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Introduction

Brain metastases represent one of the most common neurological complications of systemic cancer, in many cases resulting in significant morbidity and mortality. The incidence has increased over time as a result of advances in detection and improvements in the treatment of primary tumor and systemic disease, which have led to an increase in survival. They currently represent the most frequent intracranial tumors, outnumbering primary brain tumors.

The majority of patients who develop brain metastases have a relatively short survival, despite the fact that initial treatment is often effective. The short survival may be the result of progressive systemic disease (in more than a half of patients) or uncontrolled neurological disease. The treatment of brain metastases includes corticosteroids, anticonvulsants, surgery, radiosurgery, radiotherapy, chemotherapy, and targeted therapies. Although for many patients effective palliation is transient or not possible, other patients with metastatic brain disease do well for prolonged periods with an aggressive therapeutic approach. Prognostic factors can help to identify subgroups of patients with differing life expectancy, and tailor therapeutic approaches.

This chapter will review the state of the art and advances in the management of patients with brain metastases.

Epidemiology, Natural History and Risk Factors

Few population estimates of brain metastasis are available. The incidence of newly diagnosed brain metastasis is estimated to be 3–10 times the number of newly diagnosed primary malignant brain tumors each year [1, 2]. Brain metastases occur in up to 40% of patients with cancer, being symptomatic during life in 60–75% or discovered incidentally on CT/MRI or autopsy [3–7].

In adults, lung (36–64%), breast (15–25%), and skin (melanoma) (5–20%) are the most frequent sources of brain metastases. Less frequent are cancers from colon rectum, kidney, prostate, testis, ovary, and sarcomas. In general, any malignant tumor is able to metastasize to the brain. The primary site is unknown in up to 10–15% of patients with brain metastases. The propensity of primary tumors to spread to the brain parenchyma (“neurotropism”) differs, and is high for melanoma (20–45% of patients), small-cell lung cancer, choriocarcinoma and germ cell tumors; intermediate for breast cancer, nonsmall-cell lung cancers (being more frequent in adenocarcinomas than in squamous tumors) and renal cancer; low for cancers of the prostate, gastrointestinal tract, ovary, thyroid, and sarcomas. Cerebral metastatic disease in children is less frequent than in adults (6–10%) [8]. The childhood solid tumors that more frequently metastasize to the brain are neuroblastomas and a variety of sarcomas, including rhabdomyosarcoma, Wilms’ tumor, Ewing’s sarcoma, and osteogenic sarcoma. Among children older than 15 years, germ cell tumors have the highest incidence. Brain metastases are more commonly diagnosed in patients with known systemic malignancy (metachronous presentation) and may be the first evidence of the metastatic disease. Less commonly, brain metastases are discovered in patients at the same time as the primary tumor (synchronous presentation, up to 30%) or prior to discovery of primary disease (precocious presentation).

In the CT era around 50% of brain metastases were presumed to be single, while MRI has revealed that multiple

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lesions exist in two-thirds to three-fourths of all cases of brain metastases [9, 10]. Brain metastases from renal and abdominopelvic tumors are often single, whereas malignant melanoma and lung tumors have a greater tendency to produce multiple cerebral lesions.

The overwhelming majority of brain metastases arise from embolization of tumor cells through the arterial circulation (hematogenous spread). The occurrence of metastases in the different locations is roughly proportional to their relative mass and blood flow: lesions are located in the cerebral hemispheres in 80% of patients, in the cerebellum in 15%, in the brainstem in 5%, and are rare in the basal ganglia, pineal gland, and hypophysis [11]. Brain metastases are commonly found at the junction of the gray and white matter, and are overrepresented in “watershed” areas of the brain, consistent with the origin of metastases from tumor cell emboli carried to terminal arterioles. Melanoma is unusual in its predilection to metastasize to the cerebral cortex and basal ganglia rather than to the gray-white matter junction [12]. There are few circumstances in which non-specific hematogenous spread does not explain the observed distribution of brain metastases. Pelvic and abdominal tumors have a predilection to form posterior fossa metastases far in excess of what the proportion of blood flow supply to this region would predict. Dissemination by way of Batson’s vertebral venous plexus has long been invoked to explain this phenomenon, but this hypothesis cannot explain why patients with pelvic or abdominal tumors do not a high incidence of spinal and skull metastases as well, as these structures are also drained by Batson’s plexus.

Some clinico-pathological and molecular factors are recognized as risk factors for developing brain metastases. In NSCLC an increased risk for brain metastases has been related to an advanced disease stage, large primary tumor size, non-squamous histology (mainly adenocarcinoma) and, more recently, EGFR mutational status [13, 14].

In breast cancer, younger age at first diagnosis, the presence of lung metastases and short disease-free survival are considered as major clinical risk factors for the development of brain metastases. Patients with triple-negative tumors (ER-, PR-, HER2 wild type) are at higher risk of developing brain metastases compared with the luminal or HER2-positive subtypes [15]. HER2-positive patients with metastatic disease receiving the monoclonal antibody against HER2 trastuzumab have a higher incidence of brain metastases (30–55%) than patients with HER2-negative disease [16]. It is still debated whether patients with early breast cancer receiving adjuvant trastuzumab have a significant increase in the risk of CNS relapse as well [17, 18]. CNS disease as the first site of relapse remains relatively rare, but occurs more frequently in HER2-positive compared to HER2-negative patients [19]. There are two hypotheses to explain the higher risk for brain metastases in HER2-positive

patients [20]. The first one is that trastuzumab is not able to cross an intact BBB, thus being active against the systemic disease but not preventing CNS disease. The second hypothesis suggests that there is an increased propensity of the HER-2 lineage to colonize the brain.

Biology and Molecular Pathways

In general, metastasis of cancer cells occurs via the “metastatic cascade,” which refers to tumor cell invasion of surrounding tissue, entry into the blood stream (intravasation), attachment to local vasculature (arrest), extravasation, and proliferation at the site of metastasis. The “soil and seed” hypothesis of metastasis formation explains why circulating tumor cells may travel throughout the body, but metastases tend to form in particular organs (as in the brain in absence of lung metastases). The metastasis formation would be the result of an interaction between the organ microenvironment (the “soil”) and the adhesive and invasive capabilities of the metastasizing tumor cells (the “seed”) [21]. Neoplastic cells with the potential to colonize the brain may express unique molecular determinants and respond to brain-derived growth factors, and thereby be able to invade, proliferate, and induce angiogenesis [22]. Moreover, the brain is a unique target organ because of the presence of the blood–brain barrier (BBB) [23] and the absence of lymphatic drainage.

Several genes that mediate the spread of the different primary tumor types to the brain have been identified. Expression profiling has revealed at least five molecular subtypes of breast cancer that differ in tropism to different organs. The luminal breast cancer subtype tends to affect pleura and bone, while the basal subtype preferentially metastasizes to lung and brain [24]. Recently, a set of specific genes was identified [25] by comparing the expression profiles of murine breast cancer cells preferentially metastasizing to brain with the profiles of breast cancer samples from patients with known cerebral metastases. A distinction was made between genes that are expressed in primary tumors with metastases, and therefore called “metastasis progression-genes,” and other genes active in the metastatic tumors but not expressed in the primary tumors. The cyclooxygenase COX2, the EGFR ligand HBEGF and the α 26-sialyltransferase ST6GALNAC5 were identified as mediators of cancer cell passage through the BBB. While the EGFR ligand and COX2 are also involved in the development of lung metastases, the sialyltransferase ST6GALNAC5 is more specific to the development of brain metastases. In an invitro model COX2 was found to be crucial in the passage of the tumor cells through the BBB [25], and COX2 knock-down lowered the frequency of brain metastasis. Palmieri and colleagues [26] found hexokinase 2 (HK2) to be upregulated 1.5-fold in tumor cells in the brain

and associated with poor survival in patients following craniotomy. Moreover, HER2 overexpression does not appear to affect tumor cell arrival or intravasation into the brain, but it increases brain colonization [27]. STAT3 activation has been implicated as an important driver of brain metastasis in breast cancer and its inhibition has been recently shown to suppress development of brain metastases [28]. Few studies have investigated the genomic drivers of brain metastases from lung cancer. Grinberg-Rashi and colleagues [29] reported 12 candidate genes whose overexpression was associated with brain or systemic metastasis in a large series of NSCLC primary tumors, and three genes (CDH2, KIFC1, FAL2) were able to predict prognosis. Of particular interest is the overexpression of CDH2 (N-cadherin), which is involved in multiple processes, such as invasion, migration, and adhesion. The EGFR pathway and integrins may play a role in helping promote brain metastasis in lung and breast cancers [30]. Cancer cells of neural crest origin such as melanoma and neuroendocrine carcinoma may preferentially migrate to the brain [31]. The TGF- β 2 expression by murine melanoma is necessary for the establishment and growth of metastases in the brain [32].

