Central Nervous System Metastases

Manmeet Ahluwalia
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Editors

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Foreword

Brain metastases are one of the most challenging complications of cancer. Patients with cancer are living longer, and consequently, brain metastases are seen more often and from primaries not traditionally associated with brain metastases, such as prostate or endometrial cancer. These findings suggest that the central nervous system may be a sanctuary site for solid tumors, much in the way that it is for hematologic malignancies. If so, this suggests that microscopic tumor reaches the brain over the course of the disease, perhaps even by initial diagnosis, and therapies that may control the disease elsewhere can't penetrate an intact blood-brain barrier and eradicate the tumor residing within the brain parenchyma. This can lead to the delayed appearance of brain metastases in some patients, and in others, the brain can be the sole or residual site of disease. The therapy of brain metastases has improved over the years, in part by becoming more focal, but most patients still succumb. Much of the therapeutic challenge of brain metastases comes from the unforgiving nature of the brain itself and its relative vulnerability to the toxicities of standard treatment modalities.

The growing prevalence of brain metastases brings an urgency for better understanding of their biology and treatment. Clarity on the mechanisms of brain metastasis formation may enable the development of preventative and novel therapeutic approaches. Thus, this book is timely because it addresses both the basic mechanisms of brain metastasis formation and the current treatments that have given many patients long-term survival. The authors and editors are to be congratulated for such a comprehensive review of this critically important subject, and it is highly valuable to have the full spectrum of this topic consolidated in a single book. Hopefully, the considerable research effort now being directed towards brain metastases will lead to both improved prevention and therapeutics to reduce the morbidity and mortality associated with this deadly metastatic complication of solid tumors.

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Preface

In 2011, the first European meeting exclusively dedicated to brain metastases entitled "Brain Metastases Research and Emerging Therapies Conference" was organized in Marseille, France, on October 5, under the impulsion of Prof. Philippe Metellus with the support of Aix-Marseille Université. The goal of this meeting was to galvanize neurosurgeons, neurologists, neuro-/medical oncologists, radiation oncologists, pathologists, neuroimaging specialists, and biologists involved in the field to foster new collaborations between physicians, translational researchers, and basic scientists in this wide and growing field of interest in oncology. Interestingly, at the same year, a similar initiative was launched in Cleveland, thanks to Prof. Manmeet Ahluwalia with objectives almost identical to those of the European counterparts. Also, in 2011, the results of the first large phase III randomized clinical trial assessing the role of adjuvant WBRT after both surgery and stereotactic radiosurgery in oligometastatic brain metastatic patients were published by Prof. Riccardo Soffietti and colleagues in the *Journal of Clinical Oncology*. Since that time, we have had multiple opportunities to interact and share our experience and expertise in the field. Finally, in 2016, during a lunch at the sixth edition of the Brain Metastases Research and Emerging Therapies Conference in Marseille, France, we thought of the idea of editing a book that would represent a source reference for brain metastases.

Indeed, brain metastases are the most common intracranial malignancy, accounting for significant morbidity and mortality in cancer patients. An estimated 20–45% of all patients with cancer will develop brain metastases. Metastatic brain disease is ten times more common compared to primary brain tumors. The most frequent cancers that metastasize to the brain include lung, breast, and colorectal cancers, melanoma, or renal cell carcinoma. The number of patients diagnosed with brain metastases has increased recently. This is due to an earlier and better detection of these tumors with the widespread use of modern imaging techniques but also due to the improvement of systemic treatments resulting in an improved overall survival of these patients. Brain metastases are thought to occur via seeding of circulating tumor cells into the brain microvasculature; within this unique microenvironment, tumor growth is promoted, and the penetration of systemic medical therapies is limited. Of all sites of organ colonization, brain metastases are associated with the worst prognosis, with a median survival of less than 1 year on average, associated with an impaired quality of life due to associated physical and cognitive deficits. Despite recent improvements in the treatment of systemic

disease and associated brain metastases with multimodal approaches including the combination of surgery, radiotherapy, chemotherapy, immunotherapy, and targeted therapies, the median survival of patients with metastatic brain lesions is approximately 7–24 months from diagnosis. Therefore, understanding how cells target specific organs, whether differences exist in this targeting, and factors critical to cell survival following dissemination is also important for developing optimal treatments for metastatic and resistant tumors. Hence, a personalized plan for each patient, based on molecular characterization of the tumor used to better target radiotherapy and systemic treatment, is undoubtedly the future of brain metastasis management.

The aim of this book is to provide a comprehensive review of each aspect of brain metastases, from basic science to clinical management and potential future trials. This book comprises 32 chapters divided into 5 parts. Epidemiology, pathology, and molecular biology of brain metastases as well as preclinical model principles will constitute the first part. Clinical and radiological presentation along with symptoms management will be detailed in the second part. The third part will be dedicated to local (surgery and radiotherapy) and systemic (chemotherapy, immunotherapy, and targeted therapy) approaches with an emphasis on the combination of these modalities. In the fourth part, toxicity of treatment will be described with a focus on neurocognitive function and quality-of-life impact. Finally, the last part will cover prognostic classification issues and future trial design.

The chapters of this book represent state-of-the-art knowledge about these secondary tumors regarding their biology, clinical behavior, and management strategies. We believe that this textbook will be valuable for scientists involved in brain metastases research, for neurosurgeons, neuro-oncologists, medical oncologists, radiation oncologists, and all physicians who may called on to manage brain metastases.

We owe considerable thanks to Springer staff who have been involved in all the publications in this series. Especially, we would like to thank Donatella Rizza for her efficient and proactive support during the planning of this volume. Her input has been instrumental in ensuring publication. Above all, we thank our colleagues who wrote the chapters and put up with our frequent prodding and cajoling. They have done an outstanding job. Finally, we would like to thank Lisa DeAngelis and Michael Weller who kindly accepted to write a foreword for this book.

Cleveland, OH — Manmeet Ahluwalia
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Editorial

A new comprehensive look at central nervous system metastasis

Metastasis to the central nervous system has been a major area of clinical research at the interface between neuro-oncology and general oncology for decades. How and when in the course of disease cancer cells gain access to the central nervous system has remained enigmatic in many disease settings but is highly relevant to develop better diagnostic and prevention strategies. Because of its impact on the quality of survival, which is increasingly recognized as an important parameter of success for treatment in oncology, control of CNS metastasis will become an even more important topic in the upcoming years. This is because several approaches of systemic treatment, be it immunotherapy or targeted therapy, allow for prolonged survival in cancers hitherto associated with a poor prognosis, such as non-small cell lung cancer or melanoma. In how far these novel treatments allow the control of CNS disease is currently an area of controversy and may require further in-depth studies. Furthermore, several treatments in oncology have neurotoxicity as their major side effect, not only, traditionally, radiotherapy to the nervous system but also classical cancer chemotherapy drugs as well as novel approaches such as immune checkpoint inhibition or CAR T cell therapy.

In this framework, the editors provide a comprehensive look at the topic of central nervous system metastasis focusing on epidemiology, pathology, and molecular biology (Part I); clinical radiological presentation and management (Part II); surgery, radiation therapy, and systemic treatments (Part III); toxicity from treatments (Part IV); and, finally, prognostic classifications and future trial design (Part V). The editors are commended for having convinced a group of internationally renowned experts in the respective fields of central nervous system metastasis to provide such an up-to-date critical review of the evidence and outlook into what may be expected from the years to come.

Zurich, Switzerland — Michael Weller
Lille, France — Emilie Le Rhun

Contents

Part I

Epidemiology, Pathology and Molecular Biology

1 Epidemiology of Central Nervous System Metastases

Linda Dirven and Martin J. B. Taphoorn

1.1 Introduction

Cancer is the second leading cause of death globally, with 8.8 million deaths in 2015 [1]. Systemic cancer commonly spreads to the central nervous system (CNS) continuing to be a major cause of morbidity and mortality [2]. Although the majority of CNS metastases are parenchymal, metastases can also occur in the leptomeninges, dura, or in the adjacent cranium [3].

CNS metastases are the most common brain tumors [4], and its incidence is rising which is likely attributable to prolonged survival of patients, thereby increasing the time for tumor cells to metastasize to the CNS. The increased incidence rate of CNS metastases is a direct result of improved neuroimaging techniques to detect (asymptomatic) lesions, as well as the availability of better treatment modalities for systemic cancer [5, 6]. Moreover, the CNS is perceived as a sanctuary for metastatic tumor cells, where tumor cells are protected by the blood–brain barrier, immune system, and the tumor microenvironment from full exposure to many chemotherapeutic agents [7], as well as targeted treatment and immunotherapy. Treatment of CNS tumors therefore remains a challenge.

The exact incidence or prevalence of brain metastases is unavailable, and estimates vary considerably. This is mainly due to different data sources that have been used to estimate the occurrence of CNS metastases, ranging from large national registries to hospital-based studies and autopsy studies. Also, selection bias may have occurred in observational studies as not all patients with cancer are screened for brain metastases, particularly those who are asymptomatic, resulting in an underestimation of the true incidence. Incidence rates also vary between primary cancer types. Cancers most likely to metastasize to the brain are lung, breast, melanoma, renal, and colorectal cancers [8–10]. However, it is anticipated that in the coming years, brain metastases will be more frequently diagnosed in patients with tumors that are less likely to metastasize to the brain, due to prolonged survival of patients and better imaging techniques. Other factors that contribute to a higher incidence of brain metastases are patient- and tumor-related characteristics such as race, sex, age, and disease stage [8].

Early identification and treatment of patients with CNS metastases is important as prognosis remains poor. Median overall survival rates range from approximately 4 to 14 months [9, 11], mainly depending on primary tumor (sub) type and performance status [11], presence of extracranial disease to multiple sites [12], as well

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as first-line treatment modality [9]. Overall survival rates of patients vary significantly between primary tumor types, and subtypes, but the reported mean 5-year overall survival rate for patients with brain metastases is only 2.4% [13]. Considering the poor survival of CNS metastases patients, treatment should not only be aimed at prolonging survival, but also on limiting neurotoxicity. Maintenance of health-related quality of life and neurological and neurocognitive functioning should therefore be one of the main goals of treatment in this patient population.

Understanding the epidemiology of CNS metastases may lead to further consideration of early screening of the brain in patients with systemic cancer with a high risk of brain relapse. Also, new insights in the incidence of CNS metastases, as well as on the impact of new systemic treatment on brain metastases, may help clinicians in counselling individual patients in daily clinical practice and may help researchers to refine clinical trial design. This chapter focuses on the epidemiology of CNS metastases, in particularly of the parenchyma, of patients with lung, breast, melanoma, renal, and colorectal cancer.

