown primary cancer and BMs, a history and physical examination are the first steps, followed by imaging studies. The lung should be the primary focus of evaluation because of the high prevalence of BMs in this type of tumor. The use of blood markers (i.e., the carcinoembryonic antigen [CEA], alpha-fetoprotein, prostate-specific antigen [PSA], and Ca-125) and endoscopic exams should be realized upon suspicion. PET-CT may be used as part of the investigation, and biopsy should be reserved for cases with doubt or when the primary site is not identified [13, 14].

50.4 Prognostic Factors

The most used prognostic classification system was created by the Radiation Treatment Oncology Group, which uses recursive partitioning analysis (RPA). There are three prognostic classes with important differences in survival [15]. Class 1 patients (16–20% of all patients) have the following: a Karnofsky Performance Status (KPS) >60, aged <65 years, and no evidence of extraneural metastases or controlled primary cancer. Class 3 patients (10–15% of all patients) have a KPS <70 and class 2 patients (65% of patients) include all patients that cannot be classified under class 1 or 3.

Other known prognostics factors include the following: the performance status, age (<65 years), a favorable tumor histology, controlled primary disease, isolated brain disease, and solitary versus multiple tumors [9, 10, 16].

50.5 Treatment

In general, patients with BMs typically have a mean survival of 1 month without treatment. With treatment, survival improves, but it is still discouraging. The management of BMs is divided in two major goals: symptomatic control and specific cancer treatment [16].

50.5.1 Symptomatic Treatment

Symptomatic treatment includes the management of brain edema, hydrocephalus, prophylaxis of seizures, and possible complications. The first step consists of administering steroids and anticonvulsants. Steroids are used to minimize vasogenic edema, which leads to an improved clinical condition. The most used steroid is dexamethasone, an empiric dose of 4–16 mg daily, because it is the most potent, has the best CNS penetration, and the least mineralocorticoid side effects. As the clinical situation permits, the lowest dose of dexamethasone that controls the symptoms should be used in order to avoid adverse effects [7, 8, 16, 17]. Symptomatic treatment with steroids alone prolongs survival for approximately 2.5 months.

Seizures are one of the most commons symptoms in patients with BMs that occur in >25% of all cases and the use of antiepileptic drugs (AEDs) is recommended after the first episode and for prophylaxis immediately following surgical resection. There are no rules regarding the use of AEDs as prophylaxis for seizures in patients without a previous history of seizures [18]. Among the classes of AEDs, non-enzyme-inducing AEDs such as pregabalin, lamotrigine or topiramate are preferred to avoid drug interactions with others drugs and chemotherapy [19].

BMs are associated with an increased risk for venous thrombosis due to a hypercoagulable state, with an estimated incidence of 20% in this patient population. The main treatment is anticoagulation with a low molecular weight (LMW) heparin or warfarin. LMW is preferred because of its increased effectiveness in preventing recurrent thromboembolism, it has no interaction with other drugs, and it is convenient. In case of metastases associated with an increased risk of hemorrhage (e.g., melanoma, choriocarcinoma, thyroid carcinoma, and renal cell carcinoma) the use of an inferior vena cava filter is recommended [10, 20]. Prophylaxis with anticoagulant is not routinely indicated, and it should be reserved for the perioperative period [21].

50.5.2 Specific Treatment

Specific treatment can be realized in three main modalities, usually in combination with radiation, systemic therapy with chemotherapy, and surgical resection. The goals are to prolong survival and improve quality of life, and the approach is based on the characteristics of the tumor (i.e., the size, location, and number of metastases), KPS, patients' age, and prognosis [7–10, 16]. According to the features and RPA classification, patients with a good prognosis must be treated aggressively in an attempt to eradicate or control the disease in the brain. In patients who are not candidates for this approach, best supportive care or only whole brain external beam radiation is indicated.

Radiotherapy remains the most used treatment and includes whole brain radiotherapy (WBRT) and stereotactic radiosurgery. WBRT is preferred in cases with

multiple metastases or solitary metastases associated with extensive systemic disease in order to control the symptoms and improve quality of life [22]. WBRT can also be used after resection of brain metastases, reducing the risk of intracranial relapse and improving survival, as shown in randomized trials [23–25]. The most used protocol consists of whole brain irradiation (a total dose of 30 Gy among 10 sessions) with concomitant use of dexamethasone to reduce acute complications [16].