In order to get to the brain, tumor cells must reach the cerebral microvasculature and pass through the BBB [33, 34]. Genes coding for cell surface glycoproteins are involved in the attachment of the cells to local blood vessels, and genes regulating vascular permeability are involved in passing through the vessels. Genes involved in the formation and maintenance of the astrocytic end-feet at the opposite side of the BBB have also been implicated.

In order to proliferate, metastatic tumor cells need to switch on the expression of pro-angiogenic molecules like VEGF, MMP-9, and gelatinase B, as well as molecules degrading the extracellular matrix, allowing the growth of new vessels [35]. Increased expression levels of VEGF are necessary but not sufficient for successful formation of metastases in experimental animals [34, 36]. The absence of neo-angiogenesis in metastatic tumor cell populations keep the tumor dormant, a state of increased apoptosis of tumor cells with normal proliferation [37].

Various genes that suppress the formation of metastases have been identified, including Nm23 and CD44. Overexpression of Nm23 in breast cancer and melanoma negatively affects invasion, colonization, and motility [38], and patients with melanoma with low expression of Nm23 had increased risk of developing brain metastases [39]. The membrane glycoprotein CD44 plays a role in the adherence of circulating tumor cells to endothelium. Downregulation of the gene by DNA hypermethylation prevented the formation of metastases and, conversely, consistent expression was reported in cancers of thyroid, skin, and breast [40]. Interestingly, while the standard CD44 isoform is expressed in

primary brain tumors, the CD44 splicing variant is almost exclusively found in brain metastases [41].

Clinical Presentation

The clinical presentation of brain metastases is similar to the presentation of any intracranial mass lesion. Headache is a presenting symptom in 40–50% of patients, is more common with multiple or posterior fossa metastases, and may be mild. Papilledema is associated with headache in 15–25% of patients only. Up to 40% of patients present with focal neurological deficits, and seizures occur in 15–20% of patients. Another 5–10% of patients present with acute “stroke-like” symptoms due to an intratumoral hemorrhage (especially in melanoma, renal carcinoma, and choriocarcinoma). Altered mental status or impaired cognition are frequently seen in patients with multiple metastases and/or increased intracranial pressure, sometimes resembling a metabolic encephalopathy. Conversely, the symptoms and signs at presentation can be subtle. As a general rule, brain metastases should be suspected in any patient with known systemic cancer in whom new neurological findings develop.

Diagnosis by Neuroimaging

MRI is the method of choice for the assessment of brain metastasis. Contrast-enhanced MRI is more sensitive than enhanced CT (including double-dose delayed contrast) or unenhanced MRI in detecting brain metastases, particularly lesions in the posterior fossa or multiple punctate metastases [9, 10]. Although T2-weighted and FLAIR images are sensitive in showing vasogenic edema as areas of increased signal intensity, not all metastatic lesions have sufficient edema to be identified.

There are no specific features on MRI that distinguish brain metastases; however, a peripheral location, spherical shape, ring enhancement with prominent peritumoral edema and multiple lesions all suggest metastatic disease (Fig. 4.1). Differential diagnoses, including primary brain tumors (especially high-grade gliomas and lymphomas) and non-neoplastic conditions (abscesses, infections, hemorrhages) must be considered, even in patients with a history of cancer. Diffusion-weighted (DW) MR imaging may be useful in the diagnosis of ring-enhancing cerebral lesions (restricted diffusion is more typical in abscesses compared to unrestricted diffusion in necrotic glioblastomas or metastases), but the findings are not specific [42–44]. When employing MR perfusion imaging, there is a tendency towards lower cerebral blood volume values within the peritumoral region in brain metastases compared with



Fig. 4.1 MRI with gadolinium: brain metastasis from colon cancer in the *right* cerebellar hemisphere with edema and mass effect on the 4th ventricle

glioblastomas [45, 46]. MR spectroscopy more often shows a lower choline to creatinine ratio in brain metastases than in high-grade gliomas [47, 48]. FDG-PET and ^{18}F -FET PET do not provide sufficient differentiation between metastases and high-grade glial tumors [49, 50].

Overall, advanced functional imaging techniques cannot reliably identify the histologic origin of an enhancing brain lesion and hence histopathological analysis remains the gold standard. A tissue diagnosis by biopsy should be considered in patients with either unknown primary tumor or well-controlled systemic cancer, especially if a long interval has elapsed since the initial cancer diagnosis, or (less common) in patients with active systemic cancer when the radiographic appearance is atypical. In the modern era there is seldom a justification for irradiating “presumed brain metastases” without a histological diagnosis of cancer.

Staging

A new brain mass suspected to be a metastasis in a patient with no prior history of cancer warrants additional systemic work-up for a primary malignancy. A chest CT is always recommended given the high frequency of brain metastases from lung cancer [51, 52], CT of the abdomen and ultrasound of the testis occasionally reveal the primary tumor. Additional work-up beyond this is low yield, unless the patient’s

history or physical exam is suggestive of a specific primary site [53]. Whole-body fluorodeoxyglucose (FDG) PET can be useful [54], but the specificity in differentiating malignant tumors from benign or inflammatory lesions is relatively low. Notably, serial chest CTs may increase the probability of detection of lung cancer in patients with a brain metastasis from an unknown primary tumor, but for these patients early detection provides only limited if any, benefit in survival. [55]. Therefore, a costly extensive evaluation for the undetected primary during the follow-up is not appropriate until more effective cancer therapies are available [53, 55].

A CSF examination is not indicated in the work-up of brain metastases unless there are symptoms, signs or neuroimaging findings that suggest a coexistent leptomeningeal carcinomatosis.

Diagnostic Neuropathology

Routine hematoxylin-eosin stain of biopsy specimens usually reveals the neoplastic nature of the cerebral lesion, and can distinguish between metastases, malignant gliomas, meningiomas, lymphomas, and more rare entities. Immunohistochemical markers may aid in the further characterization of the tumor.

Cerebral Metastasis of Known Primary Tumors

In patients with a known primary tumor, the histology and the marker profile of the primary and the cerebral metastasis will usually show similarities. In general, histologic comparison between the specimen of primary tumor(s) and cerebral metastasis is mandatory, as not infrequently patients may harbor more than one tumor type.

Cerebral Metastasis of Unknown Primary Tumors

For the determination of the lineage of the metastatic tumor, basic morphology provides a first differentiation between carcinomas, lymphomas, or melanomas (Fig. 4.2a–c). In addition, immunohistochemical profiles of metastases may be indicative of the site and lineage of the primary tumor [56]; however, these show variable overlap, and most markers are not specific. In case of a cerebral adenocarcinoma of unknown primary, TTF-1 positivity is strongly associated with lung cancer (Fig. 4.3) and cancer of the thyroid. Negativity for CK7 and positivity for CK20 suggests colorectal cancer. Neuroendocrine differentiation is confirmed by chromogranin, synaptophysin and antibodies directed against specific hormones (insulin, gastrin, glucagon, serotonin and somatostatin). Similarly, there are

Fig. 4.2 a–c Hematoxylin-eosin: neoplastic cells from NSCLC with hyperchromatic nuclei, arranged in well demarcated solid foci within brain parenchyma