1.2 Detection of CNS Metastases with Imaging

Magnetic resonance imaging (MRI) is the most sensitive technique in the assessment of CNS metastases. In a study with non-small cell lung cancer (NSCLC) patients, the accuracy for detecting brain metastases was higher with whole-body MRI compared to positron-emission-tomography/computed tomography (PET/CT); 50% versus 10%, respectively. In the remaining patients, brain metastases were only detected with dedicated brain MRI, suggesting that brain MRI is superior to whole-body MRI [14]. Another study also found that brain MRI was superior to CT [15]. In this study, patients with histologically proven lung cancer underwent scanning with MRI and two CT techniques. In only 27% of patients, the CT techniques resulted in the same conclusion as MR imaging. In half of the patients in which MRI and CT results differed, the MRI detected brain lesions in which CT did not, while in the other half of the patients the CT underestimated the number of lesions. Thus, MRI seems the golden standard for the detection of CNS metastases, but other techniques may in some cases result in similar findings. This is particularly valuable for patients who do not undergo standard follow-up with MRI. In that case, PET/CT including the brain in the scanning field could be considered, because additional information can be obtained with this method, with a minimum increase in radiation burden. A large study with cancer patients showed that 1% patients had brain metastases on PET/CT, with the majority (92%) of these patients being asymptomatic [16].

Even if brain MRI is used, not all sequences seem equally sensitive in detecting brain metastases. In a study where six MRI sequences were available for patients with metastases from melanoma, it was shown that contrast-enhanced T1-weighted imaging was most sensitive. Approximately 7% of all lesions were only detected by contrast-enhanced T1-weighted imaging, and not with the other sequences [17]. These results suggest that disruption of the blood–brain barrier may be the earliest sign of CNS metastases in melanoma.

1.3 Incidence of CNS Metastases

Most recent studies on the prevalence or incidence rates of CNS metastases from systemic cancer are population-based studies, including large registries and hospital-based studies. Although several autopsy studies have been published, no recent data is available. These autopsy studies are published approximately 40 years ago, and reported brain metastases in about a quarter of all patients, which was high compared to population-based studies in the same time period [18, 19]. However, with new imaging techniques and the availability of better treatment modalities for systemic cancer, incidence rates of brain metastases from systemic cancer in currently conducted studies are more similar to those in previously conducted autopsy studies. However, differences exist between primary can-

cer types. Patients with lung, breast, melanoma, colorectal, and renal cancer have the highest risk of developing brain metastases. Also, the identification of molecular subtypes has resulted in a better differentiation in the occurrence of brain metastases. Other patient- and tumor-related factors are also associated with the incidence of brain metastases, particularly age, race, and disease stage (see Table 1.1 for an overview).

1.3.1 Lung Cancer

Incidence rates between 9 and 46% have been reported for the lung cancer population [8, 20–27]. However, the incidence varies per study design and particularly for different subpopulations. The latter may help in selecting patients who are eligible for more frequent screening of the brain.

One small study suggested that the incidence of brain metastases in NSCLC was higher than in SCLC patients [24]. However, reported incidence rates for patients with NSCLC vary widely, between 9 and 39.1% [21–23, 26, 28], with the squamous subtype having the lowest incidence [21, 24]. More consistent incidence rates have been reported for SCLC patients, ranging between 18 and 24% [21, 25, 27, 29]. Incidence over time for both NSCLC and SCLC is variable, but was found to be higher in SCLC. Over a 13-year period, 11% (1973–1985), 10% (1986–1998), and 7% (1999–2011) of non-metastatic NSCLC patients had brain metastases, versus 14%, 32%, and 15% of SCLC patients in the same periods, respectively [21].

Besides histology, the molecular profile of the tumor has also an impact on the incidence of brain metastases. The brain is the main site of relapse in NSCLC patients with EGFR-mutated tumors [26]. Indeed, the presence of an EGFR mutation in NSCLC resulted in a higher incidence of brain metastases (HR 2.24, 1.37–36.4) [22]. Incidence rates of brain metastases for patients with EGFR-mutated tumors between 35.3 and 46.2% [23, 26] have been reported, compared to incidence rates between 29.7 and 32.8% [23, 26] for patients with EGFR wild-type tumors, although EGFR subtypes resulted in similar incidence rates [22]. In contrast, the frequency of brain metastases *at diagnosis* ranged from 21.7 to 25% and was similar for patients with EGFR-mutated (24–26%) and EGFR wild-type (21.1–24.6%) tumors, respectively [23, 26]. The median time from diagnosis to the occurrence of brain metastases was not significantly different between EGFR-mutated and EGFR wild-type patients, 18 versus 14.9 months respectively [28]. Nevertheless, patients with EGFR mutation did have more often multiple brain metastases and less often cerebral edema [28]. Also other genetic variations result in different incidence rates, including ROS1-, ALK-, and RET-rearranged tumors [20]. For example, in RET-rearranged patients, an incidence rate of 46% has been reported, with 25% of patients already presenting with brain metastases at diagnosis of stage IV lung cancer [20].

An important determinant of the occurrence of brain metastases is disease stage, increasing with more advanced disease stage [30]. Indeed, the 2-year cumulative incidence rate for brain metastases was higher in patients with stage III SCLC compared to patients with stage I/II SCLC (21% versus 10%, respectively) [29]. Similarly, 3-year cumulative incidence rates of 9.7%, 18.5%, and 35.4% have been reported in stages I, II, and III, respectively [27]. The cumulative incidence of brain metastases in stage IV NSCLC was found to be 30.7% [23]. This is also shown by the finding that the incidence of brain metastases only, without concurrent metastatic disease in other sites, is low (0.8%) [30].

Besides more advanced disease [8, 21, 22, 27, 29, 30], factors that were found to be predictive for the occurrence of brain metastases included African American race [8], female sex [8, 21], and age <60 years [8, 21, 22]. For patients with SCLC, lymphovascular invasion also increases the risk of developing brain metastases [27].

1.3.2 Breast Cancer

Large registry studies have reported incidence rates of brain metastases from breast cancer ranging between 0.4% and 9.2% [8, 31–33], which has

Table 1.1 Predictive factors for the occurrence of brain metastases in lung, breast, melanoma, renal and colorectal cancer

	Predictive factors							
Cancer type	Sex	Age	Race	Tumor histology	Molecular/genetic markers	Disease stage	Tumor characteristics	Treatment
Lung cancer	Female [8, 21]	<60 years [8, 21, 22]	African-American [8]	Non-squamous tumors [21, 24]	RET-rearranged subtype [20] and EGFR-mutated tumors [22, 23, 26]	More advanced disease stage [8, 21, 22, 29, 30]	–	–
Breast cancer	–	<40 years [8, 35]	American [8]	–	HR-negative [34], HER2-positive and triple negative breast cancer subtypes [12, 31, 32, 37]	Metastatic disease to >1 site [8, 12, 32, 37]	–	–
Melanoma	Male [7]	<60 years [8]	African-American [8]	–	–	Presence of distant disease [8]	–	–
Renal cancer	–	>50 years [8, 49]	White or 'other' race [8, 49]	Sarcomatoid and clear cell subtypes [49]	–	More advanced disease stage [8, 49]	Larger tumor size [49]	previous treatment with TKI [43]
Colorectal cancer	–	<60 years [8]	White or African-American [8]		–	Presence of lung [50, 54] or liver metastases [54]	–	–

increased over time, from 6.6% in 2002 to 10.9% in 2004 [33]. An important factor that impacts the incidence of brain metastases in breast cancer is the molecular subtype [12, 31, 32, 34–36]. One study reported that particularly hormone receptor (HR)-positive tumors impact the occurrence of brain metastases [34]. In contrast, another study found that particularly human epidermal growth factor receptor 2 (HER2) was an important determinant: HER2-positive/HR-negative tumors had a higher cumulative incidence rate than patients with HER2-positive/HR-positive tumors, 14.3% versus 7.9%, respectively [35]. This was supported by two large studies showing that HER2-positive tumors have the highest incidence of brain metastases (1.0–5.9%), followed by triple negative breast cancer (0.7–4.9%), and HER2-negative tumors (0.2–1.5%) [31, 32]. Nevertheless, patients with triple negative breast cancer have a high incidence of early brain metastases [37]. Indeed, the median duration between breast cancer diagnosis and the occurrence of brain metastases was shortest for triple negative breast cancer (10–23.5 months) [37, 38], followed by HER2-positive (19 months) and HER2-negative subtypes (42 months) [38]. Moreover, the brain is the first metastatic site in a large proportion of patients (42.9%) with triple negative breast cancer compared to 20–23.6% of the patients with other subtypes [34].

Most breast cancer patients have metachronous (i.e., occurring in consecutive order) brain metastases. Only a small proportion (0.41%) of breast cancer patients had brain metastases at the time of diagnosis of the primary tumor. HER2/HR-negative patients had the highest frequency of brain metastases at diagnosis (1.09%), followed by triple negative breast cancer (0.68%), HER2/HR-positive (0.61%) and HER2-negative/HR-positive (0.22%) patients [12]. The incidence of brain metastases increases when patients already have metastatic disease is other sites, particularly for patients with HER2-positive and triple negative subtypes [32, 37].

Besides HER2-positive and triple negative breast cancer subtypes [12, 31, 32, 35] and metastatic disease in other sites [8, 12, 32], African American race [8] and age < 40 years [8, 35] were also found to be associated with the development of brain metastases in breast cancer.

1.3.3 Melanoma

Although lung cancer is the most frequent primary tumor resulting in high incidence rates of brain metastases, melanoma has the highest propensity of all cancers to spread to the brain [39]. This is supported by the finding that of all patients with distant-stage disease, those with melanoma show the highest incidence proportion for brain metastases [8]. The incidence of brain metastases from melanoma differs between studies, with incidence rates ranging from 6.9% as measured in the SEER registry [8], to 15% as measured in a clinical trial [40], and incidence rates between 10.1 and 18.5% in hospital-based studies [17, 41]. The frequency of brain metastases at diagnosis of the primary tumor is low (0.65%), while the incidence is quite high (28.2%) in case patients already have metastatic disease in other sites [10]. Next to the presence of metastases in other sites, African-American race, male sex, and age <60 years were associated with a higher incidence of brain metastases [8].

1.3.4 Renal Cancer

Reported incidence proportions for brain metastases of renal cancer are similar to those of melanoma, with an incidence proportion of 6.5% in a SEER registry [8], an incidence rate of 7% in a clinical trial [42], and incidence rates ranging between 5.3 and 22.8% for hospital-based studies [43–48]. The incidence rate of brain metastases at diagnosis of the primary tumor was low in two large registry studies, ranging from 1.37% in the National Cancer Database [49] to 1.51% in the SEER registry [8], and high (26.8%) in a small hospital-based study [46]. The incidence rates of brain metastases at diagnosis in renal cancer appear relatively stable over time, varying from 1.31, 1.65, 1.49, and 1.61% in the years 2010–2013 [49].

Currently, no molecular subtypes in renal cancer have been identified that are associated with the occurrence of brain metastases. In contrast, histological subtype [8], specifically sarcomatoid and clear cell subtypes [49], age >50 years [8,

49], white or other race [8, 49], larger tumor size [49], and more advanced disease stage [8, 49] were associated with an increased risk of brain metastases.