Stereotactic radiosurgery is a new modality of radiotherapy that provides an intense focal irradiation on a small lesion using multiple well-collimated beams that reduced radiation damage to adjacent tissue. This is important in cases with lesions in eloquent or inaccessible areas that have similar outcomes compared to surgery. Other advantages are less toxicity than WBRT, and there is no need to discontinue systemic therapy. BMs from non-small cell lung cancer, renal cell carcinoma, and melanoma that are radio-resistant show good response rates with this treatment [16, 26–29].

Surgery is another option, especially for large symptomatic solitary BMs, cases with a doubtful diagnosis or unknown primary site, and symptomatic control in cases with a significant mass effect from the tumor. Some characteristics should be evaluated before the indication, which include the accessibility and ressectability of the tumor. Recent advances in neuro-oncological surgery have led to a reduced risk of morbidity and mortality with this kind of procedure.

Historically, chemotherapy has had a limited role in the treatment of BMs because of the low penetration in the CNS, and few clinical trials support the use of chemotherapy for BM treatment. Generally, it is reserved for patients with a poor response to other modalities or with chemosensitive tumors (e.g., lymphomas, germ cell tumors, and small cell lung cancer) [30, 31]. More recently, trials with immunotherapy and targeted therapy have shown efficacy in some tumors (e.g., using lapatinib for breast cancer, gefitinib for non-small cell lung cancer, and ipilimumab for melanoma) [32].

In conclusion, BMs are becoming more frequent, and treatment is a challenge for oncologists. It is essential to have a multidisciplinary team, and the patient should be a part of the decision-making process. Patients should also be included in palliative care programs as soon as possible.

50.5.3 Prophylactic Cranial Irradiation

Prophylactic cranial irradiation (PCI) is indicated in patients who are diagnosed with limited stage non-small cell lung cancer who have achieved complete remission after primary treatment in attempt to reduce intracranial relapse and improve survival. This should be considered in cases with extensive disease, a good performance, and a good response. However, the impact on overall survival is not clear. Thus, it is necessary to consider the possible toxicity associated with PCI, especially in young patients [33–36].

References

1. Nayak L, Lee EQ, Wen PY (2012) Epidemiology of brain metastases. Curr Oncol Rep 14:48–54
2. De Angelis L, Posner JB (2009) Intracranial metastases. In: De Angelis L, Posner J (eds) Neurologic complications of câncer. Oxford University Press, New York, pp 141–193
3. Gavrilovic IT, Posner JB (2005) Brain metastases: epidemiology and pathophysiology. J Neuro-Oncol 75:5–14
4. Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE (2004) Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in Metropolitan Detroit Cancer Surveillance System. J Clin Oncol 22:2865–2872
5. Chiang AC, Massague J (2008) Molecular basis of metastasis. N Engl J Med 359:2814–2823
6. Nguyen TD, DeAngelis LM (2007) Brain metastases. Neurol Clin 25:1173–1192
7. Guillamo JS, Emery E, Busson A, Lechapat-Zalcman E (2008) Traitement actuel des metastases cérébrales. Rev Neurol 64:560–568
8. Lim LC, Rosenthal MA, Maartens N, Ryan G (2004) Management of brain metastases. Intern Med J 34:270–278
9. Klos KJ, O'Neill BP (2004) Brain metastases. Neurologist 10:31–46
10. Norden AD, Wen PY, Kesari S (2005) Brain metastases. Curr Opin Neurol 18:654–661
11. Davis PC, Hudgins PA, Peterman SB, Hoffman JC Jr (1991) Diagnosis of cerebral metastases: double-dose delayed CT vs contrast-enhanced MR imaging. AJNR Am J Neuroradiol 12(2):293–300
12. Schaefer PW, Budzik RF Jr, Gonzalez RG (1996) Imaging of cerebral metastases. Neurosurg Clin N Am 7(3):393–423
13. Agazzi S, Pampallona S, Pica A, Vernet O, Regli L, Porchet F et al (2004) The origin of brain metastases in patients with a undiagnosed primary tumour. Acta Neurochir 146:153–157
14. Polyzoidis KS, Miliaras G, Pavlidis N (2005) Brain metastasis of unknown primary: a diagnostic and therapeutic dilemma. Cancer Treat Rev 31:247–255
15. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, McKenna WG, Byhardt R (1997) Recursive portioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys 37:745–751
16. Soffietti R, Cornu P, Delattre JY, Grant R, Graus F, Grisold W et al (2006) EFNS Guidelines on diagnosis and treatment of brain metastases: report of a EFNS Task Force. Eur J Neurol 13:674–681
17. Hempen C, Weiss E, Hess CF (2002) Dexamethasone treatment in patients with brain metastases and primary brain tumors: do the benefits outweigh the side effects? Support Care Cancer 10:322–328
18. Sirven JI, Wingerchuk DM, Drazkowski JF, Lyons MK, Zimmerman RS (2004) Seizure prophylaxis in patients with brain tumors: a meta-analysis. Mayo Clin Proc 79(12):1489–1494
19. Maschio M, Dinapoli L, Gomellini S, Ferraresi V, Sperati F, Vidiri A, Muti P, Jandolo B (2010) Antiepileptics in brain metastases: safety, efficacy and impact on life expectancy. J Neuro-Oncol 98(1):109–116
20. Gerber DE, Grossman SA, Streiff MB (2006) Management of venous thromboembolism in patients with primary and metastatic brain tumors. J Clin Oncol 24(8):1310–1318
21. Schmidt F, Faul C, Dichgans J, Weller M (2002) Low molecular weight heparin for deep vein thrombosis in glioma patients. J Neurol 249(10):1409–1412
22. Li J, Bentzen SM, Renschler M, Mehta MP (2008) Relationship between neurocognitive function and quality of life after whole-brain radiotherapy in patients with brain metastasis. Int J Radiat Oncol Biol Phys 71:64–70
23. Vecht CJ, Haaxma-Reiche H, Noordijk EM, Padberg GW, Roormolen JH, Hoekstra FH, Tans JT, Lambooij N, Metsaars JA, Wattendorff AR (1993) Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery. Ann Neurol 33:583–590

24. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, Markesbery WR, Macdonald JS, Young B (1990) A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 322:494–500
25. Lin NU, Bellon JR, Winer EP (2004) CNS metastases in breast cancer. J Clin Oncol 22:3608–3617
26. Shehata MK, Young B, Reid B, Patchell AR, St Clair W, Sims J, Sanders M, Meigooni A, Mohiuddin M, Regine WF (2004) Stereotatic radiosurgery of 468 brain metastases or= 2cm: implications for SRS dose and whole brain radiation therapy. Int J Radiat Oncol Biol Phys 59:87–93
27. Jebjubsib MD, Haylock B, Shenoy A, Husband D, Javadpour M (2011) Management of cerebral metastasis: evidence-based approach for surgery, stereotactic radiosurgery and radiotherapy. Eur J Cancer 47:649–655
28. Sneed PK, Suh JH, Goetsch SJ, Sanghavi SN, Chapell R, Buatti JM, Regine WF, Weltman E, King VJ, Breneman JC, Sperduto PW, Metha MP (2002) A multi-institutional review of radiosurgery alone vs. radiosurgery with whole brain radiotherapy as the initial management of brain metastases. Int J Radiat Oncol Biol Phys 53:519–526
29. Pinkham MB et al (2015) New Developments in intracranial stereoctactic Radiotherapy for metastases. Clin Oncol 27:316–323
30. Lesser GJ (1996) Chemotherapy of cerebral metastases from solid tumors. Neurosurg Clin N Am 7(3):527–536
31. Postmus PE, Smit EF (1999) Chemotherapy for brain metastases of lung cancer: a review. Ann Oncol 10(7):753–759
32. Seoane J, De Mattos-Arruda L (2014) Brain metastasis: new opportunities to tackle therapeutic resistance. Mol Oncol 8:1120–1131
33. Aupérin A, Arriagada R, Pignon JP, Le Péchoux C, Gregor A, Stephens RJ, Kristjansen PE, Johnson BE, Ueoka H, Wagner H, Aisner J, Prophylactic Cranial Irradiation Overview Collaborative Group (1999) Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. N Engl J Med 341(7):476–484
34. Meert AP, Paesmans M, Berghmans T, Martin B, Mascaux C, Vallot F, Verdebout JM, Lafitte JJ, Sculier JP (2001) Prophylactic cranial irradiation in small cell lung cancer: a systematic review of the literature with meta-analysis. BMC Cancer 1:5
35. Slotman B, Faivre-Finn C, Kramer G, Rankin E, Snee M, Hatton M, Postmus P, Collette L, Musat E, Senan S, EORTC Radiation Oncology Group and Lung Cancer Group (2007) Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med 357(7):664–672
36. Slotman BJ, Mauer ME, Bottomley A, Faivre-Finn C, Kramer GW, Rankin EM, Snee M, Hatton M, Postmus PE, Collette L, Senan S (2009) Prophylactic cranial irradiation in extensive disease small-cell lung cancer: short-term health-related quality of life and patient reported symptoms: results of an international Phase III randomized controlled trial by the EORTC Radiation Oncology and Lung Cancer Groups. J Clin Oncol 27(1):78–84