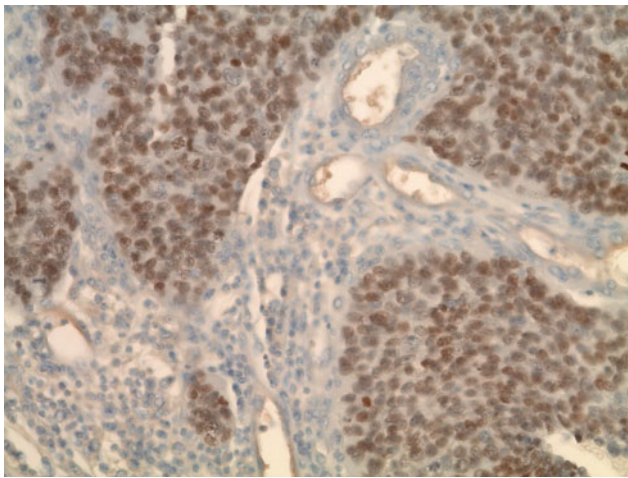
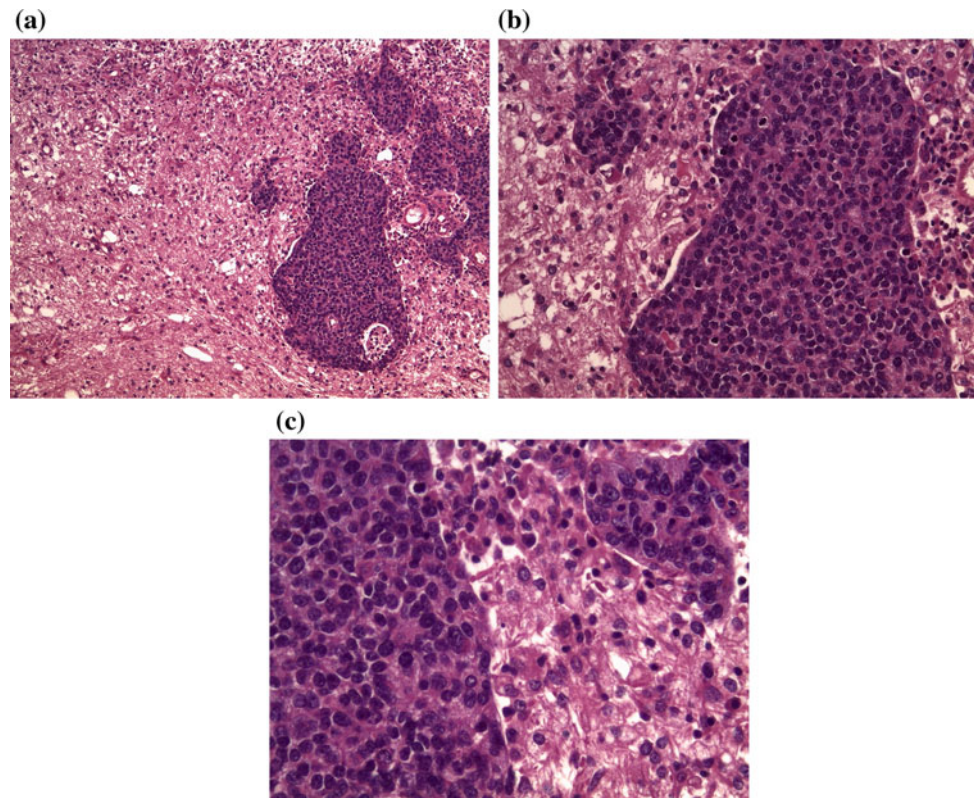


Fig. 4.3 Nuclear immunostaining of neoplastic cells for thyroid transcription factor 1 (TTF 1) in a brain metastasis from lung carcinoma

immunohistochemical panels for mesenchymal tumors (vimentin, desmin, S100).

Attempts to identify unknown primary tumors from their metastases by using RNA expression profiles are ongoing. In general, few studies have focused on the comparison of primary tumors and their cerebral metastases with respect to lineage markers and biomarkers for treatment eligibility [57, 58].

Prognostic Factors

Several factors, including Karnofsky performance status (KPS), age, primary/systemic tumor activity, neurocognitive function, number of brain metastases, primary tumor type and time from primary tumor diagnosis to the brain lesion have individual prognostic significance in patients with brain metastases [59, 60]. Of these, the KPS has consistently been shown to be the major determinant of survival. Based on the most powerful factors, prognostic indices have been developed in order to distinguish subgroups of patients with different prognosis. Utilizing recursive partitioning analysis (RPA) a three-tiered prognostic categorization (RPA Classes I, II and III) was derived from 1200 patients in the Radiation Therapy Oncology Group (RTOG) database who received WBRT [59, 61]. RPA class I represents patients with a KPS greater than 70, age younger than 65 years, controlled primary tumor and no extracranial metastases, with a median survival of 7.7 months; RPA class III represents patients with KPS less than 70, with a median survival of 2.3 months; RPA class II represents the remainder of patients with a median survival of 4.5 months.

A new prognostic index, the Graded Prognostic Assessment (GPA), derived from an analysis of an updated RTOG database of 1960 patients, has been proposed [62]. The GPA uses four factors (age, KPS, status of extra neural disease

and number of brain metastases) to subdivide patients into one of four categories with median survival ranging from 2.6 to 11 months. This new index appears equivalent to the RPA in ability to prognosticate, but is less subjective and more quantitative. Additional analysis [63] has shown that the prognostic factors for patients with brain metastases vary according to the histological diagnosis. For both nonsmall-cell and small-cell lung cancer, the significant prognostic factors were KPS, age, presence of extracranial metastases and number of brain metastases, confirming the original GPA. Conversely, for breast cancer, significant prognostic factors were KPS, age and tumor subtype (classified as HER2, estrogen receptor and progesterone receptor status), but not number of brain metastases or status of systemic disease. For melanoma and renal cell carcinoma, the significant prognostic factors were KPS and number of brain metastases. The GPA categorization has now been validated in patients with breast cancer and brain metastases [64, 65], and should be used to stratify future randomized clinical trials, estimate survival and guide the choice of management options. RPA and GPA provide group rather than individual estimates. Recently, a nomogram for the estimation of individual survival probabilities in patients with brain metastases has been proposed with use of data from RTOG database [66].

Additional prognostic scores have been developed for patients with brain metastasis undergoing radiosurgery [67, 68]. Prognosis does not differ between patients with a known and unknown primary tumor [52, 69].

Supportive Care

Corticosteroids are used to control vasogenic cerebral edema and mass effect. Two evidence-based guidelines on the role of steroids in brain metastases have been published in Europe [70] and US [71], and they substantially agree. Dexamethasone is recommended for patients who are symptomatic, with a starting dose of 4–8 mg/day, considering higher doses such as 16 mg/day or more in patients with severe symptoms. Dexamethasone is the steroid of choice because of its minimal mineralocorticoid effect and long half-life, though other corticosteroids can be effective if given in equipotent doses. A neurological improvement within 24–72 h after beginning of treatment is expected in up to 75% of patients. As monotherapy, dexamethasone can relieve symptoms for approximately one month and may slightly increase the 4–6-weeks median survival in comparison to patients who receive no treatment at all. To minimize side effects from chronic dexamethasone administration, including proximal myopathy, tapering of steroid dosing within 1 week of starting therapy and discontinuation

within 2 weeks is encouraged. Asymptomatic patients do not need steroids.

The need for anticonvulsant medication is clear in patients who have experienced a seizure. There exists no evidence to support the use of prophylactic anti-epileptic drugs (AEDs) in patients with brain tumors, including metastases. Twelve studies, either randomized trials or cohort studies, investigating the ability of prophylactic AEDs (phenytoin, phenobarbital, valproic acid) to prevent the first seizure, have been examined, and none have demonstrated efficacy [72]. Subtherapeutic levels of anticonvulsants were extremely common and the severity of side effects appeared to be higher (20–40%) in brain tumor patients than in the general population receiving anticonvulsants, probably as a result of drug interactions. Phenytoin, phenobarbital, carbamazepine, and oxcarbazepine stimulate the cytochrome P450 system and accelerate the metabolism of corticosteroids and antineoplastic agents, such as nitroso ureas, paclitaxel, cyclophosphamide, topotecan, irinotecan, thiopeta, adriamycin, methotrexate, imatinib, gefitinib, erlotinib and other tyrosine kinase inhibitors (TKIs), and thus reduce their efficacy. The role of prophylactic anticonvulsants remains to be addressed in subgroups of patients who have a higher risk of developing seizures, such as those with metastatic melanoma, hemorrhagic lesions, or multiple metastases. For patients who undergo a neurosurgical procedure the efficacy of prophylaxis has not been proven. The efficacy of novel AEDs (levetiracetam, topiramate, gabapentin, lamotrigine, lacosamide) has to date not been extensively investigated [73].

Anticoagulant therapy is the standard treatment for acute venous thromboembolism (VTE) in cancer patients. Subcutaneous low-molecular weight heparin (LMWH) is recommended for the initial 5–10 days of treatment for deep vein thrombosis and pulmonary embolism as well as for long-term secondary prophylaxis (for a minimum of 6 months) [74]. Use of novel oral anticoagulants is not currently recommended for patients with malignancy and VTE because of limited data in this patient population [75].