In contrast to the other cancers, the incidence of brain metastases in renal cancer patients is affected by previous anti-tumor treatment. The incidence of brain metastases was 1.6 times higher for patients previously treated with tyrosine kinase inhibitors (TKI), compared to those not receiving TKI [43]. On the other hand, the incidence did not differ between patients treated with or without anti-angiogenic agents (18.2% versus 15.7%, respectively) [48]. Despite the type of previous treatment, the median time to the occurrence of brain metastases was longer in treated patients: 28.9 and 28 months for those treated with anti-angiogenic agents or TKI, respectively, compared to 11.8 and 11.5 months for those not treated [43, 48].

1.3.5 Colorectal Cancer

Colorectal cancer has a low incidence of brain metastases compared to melanoma, lung, and breast cancer. Incidence rates vary between 0.5 and 8.8% for hospital-based studies [50–53], and between 0.2 and 1.8% in two large registry studies [8, 54]. The higher incidence in one of the hospital-based studies (8.8%) [50] is likely due to the fact that only metastatic patients were included, since the variation in the other studies was small (0.5–2.3%). The difference between the two SEER registry studies is striking, but may be explained by the period in which the studies were conducted. The study by Barnholtz-Sloan et al. covered the period 1973–2001 and found an incidence proportion of 1.8% [8], while Qiu et al. found an incidence proportion of 0.2% in a more limited period, between 2010 and 2011 [54]. Although the duration of the period is different, the number of patients included in the studies is similar (42.817 [8] versus 35.882 [54]), as well as other population characteristics.

Brain metastases are a late-stage phenomenon in colorectal cancer patients, with median times from primary diagnosis to the occurrence of brain metastases ranging between 21 and 39 months [51, 52], and 12.5 months in a population with metastatic colorectal cancer only [50]. Factors that are associated with the incidence of brain metastases in colorectal cancer are age <60 years, White or African American race [8], and the presence of metastatic disease in other sites, particularly the lung [50, 54] or liver [54].

1.4 Number of Brain Metastases

Many studies have shown that the number of brain metastases is independently prognostic for overall survival, in which an increasing number of metastases are associated with worse survival [37, 41, 51, 52, 55–60]. Also, the number of metastases varies widely in cancer patients. However, in the Recursive Partitioning Analysis (RPA) classification of prognostic factors, developed in the late 90s [61–63], the number of brain metastasis was not included. Studies combining different primary tumor types have shown that most patients have solitary brain metastases, ranging from 50.8% up to 81%, but that a large part also has multiple metastases [16, 60, 64–66]. It should be noted, though, that in 11% of cases brain lesions are not solitary brain metastasis, but primary brain tumors, abscesses or inflammatory reactions [67]. In patients with an unknown primary cancer, the majority (66%) of patients had multiple brain metastases [56]. The recognition that the number of brain metastases is important for prognosis led to the development of a new prognostic score, the Graded Prognostic Assessment (GPA), in which the number of metastases was included [68]. However, because it was questioned whether one index was sufficient for all different tumor types [69], the Diagnosis-Specific GPA (DS-GPA) was subsequently developed, also taken into account the primary tumor type [70]. Although these more recent prognostic scores include the number of brain metastases, it has also been suggested to include the velocity with which the brain metastases develop into the prognostic score, the Brain Metastasis Velocity (BMV). The BMV is a novel prognostic metric for survival after brain relapse.

Patients are categorized based on the number of new brain metastases per year: low (<4 metastases), intermediate (4–13 metastases) or high (>13 metastases). It was shown that BMV was the main predictor for overall survival in multivariable analysis, with increasing risk of death for the groups with higher BMV [58].

The distribution of the amount of brain metastases was found to vary between different primary tumor types, but also between subgroups of patients. Solitary brain metastases in lung cancer patients (combining all subtypes) were reported in 26.8% of the patients, while 32% had 2–4 metastases, 21.1% had 5–10 metastases and 20% had >10 brain metastases [55]. With respect to different molecular subtypes, patients with an EGFR mutation in NSCLC who developed brain metastases more than 6 months after initial diagnosis of lung cancer had more often multiple brain metastases compared to those with EGFR wild type (92% versus 63%, respectively) [28].

The percentage of patients with solitary brain metastases from breast cancer ranged from 24.9 to 57.4% [34, 55, 57, 59]. Although several studies found that the number of brain metastases was similar for all breast cancer subtypes [34, 38], one small study found that HR-negative patients had significantly more brain metastases compared to HR-positive patients (15 versus 7, respectively), and that HER2-negative patients had significantly more brain metastases compared to HER2-positive patients (15 versus 8, respectively) [71]. Although most studies reported on solitary versus multiple metastases only, Ali et al. further specified that 28.5% of breast cancer patients had 2–4 metastases, 22% had 5–10 metastases, and 21.3% had >10 brain metastases [55]. Similarly, another study found that 21.9% of breast cancer patients had 2–4 brain metastases, but that the majority (53.2%) of patients had >4 brain metastases [34].

Compared to breast cancer, similar frequencies of solitary metastasis have been reported for melanoma, ranging between 22.1 and 55% [17, 41, 55, 72]. Two studies showed that 13.2–18.3% of melanoma patients had two metastases and 34.8–41.8% more than three [41, 72]. Although the patient populations were similar, one study found that only a minority of patients had a large number of brain metastases (i.e., 8.5% had 5–10 metastases and 2.5% had >10 metastases) [55], while another study showed that a large proportion (40.5%) of patients had >5 brain metastases [17]. The distribution of the amount of metastases was relatively even distributed for patients with and without BRAF mutation; 38% versus 39% had solitary metastasis, 37% versus 45% had 2–5 metastases, and 26% versus 16% had >5 metastases, respectively [72].

The distribution of the number of brain metastases was different for those with renal and gastrointestinal cancers, where most patients have solitary brain metastases. Indeed, reported frequencies of solitary brain metastasis in renal cancer ranged between 40.8 and 68.1% [44, 46, 55]. A smaller proportion of patients had 2–4 brain metastases (34.9%), and only a minority of patients had 5–10 (16.5%) or > 10 brain metastases (7.8%) [55]. The frequency of solitary brain metastases in patients with gastrointestinal cancer was 38% [55], and ranged between 45% and 52.6% for patients with colorectal cancer specifically [51, 52]. Moreover, Ali et al. reported that 37.9% of the patients with gastrointestinal cancer had 2–4 brain metastases, 17.2% had 5–10 metastases and 6.9% had >10 metastases [55]. The two studies in patients with colorectal cancer showed that 13.3–21.1% of the patients had two metastases and between 26.3% and 41.7% of patients had >3 brain metastases [51, 52].

1.5 Spatial Distribution of Brain Metastases

Understanding the spatial distributions of brain metastases from a specific primary cancer may help informing individual patients on their prognosis [71] and in selecting the appropriate treatment strategy. It is believed that biological characteristics of tumors affect the spatial distributions of their brain metastases [38]. Sampson et al. found that brain metastases from melanoma were distributed throughout the brain in proportion to the mass of the location; 36.1% of the metastases were located in the frontal lobes, 26.4% in the parietal lobes, 18.9% in the

temporal lobes, 10.6% in occipital lobes, 7% in the cerebellum and 0.9% in the brainstem [41]. However, this may not hold true for the different primary tumor types. For example, brain metastases from colorectal cancer show a different pattern: 43.6% had metastases in the cerebellum, 25.6% in the frontal lobes, 10.3% in the temporal lobes, 15.4% in the parietal lobe, and 5.1% in the occipital lobe [53]. Moreover, for patients with brain metastases from breast cancer, it was found that the molecular subtype was associated with the location of the metastases. In a small sample of breast cancer patients, the main spot for metastases was found to be evenly distributed in the brain for triple negative breast cancer subtype, while HER2-positive and HER2-negative subtypes tended to occur mainly in the occipital lobe and cerebellum [38]. Moreover, patients with HER2-positive tumors developed cerebellar metastases significantly more often compared to patients with HER2-negative tumors, both when looking at the HER2-status of the primary breast tumor (59.8% versus 44.5%, respectively) and the HER2-status of the brain metastases (51.5% versus 28.2%, respectively) [71]. Patients with estrogen receptor (ER)- and/or progesterone receptor (PR)-positive tumors had a lower incidence of hippocampal metastases than patients with ER- and/or PR-negative tumors: 1.6%, 2.8%, 9%, and 8.3% for PR-positive, ER-positive, ER-negative and PR-negative tumors, respectively. Patients with triple negative breast cancer had significantly more often (31.4%) leptomeningeal disease as compared to non-triple negative breast cancer patients (18.3%) [71].

1.6 Synchronous Versus Metachronous Brain Metastases

In most cancer patients, brain metastases are a late-stage phenomenon [40, 50, 73, 74]. Indeed, a large population-based study showed that only a small proportion (1.7%) of cancer patients presented with synchronous brain metastases, i.e., at the time of primary cancer diagnosis, although this varied by primary tumor type, age, sex, and race [75]. Lung cancer had the highest proportion of synchronous brain metastases at diagnosis, with 15.1% for SCLC and 10.7% for NSCLC patients. Other cancers in which brain metastases occur synchronously are esophageal cancer (1.5%), renal cancer (1.4%), melanoma (1.2%) and colon cancer (0.3%). For breast cancer, the proportion depended on subtype, with 0.7% for triple negative breast cancer, 0.8% for HER2-positive and 0.2% for both HER2-negative and HR-positive tumors [75].

Limited patients develop extracranial metastases after the occurrence of brain metastases [74], while having metastatic disease in other sites facilitates spread to the CNS [12, 50]. This could be due to the spreading of metastatic disease that is mediated by mechanical vascular spreading [76], or that the delivery of cancer cells to different organs varies in efficiency [77]. The first hypothesis is supported by one study in which significantly higher rates of brain metastases in patients with rectal cancer were observed in patients who already had lung metastases when compared to those with existing liver metastases and local recurrence (22.6% versus 2.9% versus 3.6%, respectively). In addition, there was a difference in the mean time that brain metastases occurred after lung, liver or local relapse (732, 345, and 398 days, respectively) [73]. Also, the incidence of brain metastases increases with more advanced disease stage [22, 29]. The second hypothesis is currently under investigation, in which genes that mediate metastases to the brain are explored [78, 79].