Prophylaxis with LMWH is required for hospitalized patients undergoing major surgery, while in the outpatient setting it is recommended only in selected high-risk patients [76, 77].

Treatment of Newly Diagnosed Brain Metastasis

Surgery

Three randomized trials in single brain metastasis have compared the efficacy of surgical resection followed by WBRT with WBRT alone [78–80]. See Table 4.1.

Table 4.1 Results of phase III trials comparing WBRT alone with surgery plus WBRT in single brain metastasis

Author	Treatment arms	Median survival	Patterns of progression	Median time to progression
Patchell [78]	A1: WBRT ($n = 23$) A2: surgery +WBRT ($n = 25$)	A1: 15 weeks A2: 40 weeks $p < 0.01$	Local A1: 12/23(52%) A2: 5/25(20%) $p < 0.02$ distant A1: 3/23(13%) A2: 5/25(20%) $P = NS$	Local A1: 21 weeks A2: >59 weeks $P < 0.0001$
Vecht [79]	A1: WBRT ($n = 31$) A2: surgery +WBRT ($n = 32$)	A1: 3 months A2: 15 months $p = 0.04$	NR	N
Mintz [80]	A1: WBRT ($n = 43$) A2: surgery +WBRT ($n = 41$)	A1: 6.3 months A2: 5.6 months $P = NS$	NR	NR

NR not reported; NS not significant; A1 Arm 1; A2 Arm 2

The first two studies showed a survival benefit for patients receiving the combined treatment (median survival 9–10 months vs. 3–6 months). In the Patchell study, patients who received surgery displayed a reduced rate of local relapses (20% versus 52%) and a longer time of functional independence. In the third study, which included more patients with active systemic disease and a low Karnofsky performance status, the addition of surgery to WBRT did not confer a survival benefit, suggesting that this benefit may be limited to a subgroup of patients with controlled systemic disease and good performance status.

In the majority of patients, surgical resection can alleviate symptoms of intracranial hypertension, reduce focal neurological deficits and seizures, and allow for a rapid steroid taper. It should be strongly considered for lesions ≥ 3 cm and/or with significant surrounding edema and/or located in the posterior fossa with mass effect and associated hydrocephalus. Gross total resection of a brain metastasis can be achieved with lower morbidity using contemporary image-guided systems, such as preoperative functional MRI, intraoperative neuronavigation, and cortical mapping [81]. An early postoperative MRI has been recommended to detect residual tumor that is present in up to 20% of patients, and can lead to an increased risk in local recurrence [82]. The same group has suggested that a supramarginal resection (i.e., a resection including a peripheral portion of normal nervous tissue) in eloquent locations could increase the rate of gross total resection [83]. The combined resection of a solitary brain metastasis and a synchronous nonsmall-cell lung carcinoma (stage I and II) yields a median survival of at least 12 months, with 10–30% of patients surviving at 5 years [84].

Leptomeningeal dissemination (LMD) can be a significant complication of the resection of metastasis, especially in case of patients with posterior fossa lesions [85, 86]. A recent retrospective study from MD Anderson Cancer Center [86] in 379 patients with posterior fossa metastases, who

underwent either surgery or radiosurgery, revealed a significant increase of LMD in patients whose tumors underwent a “piecemeal” resection (13.8%) compared to *en bloc* resection (5–6%), and the risk of LMD after *en bloc* resection was comparable to that after SRS.

Surgery may be considered for patients with 2–3 surgically accessible brain metastases who are in good neurological condition, have controlled systemic disease and limited comorbidities (Fig. 4.4a–d). Complete surgical resection in this population yields results comparable to those obtained in single lesions [87].

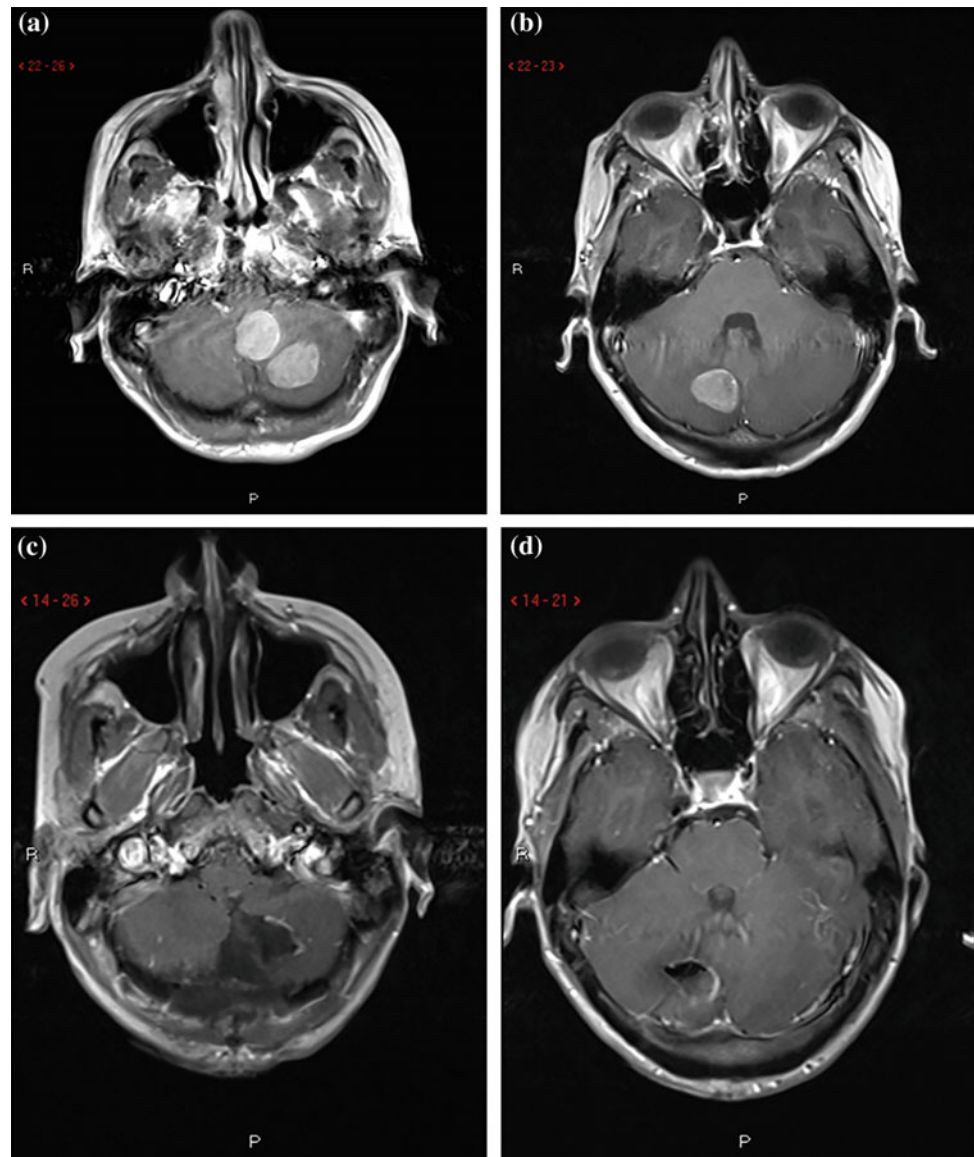
The usefulness of carmustine wafer placement in the resection cavity in newly diagnosed brain metastasis [88] has not been proven in large series of prospective trials.

The GliaSite Radiation Therapy System is an intracavitary high-activity ^{125}I brachytherapy, performed with a balloon placed in the resection cavity and filled with a radioactive solution. It delivers highly localized doses of radiation to the resection margins (60 Gy to 1 cm depth). A phase II trial in resected single brain metastasis [89] has reported an overall and 1-year local control rate of 83 and 79%, respectively, with a 17% of local failures. Seventeen per cent of patients experienced radiation necrosis. A smaller retrospective study [90] reported the results of ^{125}I brachytherapy using low-activity permanent seeds placed in the resection cavity. Local tumor control was achieved in 96% of patients, with 4% local failure. The 1-year risk of symptomatic radiation necrosis was lower than that seen in the phase II trial [89] with high-activity seeds (8% vs. 23%).

Stereotactic Radiosurgery

Stereotactic radiosurgery (SRS) is a single, high-dose radiation treatment with precise localization of the target using stereotactic frames or image guidance. Convergence of multiple beams on the target yields a highly therapeutic

Fig. 4.4 a–d 40 year-old woman with node-positive triple-negative breast cancer diagnosed two years earlier presenting with headache and gait ataxia. **a, b** Bihemispheric cerebellar metastases on post-contrast T1-weighted MRI at diagnosis. **c, d** Same case of **a** and **b** following resection



effect, while the steep dose fall-off to surrounding normal structures minimizes the risk of damage. Most brain metastases represent an ideal target for SRS, owing to the small size, spheroid shape, and distinct pathologic margins [91]. The dose is inversely related to tumor diameter and volume. Maximal tolerated doses of SRS were defined in the RTOG 90-05 study [92] in previously irradiated primary brain tumors or brain metastases: 24 Gy for ≤ 20 mm, 18 Gy for 21–30 mm and 15 Gy for 31–40 mm in maximum diameter. As a consequence, the local tumor control decreases as the size of the metastasis increases and the dose that can be given in single fraction decreases. Recently, there has been an increasing interest in hypofractionation for larger metastases (2–5 fractions of smaller doses) with the aim to give radiobiologically higher doses to improve local control and decrease the risk of radionecrosis [93–95].

Comparative studies of hypofractionated SRS versus single dose SRS are awaited.

Several retrospective series have shown single dose SRS to be effective in the treatment of newly diagnosed brain metastases. One-year local control rates of 80–90% with symptom improvement and median survival of 6–12 months have been reported [96–98]. Patients with single lesion, controlled systemic disease and KPS of 70% or greater, have longer survival [99, 100].

Metastases from radio resistant tumors, such as melanoma and renal cell carcinoma, respond to SRS as do metastases from radiosensitive tumors [101]. Radiosurgery allows the treatment of brain metastases in almost any location, including the brainstem [102, 103]. Older patients (≥ 80 years of age) may respond as well as younger patients [104]. The type of radiosurgical procedure, gamma knife or

linear accelerator (Linac)-based, does not impact the results. The imaging response to SRS has been reported to correlate with survival only in patients with breast cancer [105].

For patients in RPA classes 1 and 2 with 1–3 brain metastases, SRS has been reported to be more effective than WBRT alone in terms of local tumor control [106].

A randomized phase III study (RTOG95-08) in patients with 1–3 brain metastases, stratified by the RPA system, investigated the value of the addition of a SRS boost to WBRT [107], and reported better local control and performance status at 6 months in the combined therapy group. However, the survival advantage was statistically significant only in a subgroup of patients with single metastasis (6.5 months vs. 4.9 months). Recently, a secondary analysis of RTOG 95-08 that poststratified patients by the GPA classification has reported that the addition of SRS to WBRT conferred a significant survival advantage for patients with a good prognosis (GPA 3.5–4.0) regardless of whether they had 1 or 2 or 3 brain metastases [108]. Conversely, this benefit did not extend to patients with lower GPA and 2 or 3 metastases. It must be stressed that approximately two-third of patient in the trial had lung tumors. A small randomized trial, comparing WBRT alone versus WBRT + SRS in patients with 2–4 metastases, was stopped earlier due to the significant benefit in terms of local failure reduction at 1 year for patients receiving the combined treatment (8% vs. 100%) [109].

The role of SRS alone in patients with up to 3–4 metastases is discussed in the section on WBRT following surgery or radiosurgery.

The role of SRS alone, instead of WBRT, in patients with >4 brain metastases has been investigated in single arm trials. A prospective multicenter Japanese study investigated the use of SRS alone in 1194 patients with one, 2–4 or 5–10 brain metastases, and found similar overall survival (10.8 months) and treatment related toxicity rates between the groups with 2–4 and 5–10 metastases [100]. Salvage SRS was performed in 38% of patients and WBRT in 9%. Cumulative volume of metastases, rather than the number, seems to be a more significant prognostic factor [100, 110]. A consortium in the US is conducting a randomized trial in patients with ≥ 5 metastases to compare SRS to WBRT with neurocognitive outcome as the primary endpoint.

Acute (early) and chronic (late) complications following radiosurgery are reported in 10–40% of patients. Serious complications are rare [111]. Acute reactions (due to edema) occur more often within 2 weeks of treatment, and include headache, nausea and vomiting, worsening of preexistent neurological deficits and seizures. These reactions are generally reversible with steroids. Chronic complications include hemorrhage and radionecrosis (1–17%). Radiographically, a transient increase in the size of the irradiated lesion, with increasing edema and mass effect, with or

without radionecrosis, cannot be distinguished from a tumor progression. FDG-PET, MRI spectroscopy, and MRI perfusion can provide additional information but cannot definitively distinguish between the two diagnoses [112].

Radiation necrosis can be treated with steroids, hyperbaric oxygen, anticoagulants (with risk of bleeding), and more recently with the anti-VEGF agent bevacizumab, which allows a stabilization and normalization of the damaged vascular permeability [113].

A recent review of adverse radiation effects (ARE) following SRS in a large cohort of patients with brain metastases, either radiographic or pathologic, has been published [114]. Although the incidence of ARE after SRS was overall low, the risk increased rapidly with size and volume, leveling off at 1-year cumulative incidence of 13–14%. The authors found a wide range in the time of onset and time to improvement of ARE, and at least 75% probability of improvement over time in conservatively managed AREs. With the exception of capecitabine, neither systemic therapy within 1 month of SRS nor arterial hypertension or diabetes [114] appeared to increase the risk of adverse events in the brain.

Surgery Versus SRS

There is no prospective randomized study with sufficient power to compare surgery to SRS. Most comparisons [115–118], including an early terminated small randomized study [119], showed similar outcomes. The one exception is a small series by Bindal and colleagues [120], who reported a superiority of surgery over SRS in terms of OS (16.4 months vs. 7.5 months) and neurologic deaths (19% vs. 50%). However, only 80% of SRS-treated patients were deemed resectable retrospectively, and it is unclear whether this was due to the extent of systemic disease or tumor location.

In general, SRS is less invasive and can be accomplished in an outpatient setting, offering cost-effectiveness advantages over surgery. Patients with larger lesions (2–3 cm), however, may require chronic steroid administration given risk of tumor-related edema and swelling with SRS. Ultimately, the choice between surgery and SRS must be made on a case by case basis, with consideration given to tumor location, size, type of neurological symptoms, patient preference and physician expertise.

Whole Brain Radiotherapy Following Surgery or Radiosurgery

The utility of adjuvant WBRT following surgery or radiosurgery remains controversial. WBRT is believed to eradicate microscopic disease at the original tumor site and at

distant intracranial locations. The risk of long-term neurotoxicity and availability of potentially effective salvage treatments [121] are the main arguments against the use of adjuvant WBRT. This needs to be weighted against potential risks of omitting treatment, including CNS progression at distant sites and resultant neurocognitive and neurological sequelae. Moreover, the effectiveness of systemic salvage therapy remains unknown [122].

There are now three phase III trials [123–126], showing that the omission of WBRT in patients with newly diagnosed brain metastases after either surgery or SRS, results in significantly inferior local and distant control, without effect on overall and functionally independent survival. An American-led trial [123] investigating the role of WBRT following surgery, and a Japanese led trial [124] investigating the role of WBRT following SRS, included patients with progressive systemic disease. Conversely, the EORTC 22952-26001 trial focused on patients with stable systemic disease, i.e., on those who could maximally benefit from the addition of early WBRT. This trial randomized 359 patients with 1–3 metastases (81% had one lesion and 19% had two-three lesions), who had previous surgery or SRS, to either WBRT or observation [125]. Adjuvant WBRT significantly reduced the risk of intracranial progression, both locally and at distant sites, by about 50%, but failed to improve functional independence and OS (median 10.9 months vs. 10.7 months). A meta-analysis of the three randomized trials assessing SRS with or without WBRT has challenged our current understanding of the effect of adjuvant WBRT [127]. The investigators reported a survival advantage for SRS alone in those patients presenting with one to four metastases, KPS of 70 or higher and age of 50 years or younger. Moreover, in the subgroup of patients with <50 years, a reduction in the risk of new brain metastases with adjuvant WBRT was not observed. Conversely, in older patients (aged >50 years), WBRT decreases the risk of new brain metastases, but did not affect survival.

A retrospective study [128] has reported that adjuvant WBRT following surgery is of particular value in reducing local and distant recurrence in the brain among patients with metastases >3 cm or with active systemic disease.