As mentioned, for most cancers, brain metastases occur metachronously. Of non-squamous NSCLC patients who developed brain metastases during their disease course, nearly half of the patients already had multiple metastatic sites, compared to 73% of patients who presented with initial brain metastases [26]. Furthermore, between 57–87% of patients with renal cancer developed brain metastases metachronously [42, 46]. The most common site of concurrent metastases in renal cancer was the lung, followed by bone and liver metastases [44, 48, 49]. Nearly all patients (86.4–100%) with colorectal cancer have extracranial metastases at the moment brain

metastases are diagnosed [51–53, 74], of which the lungs, and to a lesser extent the liver, were the most common extracranial site (74–79%) [50, 52–54]. For most colorectal patients (67–69.3%) brain metastases evolved metachronously [50, 74]. Particularly in patients with a solitary brain metastasis, this metastasis developed metachronously instead of synchronously [74]. Having extracranial disease at multiple sites was associated with a higher risk of having brain metastases at diagnosis of breast cancer [12]. Indeed, patients with breast cancer had multiple metastatic sites at the moment of brain metastases diagnosis [33, 34, 80]. Of the patients with triple negative breast cancer, 43.8% had synchronous brain metastases and other metastatic disease at diagnosis, in which lymph, lung, bone, and liver were the commonly involved sites [37]. The site of metastatic disease depends on the molecular subtype, with synchronous metastatic disease occurring more often in HER2-positive and triple negative breast cancer subtypes. For example, the incidence of synchronous disease in the bone, lung, and liver was 28% and 30.8% for HER2-positive and triple negative breast cancer subtypes versus 13.2–19.6% for HER2-negative subtypes, respectively [32]. In patients with high-risk melanoma, brain metastases occurred synchronously with extracranial metastases in 44.1% of patients, and metachronoulsy after systemic metastatic disease in 42.4% [40]. The presence of extracranial metastases was not associated with BRAF-status [72]. Although unknown if the brain metastases occurred synchronously or metachronously, the proportion of melanoma patients with simultaneous brain and extracranial metastases was high, ranging between 45.9 and 83.5% [41, 72], and the lung was the site most commonly involved [41].

1.7 Conclusion

Brain metastases are the most common brain tumors, and their incidence is increasing due to improved neuroimaging techniques to detect (asymptomatic) lesions and improved treatment for systemic cancer which results in prolonged survival. Although the exact incidence of brain metastases remains unknown, incidence rates vary largely between primary tumor type and even for different subtypes. Moreover, the different tumor (sub)types vary in the number of brain metastases, their spatial distribution, and the order in which they occur (i.e., synchronously or metachronously). Understanding these patterns may guide clinicians in counselling individual patients in daily clinical practice, as prognosis of the underlying disease is a critical factor in treatment decision-making.

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Pathology of Brain Metastasis

2

Dana A. Mustafa, Rute Pedrosa, and Johan M. Kros

2.1 Introduction

With an annual incidence of around 10 cases pro 100,000 population, cerebral metastases definitely belong to the group of frequently occurring brain tumors [1, 2]. At least 25% of cancer patients will develop metastatic disease in the brain [3], while seeding in the spinal cord is relatively rare. There are substantial differences in organotropism between tumors of different organ systems. Cancers of lung, breast, GI tract, kidney, and melanomas prominently give rise to brain metastases [2, 4]. Prostate carcinomas however avoid the brain, underscoring particular predilections of circulating tumor cells of various lineages. There is great variation in the clinical situations encountered at the time cerebral metastasis is diagnosed. The cerebral metastasis may occur in the course of a known primary tumor, but may also be the first revelation of the presence of tumor. Cases in which the site or origin of the primary tumor is not known are not uncommon. The abbreviation ACUP or CUP (adenocarcinoma/carcinoma with unknown primary) is used for disseminated tumor without an apparent primary site, and is estimated to occur in up to 15% of disseminated cancers [5]. The brain metastasis may arise as single lesion, or multiple intracerebral tumors may be present. Intracerebral tumors and meningeal localization may occur simultaneously, or appear separated in time. The median survival following the diagnosis of brain metastasis varies with the different conditions and characteristics of the primary tumors and lies somewhere between a few months and 2 years. Taken into consideration all possible clinical situations, variations in susceptibility of tumors to radiation and chemotherapy, and variations in the possibility to radically remove single lesions, general guidelines for treatment are hard to provide. Obviously, the dissemination of tumor cells to the brain invariably means a serious, and often deadly, complication of cancer.

2.2 Tissue Diagnosis

As for all metastases, brain metastases will resemble their primary tumors to various extent. Classic histopathological features like the formation of tubular structures and the production of mucus by the tumor cells define adenocarcinoma but are unspecific as to the origin of the primary tumor. The same is true for the formation of keratin plugs that fits in with the diagnosis of squamous cell carcinoma. Metastases of melanoma may give away their identity by the presence of melanin pigmentation, but does not reveal where the primary tumor may be located. The same is true for signs of neuroendocrine differentiation

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in the metastasis. Immunohistochemistry to tissue sections addressing many proteins from a still growing list for classifying tumors has become a powerful tool in routine pathology practice that has prevailed for over 35 years by now. However, the profiles of different tumor entities may overlap. For instance, the particular combination of cytokeratin 7 and 20 will point to the origin of a metastatic tumor in either the upper or lower GI tract, or the respiratory system. Neuroendocrine differentiation demonstrated by the expression of chromogranin, synaptophysin, CD56, or CD57 is present in various cancers and is therefore unspecific as to tumor origin. The expression of particular transcription factors that are known for the development of particular organs from which tumors may arise, usually overlap and are therefore not specific either. However, the relative frequency of the occurrence of tumors may facilitate making the diagnosis. For instance, the expression of the transcription factor TTF-1 is a strong hint to the lung as organ of origin, while this factor is also expressed in tumors originating from the thyroid. There are only few truly specific markers as PSA and PSAP for prostatic carcinomas, or thyroglobulin for tumors derived from the thyroid. For making the diagnosis of germ cell tumors and lymphomas, immunohistochemistry is inevitable, but will not be decisive if the tumor represents primary or metastatic tumor. In recent years molecular characterization, in particular the use of molecular techniques for clonal analysis, became an important tool to match the primary tumor with the metastasis, particularly in cases of simultaneous presence of more than one primary tumor.

2.3 Gateways to the Brain

Currently, there is great interest in the behavior of tumor cells that have entered the blood stream and their potential to home to distant sites. The process of crossing the blood–brain barrier (BBB) and subsequent proliferation in brain tissue are crucial steps for the rise of cerebral metastases.

Apart from the BBB, there are more entry sites to the brain that are often overlooked (Fig. 2.1). There is an interface of the cerebrospinal fluid (CSF) with choroid plexus (blood–CSF barrier); an interface of CSF with ependymal cells (neuroependymal CSF-brain barrier) and an interface of the outer rim of the cerebral cortex, the pial astrocytes, with CSF (pia-arachnoid -CSF barrier) [6]. Basically, all these barriers have to be considered when scrutinizing the entrance sites of tumor cells into the CNS, but usually only the BBB is taken into consideration and implicated in investigations. Besides intracerebral localization, tumor cells may be present in the subarachnoidal space where they freely float in the CSF. One may wonder if the tumor cells used the choroid plexus as entrée or, alternatively, made their way by somehow passing through the dura and arachnoid, which would constitute yet another routing. It is estimated that between 4% and 15% of cancer patients develop CSF metastases. This condition ("carcinomatous meningitis") comes with distinct clinical symptomatology [7]. There is preference of particular cancers to disseminate into CSF: cancers of the breast, the lung, and the gastrointestinal tract, and melanomas are the most common tumors presenting with CSF metastasis. The tumor cells are detected upon sedimentation, or following spinning (centrifugation) of the sample (Fig. 2.2). More than is the case in brain biopsies, the morphology of tumor cells present in CSF may be unspecific so that immunocytochemistry is needed in order to proceed in the diagnostic process. There are major issues of sensitivity and specificity in CSF diagnostics and there are ongoing efforts using mass spectroscopy to trace tumor localization in the absence of tumor cells [8–10].

2.4 Mechanisms to Pass the Blood–Brain Barrier and Intracerebral Outgrowth

In order to reach the brain, tumor cells first need to dissociate from the primary tumor and enter the blood stream, then cross the blood vessel walls of the brain. Dissemination from a metastatic site may also occur. After crossing the BBB, tumor cells must survive and proliferate in the brain

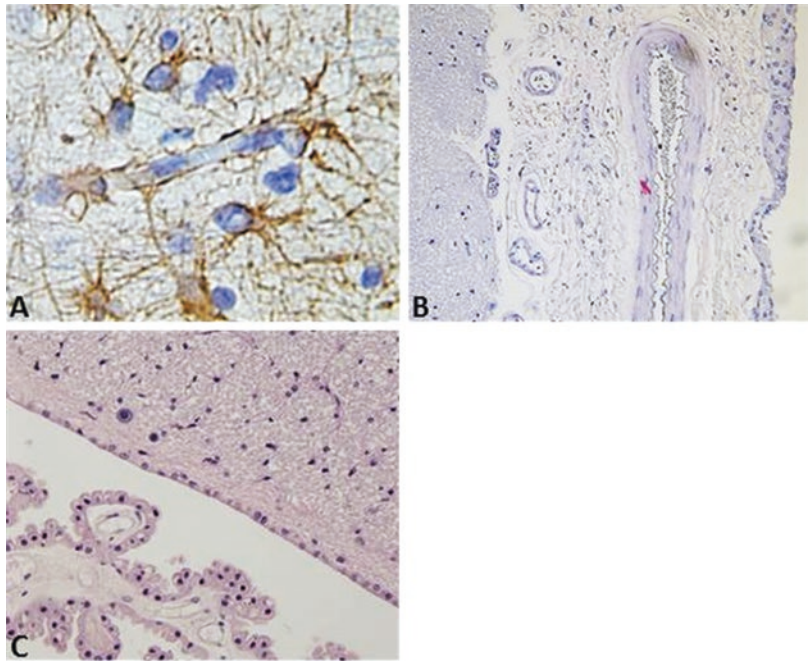

Fig. 2.1 (**a**) Blood–brain barrier: The endothelial cells of the blood vessel (central, horizontal structure) are covered by the end-feet of astrocytes (brown) (magnification ×400; GFAP staining). (**b**) Pia-arachnoid-CSF barrier: the arachnoidal space is bordered by the brain surface (pia, left side) and the outer arachnoidal layer (right side). There are blood vessels running through the arachnoidal space (magnification ×100; H&E staining). (**c**) Neuroependymal CSF-brain barrier and blood–CSF barrier: the cerebral ventricle lined by an ependymal cell layer (brain tissue is covered by these cells; upper part) and choroid plexus present in the ventricle (lower part) (magnification ×200; H&E staining). Yet, another entrée routing to brain are the blood vessels of dura and outer part of the arachnoid, that connect the peripheral circulation with the CSF

tissue to develop brain metastasis. Studies have shown that very few breast cancer cells that enter the brain survive (less than one pro 1000 cells) [11]. Particular tumor cell subsets have the invasive capacity to give rise to metastasis [10, 12]. For instance, breast cancer cells need to have a $CD44^{+}/CD24^{-}$ phenotype to successfully sustain in the cerebral microenvironment. It is speculated that there are specific niches where circulating tumor cells (CTCs) reside in a dormant state for an unknown period of time, before moving on to finally home in particular organs or tissues [13]. The CTCs need time to arrest in blood vessels before migrating into distant organs, a process known as metastatic latency [14]. The adhesion of the CTCs to the vascular endothelium is an essential step in the process of metastasis and specificities of the vascular cells on the one hand, and the expression of particular surface receptors by the CTCs, on the other hand, are crucial for successful homing and subsequent transgression [15]. In the process of adhesion, inflammatory cytokines play a role, but many more molecules are involved [16, 17].