The impact of adjuvant WBRT on cognition and quality of life has been examined in several recent studies. Aoyama and coworkers [129] compared the neurocognitive function of patients who underwent either SRS alone or SRS + WBRT. More than 50% of patients experienced significant improvement in the MMSE score shortly after therapy (2–3 months), regardless of treatment, but there was evidence of neurocognitive decline in long-term survivors (up to 36 months) after WBRT. In a randomized controlled trial, Chang and coworkers [130] showed that patients treated

with SRS plus WBRT were at greater risk of a significant decline in learning and memory function by 4 months compared with the group receiving SRS alone.

A recently completed randomized phase III trial (NCCTG N0574) compared SRS alone versus SRS + WBRT in patients with 1–3 brain metastases using a primary neurocognitive endpoint, defined as a decline from baseline in any six cognitive tests at 3 months [131]. Overall, the decline was significantly more frequent after SRS + WBRT versus SRS alone (88% vs. 61.9%, respectively). Specifically, there was more deterioration in the SRS + WBRT arm in immediate recall (31% vs. 8%), delayed recall (51% vs. 20%) and verbal fluency (19% vs. 2%). Intracranial tumor control at 6 and 12 months was higher in the combined arm, but not statistically significant.

Soffiatti and coworkers [132] analyzed the quality of life data of the EORTC 22952-26001. They found no significant difference in the global Health-Related Quality of Life over a one-year follow-up period, but patients who underwent adjuvant WBRT had transiently lower physical functioning and lower cognitive functioning scores.

These data suggest that adjuvant WBRT after SRS in patients with a limited number of metastases (up to 3–4) improves intracranial control without improving survival, and carries a high risk of neurocognitive decline, and is therefore not unequivocally recommended. In this regard, the American Society for Radiation Oncology (ASTRO) has recently recommended in their Choose Wisely campaign SRS without adjuvant WBRT for the treatment of limited number of brain metastases [133].

The need for WBRT following surgical resection remains debated, as randomized trials [123, 125] have reported a higher rate of local relapses following surgery alone (about 60% in the EORTC trial) compared with SRS alone.

In general, omission of WBRT, following either SRS or surgery, requires close monitoring with serial imaging (every 3–4 months).

SRS Following Surgery

Postoperative SRS is an approach used to decrease local relapse and avoid the cognitive sequelae of WBRT. Several cohort studies and one phase II trial have reported local control rates of 85–95% [134–136]. The median survival in published studies is around 4 months (range 10–20.5 months). The improved local control and survival rates suggest that postoperative SRS may be as effective as WBRT.

Postoperative SRS is advantageous because it can be delivered within a day or two following surgery and completed in one day. WBRT cannot be initiated for at least

10 days but usually up to two weeks postoperatively to allow for adequate wound healing. For patients receiving systemic therapy, a break from chemotherapy is necessary during WBRT administration, and up to one month following its completion. With postoperative SRS, there is minimal to no interruption of systemic agents, thereby decreasing time off treatment and risk of systemic disease progression.

Despite a growing body of literature [134, 136–139], SRS to the resection cavity does not seem to be superior over WBRT in terms of local control at 1 and 2 years. Moreover, SRS may pose increased risk over WBRT of radionecrosis and other neurological complications, as well as leptomeningeal relapse.

Several questions remain regarding SRS following surgery [135, 140, 141]. The optimal dose and fractionation schedule, especially for large brain metastases (>3 cm) associated with higher risk for local failure, are unknown. The same holds true for the optimal margin around the resection cavity to be included in the treatment field. From a clinical standpoint, there remain little data about the impact of postoperative SRS on HRQOL and neurocognitive function. The timing of SRS after surgery also remains unclear. There is little evidence that SRS administered in the immediate postoperative period is more effective than when administered at the time of tumor progression.

The risk of radionecrosis following postoperative SRS [135, 141–143] is higher (between 9 and 17.5%) than that reported by the EORTC study with WBRT following either surgery or radiosurgery (2.6%), and could increase over time (7% at 1 year and 16% at 2 years) [141]. However, the actual incidence of pathologically proven radionecrosis is unknown, as often the values reported in the different series represent a combination of biopsy proven and MRI suspected cases of radionecrosis. Several advanced neuroimaging techniques (MRS, MRI perfusion, PET with FDG or amino acids) can aid in the diagnosis of radiation necrosis but oftentimes produce conflicting results. Treatment may include the use of bevacizumab [113], but not without significant financial costs. Alternatively, steroids can reduce symptoms and edema related to radiation effects, but their use increases risk of steroid dependency. The average frequency and duration of steroid using following postoperative SRS remains unknown.

The use of SRS to the resection cavity without the addition of WBRT may be associated with increased risk of leptomeningeal disease (LMD). The incidence has been found to range from 8 to 13% [139, 141–146]. Patients with breast histology may be at higher risk (at 1 year 24% vs. 9%) [146]. It is unclear whether the inclusion of WBRT would decrease this risk or whether the increased risk for LMD seen in patients with brain metastases from breast is associated with the biology of this tumor type. To better characterize this risk of LMD, future reports on the use of

SRS to the resection cavity should distinguish between compartments of failure: local, distant and leptomeningeal.

In conclusion, the main limitations of available studies on postoperative SRS in single brain metastasis include relatively small sample size, short follow-up, heterogeneous primary histologies, unknown disease stage, and concurrent use of chemotherapy. Given the lack of clear risk/benefit data and increased associated financial costs, additional research in this area is needed before the use of postoperative SRS becomes routine clinical practice [147].

WBRT Alone

WBRT alone is the treatment of choice for patients with any of the following: single or multiple brain metastases not amenable to surgery or radiosurgery, a low KPS (≤ 50) or active systemic disease. Complete and partial responses have been reported in up to 60% of patients, with a neurological improvement that probably is in part attributable to steroids. Tumor volume reduction after WBRT seems to be associated with better neurocognitive function preservation and prolonged survival [148]. Median survival following WBRT alone ranges from 3 to 6 months, with 10–15% of patients alive at 1 year. A meta-analysis of 39 trials involving 10,835 patients concluded that, in comparison to standard fractionation (30 Gy in 10 fractions or 20 Gy in 5 fractions), altered WBRT dose fractionation schemes do not improve overall survival, neurologic function or symptom control [149]. However, a recent randomized trial in patients with NSCLC not candidate for either surgery or radiosurgery, did not show any difference in overall survival and quality of life between WBRT and supportive care alone [150].

Nausea, vomiting, headache, fewer and worsening of neurological symptoms can be observed in the initial phase of therapy, requiring steroid administration for control.

Up to date, radiosensitizers have not provided any clear additional benefit over conventional treatment. Recently, the addition of motexafin gadolinium to early WBRT in patients with brain metastases from NSCLC yielded an improvement in time to neurological progression over WBRT alone (5.5 months vs. 3.7 months) [151]. Likewise, the addition of efaproxiral (RSR 13) to WBRT in patients with brain metastases from breast cancer has reduced the death rate by 46%, while improving quality of life [152].

Cognitive Dysfunctions Following WBRT: Risk Factors, Pathogenesis, and Prevention

A radiation-induced dementia with ataxia and urinary incontinence has been reported in up to 30% of patients by one year from receiving unconventional large size fractions

of WBRT (6–8.5 Gy) [153]. The picture on CT/MRI is that of a leukoencephalopathy (diffuse hyperintensity of the periventricular white matter on T2-weighted and FLAIR images) with associated hydrocephalus. Ventriculo-peritoneal shunt may be of clinical value in some patients. When using more conventional size fractions (up to 3 or 4 Gy per fraction) the risk is that of milder cognitive dysfunctions, consisting mainly of deficits in learning and memory with associated white matter damage and cortical atrophy on MRI. Patients with arterial hypertension, diabetes or other vascular diseases are at higher risk of developing cognitive dysfunctions. The pathogenesis of this radiation-damage is thought to include injury to the endothelium of small vessels, resulting in accelerated atherosclerosis and ultimately in a chronic ischemia similar to small vessel disease of vascular dementia. For this reason, there is interest in investigating vascular dementia treatments to prevent or reduce radiation-induced cognitive decline. One of these approaches is using memantine in combination with WBRT. Memantine is a non-competitive, low affinity antagonist of the N-methyl-D-aspartate (NMDA) receptor, a receptor activated by the principal excitatory neurotransmitter glutamate. Memantine has the potential to block the excessive NMDA stimulation following ischemia that may lead to excitotoxic damage of the normal brain. In two placebo-controlled phase III trials memantine was well tolerated and effective in treating patients with small vessel disease [154, 155]. In a recently published randomized, double-blind, placebo-controlled phase II trial of RTOG (RTOG 0614) the use of memantine during and after WBRT resulted in better cognitive function over time, specifically delaying time to cognitive decline, and reducing the rates of decline in memory, executive function and processing speed [156].

Radiation-induced cognitive deficits may also result, at least in part, from injury to neuronal stem cells in the subgranular zone of the hippocampus [157, 158]. Stem cell neurogenesis critical in memory function, especially for encoding new episodic memories. Low-dose irradiation in rodents results in a blockade of hippocampal neurogenesis and damage of the neurogenic microenvironment, leading to significant short-term memory impairment. Sparing the hippocampus during WBRT could prevent damage to neuronal progenitor cells and improve memory function [159]. Hippocampal avoidance WBRT (HAWBRT) uses intensity modulated radiotherapy (IMRT) to conformally reduce the radiation dose to the hippocampus, while applying the usual higher dose to the whole brain. A potential concern is whether hippocampal avoidance could lead to loss of control of metastases in or around this region. However, recent studies analyzing the distribution of recurrent brain metastases have shown that the metastatic involvement of the limbic circuit is uncommon [160, 161]. The recent single arm phase II RTOG 0933 suggested that the conformal

avoidance of the hippocampus during WBRT spares memory and QoL. Performance at 4 months on standardized memory tests declined 7% from baseline in patients treated with HAWBRT compared with 30% in a historical control group [162]. Importantly, the trial reported that of the patients who developed intracranial progression only 4.5% experienced progression in the hippocampal avoidance area.

Building on results of RTOG 0933 and RTOG 0614, NRGCC001 is a US National Cancer Institute approved phase III trial that will evaluate the potential combined neuroprotective effects of hippocampal avoidance in addition to memantine during WBRT for brain metastases [163]. Given the increased cost of hippocampal avoidance, the trial will also perform a comparative cost-effectiveness analysis.

Treatment of Recurrent Brain Metastasis

Re-resection can afford neurological improvement and prolongation of survival in patients with local accessible brain relapse, high performance status, stable extracranial disease, and relatively long time to recurrence (>6 months) [81, 164–166]. Salvage WBRT following previous WBRT or SRS is now rarely employed. Salvage SRS after WBRT has been widely used during the initial development of SRS, and RTOG 9005 [92] has established the standard doses according to diameter. Several retrospective studies have reported reasonable local control and survival rates with SRS for salvage after WBRT [167–170]. A population-based study has suggested similar survival outcomes following either salvage SRS or boost SRS [171].

Reirradiation with SRS after local recurrence at a site treated with SRS has been employed in a limited number of patients, and the long-term risk of radionecrosis should be considered against the benefit [172].

Multiple courses of SRS for new brain metastases after an initial course of SRS, with continued deferral of WBRT, may yield high rates of local control, low risk of toxicity, and favorable duration of overall and neurologic progression-free survival [100, 173, 174]. A recent large retrospective series [175] has reported that in patients undergoing multiple courses of SRS the aggregate volume, but not the cumulative number of brain metastases, and the GPA score, as recalculated at the second course of SRS, correlate with duration of survival and help guide management.

Chemotherapy and Targeted Therapies

For many years chemotherapy has not been considered to play a major role in the treatment of patients with brain metastases, due to the presence of the blood–brain barrier (BBB) which limits the access of hydrophilic and/or large

drugs into the CNS. However, the BBB is partially disrupted in many brain metastases (>1 mm in size) allowing for many chemotherapeutic agents to reach the tumor cells. Intrinsic chemosensitivity of tumor cells is a more critical factor for the response to chemotherapy [176]. Response rates of brain metastases often reflect the sensitivity of the primary tumor: relatively high response rates in SCLC (30–80%), intermediate rates in breast cancer (30–50%) and NSCLC (10–30%), and low rates in melanoma (10–15%). Importantly even in the most chemosensitive tumors response to chemotherapy is typically equivalent to that observed with radiotherapy.

The combination of radiotherapy and chemotherapy may improve response rates compared to radiotherapy alone, but does not improve survival [177], as in the case of radiotherapy combined with temozolomide (TMZ) for brain metastases [178, 179].

At least two theories may help to explain the disappointing results with chemotherapy. First, metastatic tumor cells in the brain may be resistant to chemotherapy. Brain metastases often develop later in the course of disease after multiple rounds of prior chemotherapies, allowing for the development of resistance through the accumulation of different mutations. Second, permeability of BBB in brain metastases is likely heterogeneous, thereby preventing sufficient drug accumulation and distribution. It has been hypothesized [180] that brain metastases from primary tumors with an intrinsic low expression of P-glycoprotein (an ATP-dependent efflux pump linked to chemoresistance) may be more permeable to antineoplastic drugs.

Recent advances in the understanding of the molecular pathways of tumor growth in many solid tumors have allowed the development of agents targeting specific molecular pathways both in extracranial and intracranial disease [181, 182]. Overall, the response rates to targeted agents seem higher than those observed after conventional chemotherapy. However, for some of these agents passage across the BBB remains an issue. Most of these new compounds, similarly to the old chemotherapeutics, have been shown to be substrates of one or more active efflux transporters.

The promising activity of several TKIs in brain metastases from different primaries has led to two main avenues of clinical investigation [183]. The first is the use of targeted agents as radiosensitizers, which has led to the combination of targeted agents with radiotherapy (WBRT, SRS). The second is the upfront use of targeted agents to control micrometastases, which would allow WBRT to be withheld. Clinical and translation work is ongoing to fully characterize the potential utility of TKIs in the management of brain metastases.

The antiangiogenic drug bevacizumab, a monoclonal antibody targeting VEGF with activity in high-grade, is now being investigated in brain metastases from miscellaneous

solid tumor types. Its associated risk of bleeding has been shown to be quite low [184].

Two important factors can limit the impact of targeted agents on brain metastases: a lack of molecular concordance between the primary tumor and brain metastasis and the emergence of secondary resistance.

Brain Metastases from NSCLC

Platinum compounds (cisplatin, carboplatin), alone or in combination (etoposide, vinorelbine), are the most commonly used chemotherapeutics against brain metastases from NSCLC, either upfront or after radiation at the time of recurrence [176]. Pemetrexed and temozolomide also have some activity. The role of EGFR tyrosine kinase inhibitors (gefitinib, erlotinib) in the management of brain metastases from NSCLC is emerging. A pooled analysis of published data to evaluate the efficacy of EGFR TKIs in NSCLC patients with brain metastases has been recently published [185]. Sixteen studies were included in the analysis, with a total of 464 enrolled patients. The EGFR mutational status was unknown for 362 (unselected group) and 102 had activating EGFR mutations. A higher response rate (85% vs. 45.1%), and a longer PFS (12.3 months vs. 5.9 months) and OS (16.2 months vs. 10.3 months) were observed in the EGFR mutation group compared with the unselected group. These data strongly suggest that the EGFR TKIs are an effective treatment for NSCLC patients with brain metastases, particularly for those patients harboring activating EGFR mutations. However, even in EGFR wild-type patients EGFR-TKIs represent a valuable second-line therapy with a response rate of around 10% [14].

Based on the high intracranial response rates, TKIs monotherapy may be used in lieu of WBRT in patients harboring activating EGFR mutations and asymptomatic brain metastases (i.e., not needing the palliation from WBRT) [186–188]. However, it is important to note that the discordance rate of EGFR mutations between the primary tumor and brain metastases can be as high as 32%, and the CSF penetration rate of gefitinib (1–10%) and erlotinib (2.5–13%) is limited. A systematic review and meta-analysis of the literature has suggested that upfront cranial radiotherapy (SRS or WBRT), alone or with TKIs, may improve survival outcome relative to TKIs alone. On the other hand, the combination of erlotinib with radiation therapy (SRS or WBRT) in patient cohorts not specifically selected for target expression has failed to demonstrate superiority over radiotherapy alone [189–191]. To date, there are no published data on the efficacy for brain metastases of the newer EGFR TKI inhibitors (afatinib, dacomitinib, and icotinib).

Other “druggable” alterations seen in up to 5% of NSCLC patients include rearrangements of the “anaplastic lymphoma

kinase" (ALK) gene. In particular, ALK translocations have been found in 3% of brain metastases from NSCLC, and appear to be concordant between brain metastasis and primary tumor [192]. NSCLC with ALK activating translocations has been shown to be sensitive to treatment with the ALK inhibitor crizotinib. A recent study on brain metastases from ALK-rearranged NSCLC [193] has reported that crizotinib was associated with a 55% rate of disease control within CNS at 3 months of therapy in both RT-naïve and RT-pretreated patients. Moreover, crizotinib was associated with a moderate (18–33%) RECIST-confirmed response rate.