The BBB consists of the endothelium of the intracerebral vessels, the end-feet of astrocytes, the basal membranes between these cells and the surrounding cells, i.e., pericytes and possibly other mural cells [18]. The BBB endothelial cells are interconnected with more tight junctions than endothelial cells elsewhere usually have. Tight junctions consist of proteins like occludin and claudin and junctional adhesion molecule like JAM-A, JAM-B, and JAM-C [19]. The constituents of the basal membrane between the endothelial cells and the surrounding cells are only partly known [20]. There is little data on local variation in the composition of the basal laminas, and also individual variations, for instance, due to aging, and have not been yet explored

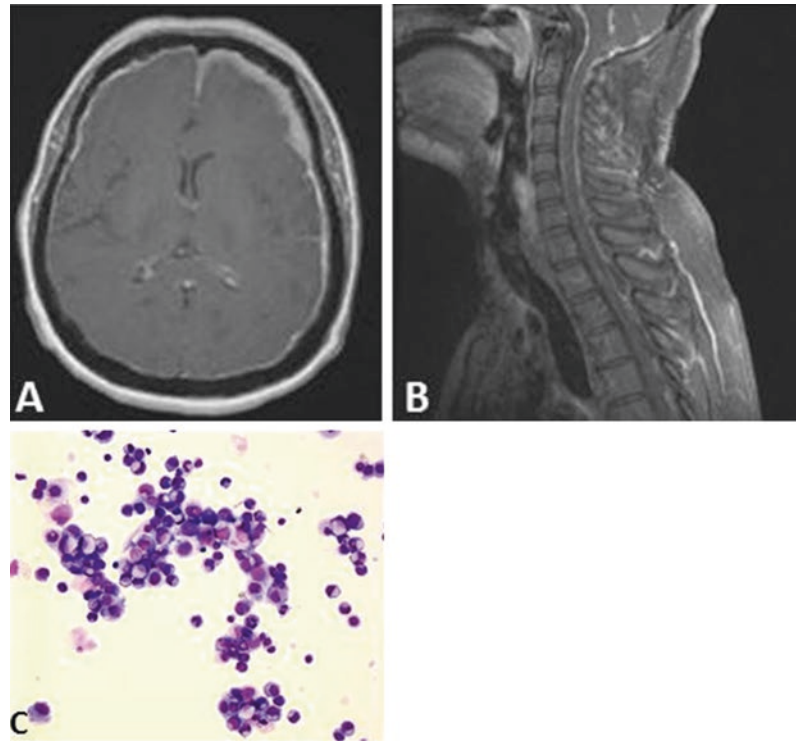

Fig. 2.2 (**a**) T1-weighted image (gadolinium) with attenuation of the meninges, most obvious at the left frontal lobe, indicative of CSF dissemination of tumor. (**b**) T1-weighted image (gadolinium) showing attenuation of the meninges around the spinal cord, compatible with CSF dissemination of the tumor. (**c**) CSF spin preparation revealing tumor cells (toluidine staining, magnification ×100)

in detail. Astrocytes secrete factors that lead to the adequate association between the cells of the BBB and the formation of strong tight junctions. Astrocytes end-feet express Kir4.1K$^+$ channels and aquaporin 4 that regulate BBB ionic concentrations [21]. Additionally, astrocytes secrete various growth factors that are important to the formation of tight junctions, like vascular endothelial growth factor (VEGF), glial cell line-derived neurotrophic factor (GDNF), basic fibroblast growth factor (bFGF), and angiopoietin-1 (ANG-1) [22]. Pericytes are located between the endothelial cells and the end-feet of the astrocytes. They are important regulatory cells for the maintenance of both homeostasis and hemostasis in the BBB [23]. Both pericytes and astrocytes are essential for BBB maintenance through the activation of platelet-derived growth factor receptor-B (PDGFRB) signaling, and the regulation of proteins like occludin, claudin and ZO-1 [24]. The specific role of pericytes and other mural cells and possibly other cells like microglia and macrophages in maintaining the BBB is largely unknown. Tumor cells clasp to the blood vessels to get nourishing and protection, and may eventually start dividing to form sheaths around the vessels. Following a certain time period of adhesion to the vascular walls, tumor cells will make efforts to pass through the vessels to reach the brain tissue. The tumor cell migration through the blood vessels may occur in various ways, e.g., by migrating between endothelial cells (paracellular diapedesis), or through pores present in individual endothelial cells (transcellular diapedesis).

Once penetrated through the BBB, tumor cells may again reside in a dormant state for unknown time periods, before the cells further progress into the brain. Tumor outgrowth in the brain microenvironment is based on the genetic predisposition and cellular adaptation mechanisms of the tumor cells and is largely dependent on the cross-talk between tumor cells and brain-resident cells [25] (Fig. 2.3). Once tumor cells make contact with astrocytes, extensive cross-talking ultimately resulting in the progression of the tumor cells in the brain takes place (Fig. 2.4). The first cells to interact with are the astrocytes, either the

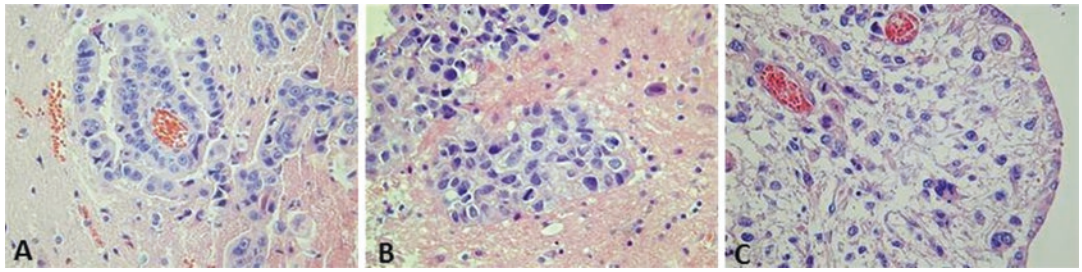

Fig. 2.3 Microscopic images showing various patterns of infiltration of metastatic tumor cells. (**a**) Perivascular tumor propagation, with incipient infiltration of neuropil. (**b**) Metastatic tumor infiltrating in brain. The brain tissue contains reactive glial cells. (**c**) Subependymal tumor spread. Tumor cells are present under the ependymal lining of the ventricle. Similar tumor cell routes may be seen under the pial surface or along white matter tracts. (**a**: magnification ×100; **b**, **c**: magnification ×200; all H&E stained)

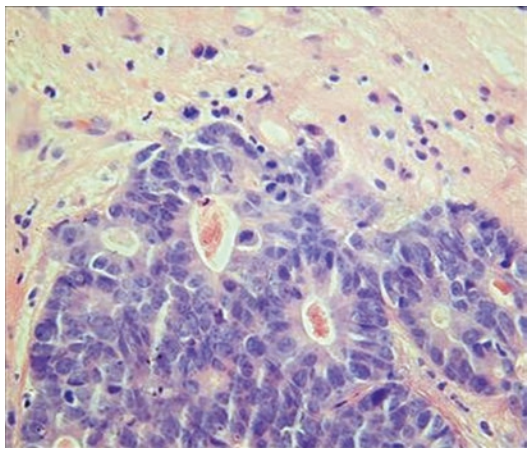

Fig. 2.4 Tissue biopsy of brain metastasis (H&E staining, magnification ×200). Adenocarcinoma (glandular organization of the tissue) infiltrating brain tissue, in which reactive astrocytes and some inflammatory cells are present

subset that takes part in the BBB complex, or other astrocytes present in the neuropil. During the first encounter between the tumor cell with the astrocytes IL-1β, tumor necrosis factor-α (TNF-α), tumor growth factor-β (TGF-β), and IL-6 are expressed by the astrocytes [26]. Upon stimulation by cGMP, also factors as interferon-alpha (INFα) and tumor necrosis factor (TNF) are expressed [27]. On their turn, these factors activate signal transducer and activator of transcription 1 (STAT1) and NF-κB pathways in the tumor cells that promote further cell proliferation [28]. Matrix metalloproteinases (MMPs) play an important role in intracerebral tumor progression [29]. The particular subtypes of MMPs are capable of specifically degrading occluding and claudin, structural proteins that are components of the BBB. Other MMPs degrade collagen type IV that is a major component of the blood vessel basal membranes. There are interactions between cyclooxygenase 2 (COX-2) and particular MMP subtypes [30]. Interestingly, the expression of COX-2, the epidermal growth factor receptor ligand *HBEGF*, and the *α2,6-sialyltransferase ST6GALNAC5* genes were associated with the formation of brain metastasis in breast cancer patients [31, 32].

In order to further colonize the brain, the tumor cells will use strategies to adhere to the basal laminas and start interacting with the brain microenvironment to proceed. At this stage of infiltration, there is continuation of the interaction with matricellular proteins (CD44, CD24) and matrix metalloproteinase (MMP2) in concert with interleukins and plasma urokinase [33]. The NF-κB pathway stimulates the MMPs by uPA to activate endopeptidases to make way for the tumor cells [28]. The chemokine stromal cell-derived factor 1α (SDF-1α, also known as CXCL12) and its receptor CXCR4, a frequently expressed receptor in a variety of tumor cells, are also involved in the invasion of the cancer cells [34]. Other proteins that relate to the formation of brain metastases include heparanase and cathepsin B [35]. Heparanase is regulated by EGFR/HER2 signaling and is expressed by astrocytes as well as endothelial cells [36]. Although certain molecular interactions are general to tumors

of different origin, there may well be differences based on properties of particular tumor cell lineages. So far, this important aspect has largely remained unexplored.

2.5 Cancer Stem Cells and the Epithelial–Mesenchymal Transformation

Over recent years, the phenomena guiding tumor cells to the brain became the object of investigations. The concept of cancer stem cells (CSC) that guarantee unlimited cellular proliferation, and that of epithelial to mesenchymal transition (EMT) have been proposed to describe the cellular and molecular mechanisms by which tumor cells metastasize [37]. CSCs are defined by patterns of particular gene expression and are pivotal for tumor self-renewal, but also for keeping tumor cells in a quiescent state prior to reactivation and becoming metastatic. CSCs undergo the process of EMT to deliver cells ready for metastasis. The underlying molecular pathways are mediated by transforming growth factor β (TGFβ) that downregulates epithelial genes and, at the same time, upregulates genes active in the mesenchymal cells [38]. For the maintenance of CTCs and the EMT, aberrant signaling of the Notch, Hedgehog and Wnt/β-catenin pathways is essential. By the influence of TGFβ the adhesion molecule E-cadherin is suppressed and the cells lose their epithelial characteristics and together with stimulating mesenchymal genes, transform into a proinvasive phenotype. In fact, these cells combine mesenchymal characteristics as the expression of fibronectin and vimentin with the expression of stem cell genes [39]. TGFß orchestrates the expression of transcription factors, the zinc fingers SNAI1 (Snail), SNAI2 (Slug), and E-homeobox 1 (Zeb1) and 2 (ZEB2), characteristic of mesenchymal transformation, while the expression of E-cadherin is suppressed [40]. Besides TGFß also signal transducer and activator of transcription 3 (STAT3) plays a role in the activation of TWIST [41]. In the cerebral metastases of breast, lung, kidney, and colon, upregulation of these transcription factors was described, underscoring their role in invasiveness of the tumor cells.