Other multitarget ALK-TKIs, such as ceritinib and alectinib, which are active in patients with ALK-rearranged NSCLC who are either naïve or resistant to crizotinib, are now being investigated in patients with brain metastases. Veliparib, a PARP 1, 2 inhibitor, is another interesting compound currently under investigation in combination with WBRT for the treatment of brain metastases from NSCLC.

Brain Metastases from SCLC

Various combinations of etoposide, teniposide, cisplatin or carboplatin are active against brain metastases [176]. So far, there are no effective targeted agents available.

Brain Metastases from Breast Cancer

Chemotherapy regimens, variably combining cyclophosphamide, 5-FU, methotrexate, vincristine, cisplatin, and etoposide are active in patients with brain metastases from breast cancer [176]. Capecitabine monotherapy has activity against breast cancer brain metastases. In a retrospective review conducted at MSKCC [194], three out of four patients showed complete response, and three had stable disease, with a median overall and progression-free survival after treatment of 13 and 8 months respectively. Capecitabine, combined with TMZ, has some efficacy as well [195]. Likewise, high-dose methotrexate has activity in recurrent brain metastases [196]; however, the risk of leukoencephalopathy, especially when administered after WBRT, is a limiting factor.

The dual EGFR and HER2 tyrosine kinase inhibitor lapatinib has shown modest activity in a phase II study in HER2-positive breast cancer patients with brain metastases, following trastuzumab-based systemic chemotherapy and WBRT [197]. CNS objective responses to lapatinib were observed in 6% of patients, and 21% experienced $\geq 20\%$ volumetric reduction in the CNS lesions. A recent phase II single arm study (LANDSCAPE) has shown that the combination of lapatinib and capecitabine in patients with previously untreated brain metastases from HER2-positive

metastatic breast cancer yields durable responses in up to 65% of patients [198]. Based on the strength of these data, a randomized trial comparing lapatinib and capecitabine versus WBRT has been launched. In addition, trials of other HER2 directed TKIs, including neratinib and afatinib, are currently in progress.

It is not clear whether trastuzumab, with limited blood-brain barrier penetration, may be active as well [20].

Brain Metastases from Melanoma

Fotemustine (response rate of 5–25%) and temozolomide (response rate 6–10%), either as single agent or in combination with WBRT, are the most active chemotherapeutics against brain metastases from melanoma [176, 199].

BRAF V600E inhibitors are emerging as treatment options for patients with BRAF-mutant melanoma metastatic to the CNS. The activity of vemurafenib is meaningful. Both retrospective [200] and phase II trials [201] have reported an intracranial response rate of 16–50%, despite disappointing results on OS. A phase II study of dabrafenib in patients with BRAF-mutated melanoma and brain metastasis reported an overall intracranial objective response rate of 31%, with little difference between patients who progressed after prior CNS therapy and patients who were treatment naïve [202].

The activity of BRAF inhibitors on brain metastases appears to be superior to that of ipilimumab [203–205], a monoclonal antibody with immunomodulatory activity that has been approved for the treatment of metastatic melanoma. An open-label phase 2 multicenter trial in the US [204] showed that ipilimumab has activity in patients with asymptomatic melanoma brain metastases off steroids. Disease control (CR + PR + SD) after 12 weeks of treatment was 16% in the cohort of asymptomatic patients without steroids compared with 5% in the cohort of symptomatic patients receiving steroids. Steroid use may suppress the immune response thereby limiting the effect of immunotherapy, though this remains to be clearly established. Importantly, the investigators did not report any neurological deterioration as an effect of an inflammatory response to treatment in the CNS, even in patients who had received prior radiation therapy. There is some interest in combining ipilimumab with radiation therapy [206], and new molecular agents, such as trametinib, are being investigated.

Prophylaxis

The brain can be a sanctuary for micrometastases that can become radiologically and/or clinically evident after the primary tumor has been controlled by effective therapies. Thus, treating the subclinical disease could prevent the

development of overt brain metastases. This strategy is particularly relevant for SCLC where prophylactic cranial irradiation (PCI) reduces the risk of brain metastases at 2 years and increases overall survival in patients with SCLC who achieve complete remission after upfront therapy [207, 208]. Cognitive decline in SCLC patients after PCI is relatively uncommon up to 2 years after PCI [209, 210]. There is currently insufficient evidence to support PCI in high-risk NSCLC patients [211].

In patients with metastatic HER2-positive breast cancer, PCI or newer drugs with improved penetration of an intact BBB (i.e., TMZ, lapatinib) might be useful. The combination of these agents with radiation could allow a lowering of the PCI dose.

Effective agents are needed to prophylactically treat micrometastatic disease in patients at high risk for brain metastases. Well-designed clinical trials that include detailed neuropsychological assessments are needed to both identify effective agents and establish the role for CNS prophylaxis in different systemic malignancies.

Prevention Strategies: Molecular and Clinical Data

Numerous molecular compounds have been tested in pre-clinical models in a prevention setting and overall the studies have shown that prevention of brain metastases is feasible [212, 213]. Experimental models have shown that bevacizumab may prevent early angiogenesis and induce prolonged dormancy of micrometastases [214]. Lapatinib, vorinostat, and pazopanib are able to prevent the formation of metastases by brain-topic breast cancer cells [215–217]. The selective PLK1 inhibitor GSK 4611364A, inhibits the development of large brain metastases and prolongs the survival in a xenograft model of breast cancer brain metastases [218]. Limited clinical data have shown that prevention of brain metastases can also be achieved in clinical settings. In a metastatic breast cancer trial of lapatinib plus capecitabine versus capecitabine alone there was a significant reduction in the incidence of metastases in the brain as first site of relapse after combined treatment [219]. A retrospective review of a sub-cohort of patients with advanced EGFR-mutated NSCLC treated with gefitinib or erlotinib reported 1-year and 2-year CNS relapse rates of 6 and 13%, respectively, an improvement from historical data [220]. A retrospective analysis of the clinical trial data from sorafenib in patients with renal cell cancer (RCC) and brain metastases demonstrated a 75% prevention of brain metastases development, compared with 4% response rate for established metastases [221]. A recent review of patients enrolled in a phase III trial on RCC (TARGET trial) revealed

a significantly lower incidence of brain metastases in patients who received sorafenib (3%) than in those who received placebo (12%) [222]. The protective effect of TKIs (sorafenib, sunitinib, pazopanib) on the development of brain metastases from RCC has been recently outlined [223].

A major challenge in the field has been the identification of patients at highest risk of developing brain metastases because of tumor and host factors. Up to date, only HER2-positive breast cancer patients have entered prevention trials to better define the role of lapatinib.

Challenges in Developing Trials in Brain Metastases

The design of clinical trials in brain metastases can be challenging [224–226]. The choice of endpoints is influenced by several factors including the patient population, primary tumor type, phase of trial and the setting (treatment of established brain metastases or prevention). The ideal measure of drug activity in the brain is the assay of target modulation within the tumor obtained after resection in patients treated preoperatively. Moreover, advanced neuroimaging techniques may provide valuable surrogate pharmacodynamic information. Objective response has been commonly used as primary endpoint for phase II trials in patients with brain metastases, being a possible surrogate for other markers of clinical benefit, such as neurological status, neurocognitive decline or neurological deterioration free survival. Unfortunately, none of the standard response criteria (RECIST, WHO, MacDonald, RANO) were designed specifically for brain metastases. There is a need to standardize MRI criteria for lesion measurement (tumor area versus volume) and the definition of response to treatment, including use of both steroids and neurological symptoms in the response criteria. Use of unique therapies such as antiangiogenic agents and immunomodulators will require specific adaptations. A clear distinction between intracranial, extracranial and overall progression-free survival is important. When the concurrent systemic disease is controlled by a standard systemic regimen, the safety (not only the efficacy) of concurrent use of an investigational agent for brain metastasis must be carefully evaluated.

As the number of experimental agents increases and available resources become limited, new trial designs should be considered. Adaptive randomization can make clinical trials more efficient in reaching endpoints with fewer patients than with conventional randomization [227].

The RANO Brain Metastasis Group has recently proposed new response criteria for clinical trials in patients with brain metastases [228]; these need validation in the next generation of studies.

Other Cranial Metastases

The topics of skull and dural metastases are covered in Chap. 23 (Neurological Complications of Breast Cancer and Its Treatment).

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