The MAP kinase pathways are also involved in the process of EMT by downregulation of E-cadherin and upregulation of N-cadherin and matrix metalloproteinases [42, 43]. There is a link with $BRAF^{V600E}$ mutations that are common in melanomas, which are known for their predilection of spreading to the brain [44]. TGFß also activates P13K that on its turn uses integrins to activate Akt kinase [45]. Interestingly, the alpha-v integrin levels are associated with the number of cerebral metastases, probably by its involvement of adhesion of cancer cells to endothelial cells and the tumor cell motility. There are data indicating that particular genetic variants in P13K, PTEN, Akt, and mTOR are predictive of the rise of brain metastasis in NSCLC [46]. Lastly, TGFβ regulates Rho GTPase activity in the regulation of cytoskeletal organization, degradation of tight junctions, and cellular migration [38].

There are several microRNAs involved in the process of EMT. The genes orchestrated by these microRNAs mainly influence cellular adhesion molecules, proteins involved in cellular migration, and oncogenes [47, 48]. It has been demonstrated that the miR-200 family is related to the EMT and is specifically downregulated by TGFβ [49]. The miR-200 negatively influences the expression of ZEB1 and SIP1 and also represses EMT by silencing ZEB1 and ZEB2. The expression of miR-429 is correlated with downregulation of the mesenchymal genes MMP2, Snail, and ZEB2 [50], and the overexpression of miR-200 leads to increased levels of E-cadherin mRNA stimulating the MET. In metastatic cells from NSCLC, reduced expression of genes involved in aggressive invasion was correlated with the expression of miR-200 [51]. Apart from regulating the EMT–MET phenomena, miRNAs are also steering CSC reproduction and differentiation. Specifically, miRNAs—miR-107, miR-0153, miR-204, and miR-218 influence glioma stem-like cells [52]. Interestingly, particular miRNAs have shown to be associated with the various primary tumors giving rise to brain metastases, and expression studies focused

on miRNAs have correctly identified the primary tumors in over 80% of metastases [53]. Other recent studies demonstrated specific miRNA expression in the metastases, pointing to a role in homing of CTCs at particular sites [54]. There are indications that miRNA action is influenced by the cancer microenvironment. It was recently shown that astrocytes are capable of altering the expression of miRNAs of invading tumor cells [55]. Various TCGA analyses have revealed site-specific interactions between microRNAs, CSCs and cells in the brain microenvironment. The expression of particular miRNAs in relation to the expression of factors operative in transgression of tumor cells through the BBB and subsequent invading of tumor cells in brain tissue is an important observation that may well have repercussions for the development of future therapeutic strategies [36, 56].

2.6 Therapeutic Targets

There is a growing list of targetable molecules for primary tumors. As a result, there is an increasing demand to include information on therapeutic susceptibility in the tissue diagnosis of tumors—and also their metastases. For instance, epidermal growth factor receptor (EGFR) mutations are targets for tyrosine kinase inhibitors (TKIs) and are present in a minority of non-small cell lung cancers (NSCLC). In addition, ALK mutations that occur in a small (<5%) fraction of nonsquamous cell lung carcinomas can be targeted by TKIs. Addressing the EGFR mutation status of the cerebral metastasis seems relevant, particularly because discordance rates between the primary tumors and their metastases reportedly are within acceptable limits. Other examples of targets for chemotherapy are BRAF mutations, mutations in ROS1 and CMET. Mutations in CMET may be present in the cerebral metastasis, while not in the primary tumors. Recently, therapeutic immunomodulation by immune checkpoint inhibitors of PD-1 and PDL-1 is added to the therapeutic arsenal. The concordance rate of the estrogen and progesterone receptor status between primary breast cancers and their brain metastases is not precisely known, but in general, data point to receptor loss in the metastases. In addition, the hormone receptor status between various cerebral metastases is unexplored—but needs to be investigated to select for relevant treatment strategies. There is only a minority of HER2-positive tumors and HER2 status of primary breast cancers and their brain metastases allegedly varies with discrepancies up to 25%. Further exploration is indicated not to miss out on potential successful treatment results of the cerebral tumors. Since the $BRAF^{V600E}$ mutation is present in about half of melanomas and there is data that there is a high concordance rate of the BRAF status between metastatic sites, testing for BRAF mutation in any of the melanoma metastasis would be relevant for treatment.

Questions that need to be answered are: to what extent the molecular make-up of the metastasis resembles that of its metastasis? Are the targetable molecules present in all metastases? And are the targets also present in the metastases outside of the brain—so that more easily accessible tumor sites can be used for evaluation of the therapeutic targets? Apart from the presence of these targets, the accessibility of the brain for the drugs is important for treatment. Agents against HER2 like trastuzumab and pertuzumab do not cross an intact blood–brain barrier (BBB) easily. It has been demonstrated, however, that they do cross when the BBB has been damaged by radiotherapy or tumor progression. In addition, higher penetrance of drugs into the brain can be reached by the potentiating effect of the administration of particular combinations of agents. Lastly, there is lack of data on the effect of drugs on CTCs, particularly those CTCs that are capable of crossing the BBB.

2.7 Molecular Characteristics Associated with Brain Metastasis

There is ongoing debate about the inherent significance of particular genetic aberrations to the metastatic potential of tumor cells (Table 2.1). In addition, it is questionable whether these aberra-

Table 2.1 Genes associated with brain metastasis

Primary tumors				
Breast	Lung	Melanoma	Colon	Kidney
HER2	KRAS	STAT3	KRAS	VHL
EGFR	LKB1	BRAF	BRAF	BAP1
Cox2	CDH2	NRAS	NRAS	PIK3R1
HBEGF	KIFL1	SIC1	PIK3CA	
TP53	ALK	P13K/AKT		
ST6GALNAC5	FALZ			
BARD1				
RAD51				

tions are operative in any of the sequence of events leading to brain metastasis, or just provide basic aggressive properties to the tumor cells leading to invasive characteristics. The interaction between cancer cells and their surroundings is defining metastatic potential in the first place, albeit that such epigenetic interaction may well be influenced by the genetic make-up of the tumor cells.

2.7.1 Lung Cancer

Small cell lung cancers (SCLC), consisting of approximately 20% of lung cancers, develop most brain metastases of all lung cancers. SCLC is treated with chemotherapy and radiation but relapses are common. The use of checkpoint inhibitors is being explored, but unfortunately, not much is known about the consistency of molecular targets between the primary tumors and their cerebral metastases. The most common primary tumor to metastasize to brain is non-small cell lung cancer (NSCLC), and among these, the adenocarcinoma histology is most frequently seen (Fig. 2.5). NSCLC represents over 75% of all lung cancers and spread to brain in roughly 25% of the cases. With survival rates of no more than 2 months when brain dissemination has occurred, lung cancer brain metastasis is among the most deadly complication of cancers. In contrast to breast cancers that usually metastasize to brain late in the course of disease, lung cancer brain involvement generally occurs far more quickly. Up to 15% of NSCLC have activating mutations in epidermal growth factor receptor (EGFR) tyrosine kinase domain that matches sensitivity to EGFR tyrosine kinase inhibitors (TKIs) [57]. So far, good responses have been reported, particularly by using next-generation TKIs. Despite response rates of up to 75% for the treatment of primary tumors, no prospective study results are available concerning the susceptibility of the brain metastases to the TKIs. There are data suggestive of EGFR TKIs playing a role as radiosensitizers for subsequent whole brain radiotherapy [58]. Between 3% and 7% of NSCLC come with the echinoderm microtubule like protein 4 and anaplastic lymphoma kinase fusion (EML4- ALK) resulting in a chimeric protein with constitutive kinase activity [59, 60]. ALK TKIs and ALK inhibitors are successfully applied to the primary tumors. As to the brain metastases, The ALK TKI crizotinib seems to sort some effect in the treatment of the cerebral metastases [61]. However, crizotinib does not prevent the rise of new cerebral metastases, partly explained by poor cerebral penetration of this drug. Next-generation ALK TKIs, however, seem to sort better results with responses around 75%. This would be compatible with ALK rearrangements being present in the cerebral metastases, but this has not been confirmed by direct investigation of the brain tumors.

In expression analyses comparing lung cancers with and without metastases, over 1500 genes were found to have altered expression, most of which associated with cell adhesion, motility, and angiogenesis [62]. In addition, genes with reduced expression were associated with cell death and neuroprotection. The expression of CDH2, KIFL1, and FALz was found to be predictive of brain metastasis [63]. Interestingly,

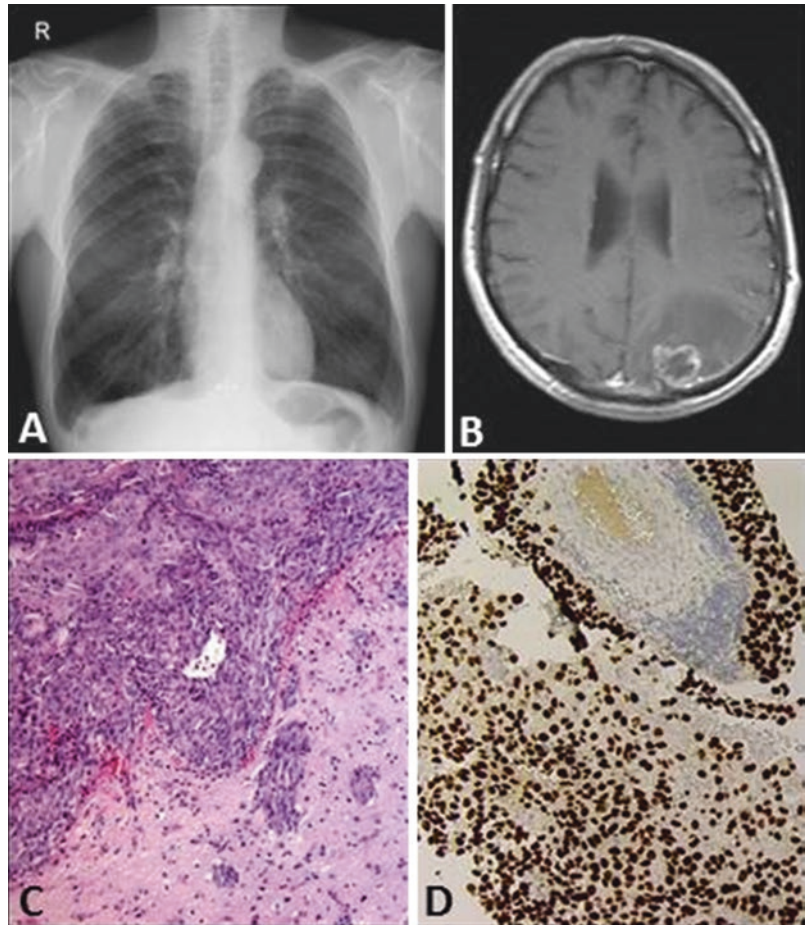

Fig. 2.5 (**a**) X-ray thorax showing lymphadenopathy and tumor compatible with lung cancer. (**b**) T1-weighted image (gadolinium) showing ring-enhancing lesion in the left occipital lobe. (**c**) Tissue biopsy of the lesion shown in **b**, revealing tumor tissue (upper left) infiltrating into brain tissue (lower right) (H&E staining, magnification ×100). (**d**) Tumor tissue shown in **c**, stained for TTF-1. The nuclei appear dark brown following positive identification of TTF-1 expression by specific immunohistochemistry (magnification ×200, IHC for TTF-1)

CDH2 regulates cell adhesion and is involved in EMT. In addition, loss of LKB1 and mutation of KRAS also appeared to be predictive of the appearance of brain metastases [64]. The expression of programmed cell death ligand-1 (PD-L1) was demonstrated in over 20% of brain metastases of NSCLC and appeared to be correlating with smoking history and preoperative radiation therapy [65].

2.7.2 Breast Cancer

In general, breast cancer usually metastasizes to brain relatively late in the course of disease (Fig. 2.6). This may indicate that at first the tumor cells lack the potency to disseminate through the BBB, and not until cellular subsets have acquired (or were selected for) particular capacities to cross, colonizing the brain is possible. Roughly, 25% of patients with breast cancer have amplification of HER2 and these patients are more predisposed to develop brain metastases. It seems that HER2 positive tumors inherently have a predilection for brain. The risk for this complication increases if the tumors have negative hormone receptor status. Particularly, the triple-negative tumors are associated most with brain metastasis, which is attributed more to lack of effective systemic treatment than specific CNS affinity of these tumors. Although women with HER2-positive cancers are treated successfully with trastuzumab, a monoclonal antibody directed to the extracellular domain of HER2, 25% will develop recurrent disease and there are indications that these women are more prone to develop cerebral relapse. The fact that trastuzumab does not easily pass the BBB

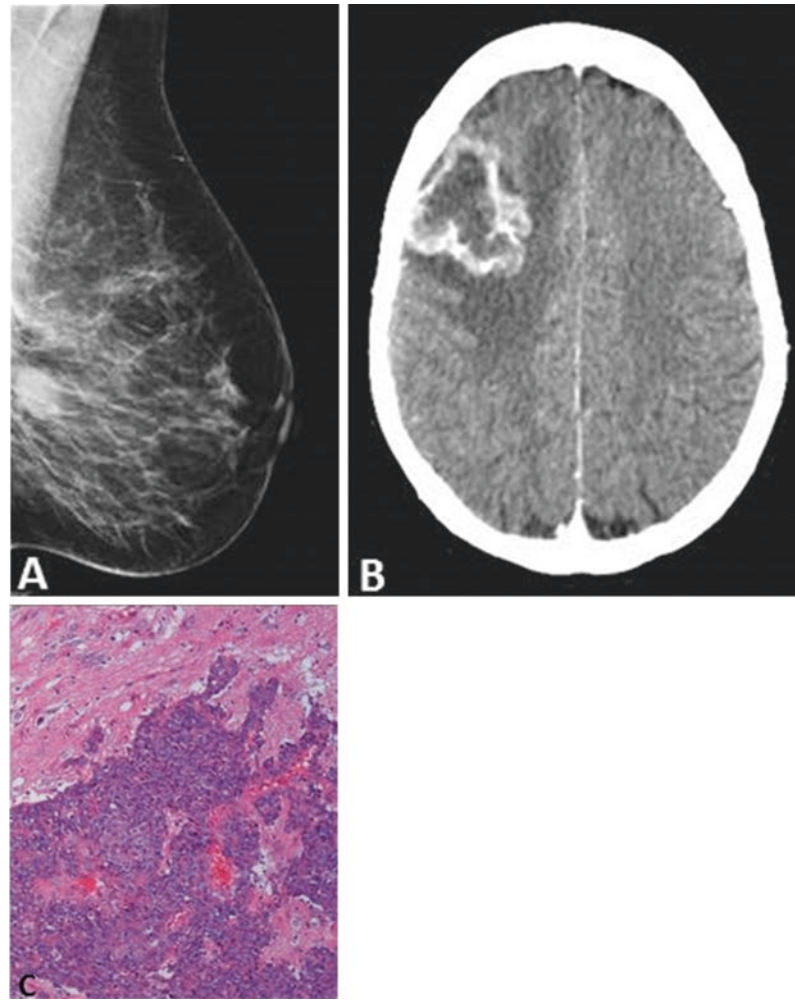

Fig. 2.6 (**a**) Mammography revealing tumor, compatible with primary breast cancer. (**b**) T1-weighted image (gadolinium) showing ring-enhancing lesion in the right frontal lobe, compatible with metastatic disease (or high-grade glioma). (**c**) Tissue biopsy of the lesion shown in **b**, compatible with adenocarcinoma (H&E staining, magnification ×100)

is an explanation of the association between HER2-positive tumors treated with trastuzumab and deadly CNS relapse. Recent clinical studies revealed a better response of the brain sites to lapatinib, an inhibitor of HER2 and EGFR. Also treatment with pertuzumab that inhibits dimerization of HER2 with other receptors has shown some improvements in the treatment of the brain metastases. Gene expression analysis of cohorts of primary breast cancers revealed that 17 out of 243 genes that were associated with metastatic behavior, were exclusively operative in spreading of cancer cells to brain. The genes COX2, EGFR ligand HBEGF, and a2,6-sialyltransferase ST6GALNAC5 affect cancer cell homing and passage through the BBB [32]. A recent study demonstrated the involvement of guanylate-binding protein 1 (GBP1) in crossing the BBB by ER-negative breast cancer cells upon immune escape from T cell action [66]. Although mutations of TP53, PIK3CA, KIT, MLH1, and RB1 were traced in brain metastases of breast cancers, none were specific for the cerebral sites [67]. Differences in methylation status of genes between primary tumors and their brain metastases were found that underscore differences in epigenetic gene regulation [68]. Such differences will have implications for therapeutic strategies aimed at either the primary tumor, or its cerebral metastases.

2.7.3 Melanoma

With percentages of over 50% cerebral dissemination, melanoma is highest on the list of cancers with predilection for brain. So far, the typical BRAF oncogene mutation that activates mitogen-activated protein kinase (MAPK) signaling pathway may influence metastatic potential, but is not specific to brain [69]. The BRAF mutation is essential for the development of the tumor, while the MAPK/ERK pathway is operative in tumor progression and dissemination [70]. The $BRAF^{V600K}$ mutation, associated with more aggressive behavior, is predictive of spreading of melanoma to brain and lung [71]. Patients with advanced melanoma were treated with an anti-CTLA-4 antibody (Ipilimumab) and the success in response rates was doubled when this agent was given to patients with BRAF wild-type tumors that expressed the immune checkpoint programmed cell death ligand-1 (PD-L1) [72]. The success rates of treatment with nivolumab, an inhibitor of programmed cell death-1 (PD-1) also improved if tumors are PD-L1-positive. These response rates are suggestive of specific intracerebral action of these agents, but data from specific studies in PD-L1-positive brain metastases are lacking. However, there is specific data on cerebral relapse by the finding that STAT3, SOC1, and P13K/AKT are operative in brain metastases derived from melanoma [73]. It is as yet unclear if activation of the P13K/AKT pathway results from interaction of melanoma cells with the brain microenvironment and also, what the role of MAPK pathway signifies in this respect.

2.7.4 Colorectal Carcinoma

The genes identified in colorectal carcinomas that play a role in metastatic behavior include KRAS, BRAF, PIK3CA, and NRAS. The BRAF mutation was shown to be responsible for a shorter term to the development of metastases, and the development of brain metastases in particular [74]. In addition, there are incidental findings of $BRAF^{V600K}$ present in a cerebral metastasis of colorectal carcinoma [71]. The common KRAS mutation of colorectal cancers seems not to be specifically linked with brain dissemination, although KRAS mutations were seen 10 times more in a small number of colorectal cancers that gave rise to brain metastases [75]. A similar weak association is reported for the PIC3CA mutation, which is strongly associated with the presence of mutations in KRAS [76].

2.7.5 Renal Cell Carcinoma

Patients with renal cell carcinoma (RCC) who developed intracerebral tumors live significantly shorter than those with disseminations to other organs. Mutations in the von Hippel-Lindau gene and mTOR are the main drivers in tumorigenesis and progression of RCC [77, 78]. Metastatic RCC is treated with targeted agents that mainly address angiogenesis and mTOR signaling. There is suggestion that antiangiogenic agents decrease the intracerebral complications, but substantial data are absent [78]. There are also no significant data on the effects of treatment with TKIs in patients with RCC who developed brain tumors, although a single retrospective study has reported improvements in median survival times [79]. At this point, the effect of TKIs on the cerebral tumors are largely unknown. Expressional differences were reported between RCCs with and without metastases and the genes that were identified appeared to be mainly active in cell adhesion and extracellular matrix proteins, while no genes specifically acting in brain dissemination were reported [80].

2.8 Concluding Remarks

With the increase of numbers of patients suffering from cancer worldwide, the complication of brain metastases has risen. Cerebral metastases may occur early or late in the course of disease and are usually fatal. Therapeutic interventions are limited, but targeted therapies, commonly

directed by the molecular targets present in the primary tumors, are increasingly used.

The future will learn if drug interventions directed against particular molecules or pathways operative in the process of brain invasion from common primary tumors will be successful in the clinical setting. Various issues are at stake when considering such therapeutic intervention. One may target the metastasized tumor cells, i.e., the tumor cells present in the brain. To various extent, intracerebral tumor tissue will still reflect the molecular characteristics of the primary tumor. The similarities, but also dissimilarities, between the tumor cells of the primary tumors and their cerebral metastases should be taken into consideration when choosing adequate therapy. In parallel, for targeted treatment of leptomeningeal disseminated tumor cells, the characterization of the primary tumor, and of the tumor cells in the CSF, is important. Obviously, the penetrance of drugs into the distinct CNS compartments plays a crucial role in effective treatment of the disseminated tumor.

Apart from treatment of intracerebral tumor, strategies to prevent tumor cells to seed to brain are very important. The molecular and cellular steps in the penetration of tumor cells through the BBB and further into the brain tissue need to be further detailed and characterized for commonalities and differences between different primary tumors. The complex role of the immune response present in the primary tumor, or at the metastatic sites, is the object of current research and may also direct future therapeutic approaches.

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3 Molecular Mechanisms in Brain Metastasis

Ekrem Emrah Er and Adrienne Boire

3.1 Introduction

Although responsible for the vast majority of cancer deaths [1], understanding of the molecular mechanisms underlying metastasis lags far behind that of other aspects of carcinogenesis. Of all sites of metastases, those to the central nervous system (CNS) result in disproportionate disability and death [2, 3], reflecting both the physiologic primacy of the CNS and our insufficient understanding of this site of metastasis. Metastasis is perhaps the most overt expression of cancer's evolutionary dynamics. A central tenant of this paradigm is that tumor heterogeneity provides the necessary variability to allow cancer to adapt to and ultimately flourish within a target secondary organ [4]. In support of this, genomic investigative approaches have found that cancer cells metastatic to the CNS are genetically divergent from their preceding primary tumors [5] and display decreased genetic heterogeneity consistent with a founder effect [6]. It is tempting to posit that common genetic drivers for brain metastasis may result from such selective processes, somatically acquired and selected during tumor evolution. However, despite large-scale efforts, genetic changes have not been found to *dictate* site of metastasis [4, 7].

As can be appreciated from even a cursory inspection of the literature, metastasis represents a remarkably complex biological process. In an effort to define this process, several key concepts have emerged: First, in order to successfully inhabit a novel environment, the cancer cells must possess a transcriptional and metabolic "toolkit" that will enable growth in the new space. How cancer cells acquire these capacities (indeed, successful metastasis requires the acquisition of multiple traits) is an area of active study in the field. A current hypothesis suggests that a minor subpopulation within the heterogeneous primary tumor possesses traits sufficient to enable successful colonization of a target organ [4]. A second hypothesis posits that a subpopulation of cells within the primary tumor are exceptionally plastic, with capacity to adapt to any number of environments [8]. A third model envisions a "pre-metastatic niche," a microenvironmental milieu that enriches for a subpopulation of cells competent to inhabit a metastatic site [9, 10]. As is the case in complex biological systems, it is likely that all three models, to a greater or lesser degree, play a role in brain metastasis.

While genetic changes do not drive metastatic site, epigenetic and transcriptomal changes

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do appear to dictate cancer cell metastatic site, resulting in conserved transcriptional programs for parenchymal and leptomeningeal brain metastases, regardless of primary tumor identity [11–15]. To date, these conserved site-specific metastatic signatures have been uncovered largely through mouse modeling, with validation in clinical specimens [16, 17]. These efforts have uncovered the stepwise molecular events that govern cancer cell entry and growth into the central nervous system. It is worth noting that these molecular events largely occur as a result of cancer cell–microenvironmental interactions. This is not surprising given the unique microenvironments encompassed by the central nervous system:

The CNS comprises two distinct anatomic compartments: the parenchyma and the leptomeninges. These compartments remain isolated from the systemic circulation and from each other by means of anatomic barriers. In the case of the brain parenchyma, the blood–brain barrier consisting of vascular endothelial cells, pericytes, and astrocytic end-feet limits entry of plasma contents into the brain. In contrast, the leptomeningeal space remains sequestered from the systemic circulation by means of the blood–CSF barrier; the choroid plexus epithelial cells. Diffusion of small molecules and cells between the parenchyma and the leptomeninges is prevented, in a size-dependent fashion, by the glia limitans, a membrane generated by the pia and astrocytic end-feet [18, 19] (Fig. 3.1). Small molecules may enter and exit the parenchyma via perivascular (Virchow-Robin) spaces; the functional relevance of these CSF circulatory routes remains an area of active study [20]. Microenvironmental interactions are therefore paramount for understanding of metastasis to the CNS, as is an appreciation for the unique anatomic structures present within the CNS. We will therefore address the molecular mechanism governing CNS metastasis from this dual perspective (Fig. 3.2).

3.1.1 Extravasation into the Brain Parenchyma

Once within the systemic circulation, cancer cells will inevitably enter the vasculature of

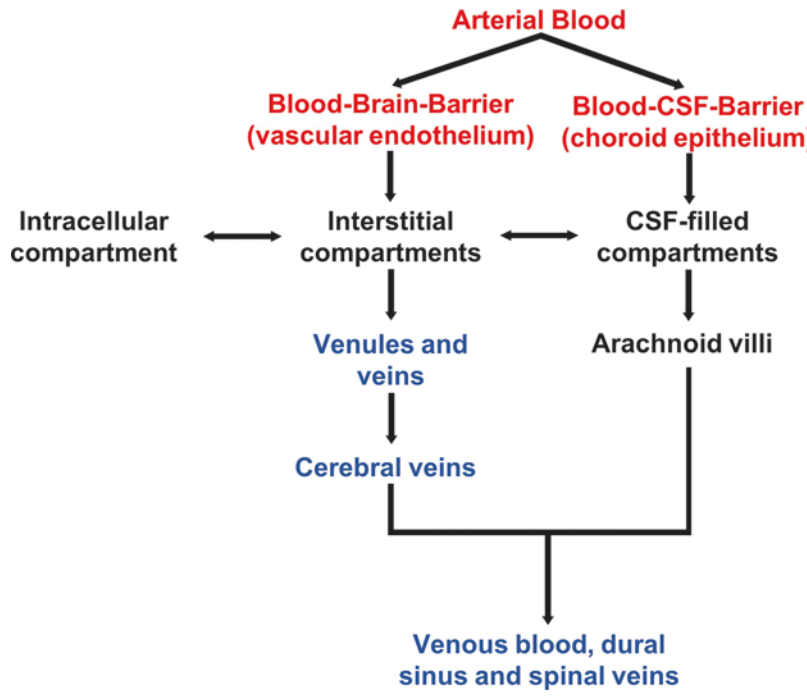

Fig. 3.1 Arterial and venous circulations communicate through compartments across the blood-brain and blood-CSF barriers (Adapted from Malcolm B Carpenter. Human Neuroanatomy. 7th ed. United States: Baltimore: Williams & Wilkins, c1976; Carpenter's Human Neuroanatomy)

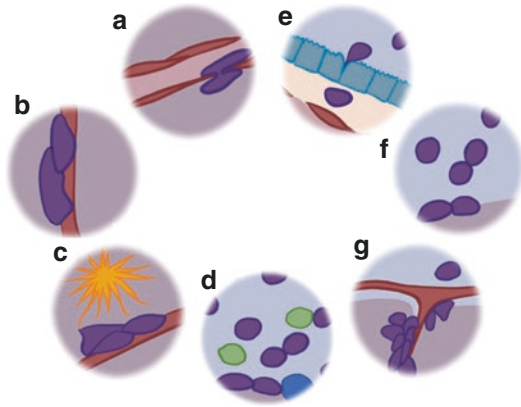

Fig. 3.2 Key mechanistic steps in metastasis to the central nervous system. (**a**) Extravasation into the brain parenchyma. (**b**) Vascular cooption and residence within the perivascular niche. (**c**) Astrocyte interactions. (**d**) Immune Evasion. (**e**) Cancer cell entry through choroid plexus to enter the leptomeningeal space. (**f**) Survival and growth within the leptomeninges. (**g**) Invasion of the glia limitans

the well-perfused brain and spinal cord. Arrest of these circulating cancer cells rests upon two main factors: tropic, brain-specific arrest signals, and transient, inflammatory nonspecific arrest signals. Tropic, brain-specific signals are typified by expression of ST6GalNac5 and AKR1B10 on cancer cells [11, 21]. This enables cancer cells to arrest and engage with brain capillaries. This signal is joined by nonspecific entry signals such as ANGPTL4, COX2, and LRP1 [11, 22]. Together, these enable cancer cells to extravasate through brain capillaries. This signaling alone does not explain the observed relationship between inflammation and cancer. Brain inflammation, in the form of stroke, results in upregulation of S100A8, S100A9, ANGPTL4, COX2, IL-8, and MMP1 recruiting circulating neutrophils, which, in turn, enable metastatic seeding [23, 24], in effect preparing the premetastatic niche. A high ratio of neutrophils to lymphocytes in the peripheral circulation is associated with reduced survival after surgical resection [25]. Together, these observations suggest that pathologic inflammation may enhance tropic mechanisms of cancer cell arrest within the capillaries of the brain parenchyma, improving cancer cell access to the brain.

3.1.2 Residence Within the Perivascular Niche

Having entered the brain parenchyma, cancer cells must cope with this challenging environment. Advanced microscopy techniques, including intravital imaging, demonstrate that after having entered the parenchyma, cancer cells remain closely associated with the basal lamina of the vasculature [14]. Fascinatingly, cancer cells alter their shape to maximize interactions with the basal lamina, wrapping the vasculature and competing with pericytes [26]. Closely associated with the vascular basement membrane [27], within the perivascular niche, cancer cells inhabit a microenvironment classically associated with neural stem cells [28]. It is therefore argued that within this space, cancer cells will acquire plasticity essential for acquisition of the multiple traits needed for successful brain metastasis [10]. Beyond this stem-cell niche hypothesis, this location could conceivably provide improved access to nutrients and oxygen; however, this phenotype is also observed in ex vivo brain slice culture models, devoid of circulation [12]. The generally accepted view of vascular cooption is that proximity to endothelially produced angiocrine factors [29, 30] supports cancer cell growth within the parenchyma. Importantly, this interaction, termed vascular cooption [29], is distinct from angiogenesis. Reflecting the conserved nature of this process, it has been observed in mouse models and clinical samples of parenchymal brain metastasis from lung cancer, breast cancer, and melanoma [12, 14, 31]. Molecularly, this process is dependent on integrin β1 and L1CAM [12, 27, 32], and results in activation of YAP and MRTF, which are transcription factors that respond to biophysical properties of the cell such as membrane tension and the stiffness of the basal lamina of the vascular endothelium [26]. Moreover, having displaced pericytes, the presence of cancer cells within this space likely impacts neurovascular coupling function of the brain vascular endothelium, and local delivery of glucose to support neuronal function [33].

Remarkably, this process is not uniform. Instead, tumor cell–endothelial cell interac-

tions alter blood–brain barrier function to such an extent that many have proposed a blood–tumor barrier [34]. Functionally, this results in inconsistent, patchy perfusion of these metastases, and thereby inconsistent perfusion of these tumors with systemic therapy [35]. The molecular basis for this inconsistent blood–tumor barrier remains under active study. Well-perfused tumor areas are associated with an increase in desmin-positive pericytes, which are very low in abundance in normal brain, whereas the poorly perfused areas are associated with a decrease in CD13 positive pericytes with minimal gains in desmin-positive pericyte populations [34]. Strikingly, size of tumors does not predict perfusion, and the major predictor of permeability appears to be expression of S1P3 in brain metastatic cells [35]. Clearly, improved understanding of this process portends advances in systemic drug delivery to brain metastases.

3.1.3 Astrocyte Interactions

On entry into the brain, cancer cells encounter reactive astrocytes [31], serving a protective role. These foreign cells are detected by astrocytes through expression of damage-associated molecular patterns (DAMPs) [36]. In parenchymal brain metastasis, reactive astrocytes generate a number of mediators [36], including IL-6, CCL2 [35], and plasmin [12]. Together, these mediators serve to reduce the number of cancer cells. In addition, exosomes containing miR-19a secreted from reactive astrocytes reach cancer cells, where it induces downregulation of PTEN and increases the aggressiveness of cancer cells in the brain [37]. Beyond these local effects, activated astrocyte secretory products, including vesicles, can reach the systemic circulation they can attract circulating tumor cells to the brain [38]: These vesicles, together with cytokines, activate PPARα to promote transmigration of circulating lymphocytes into the brain metastatic site. In this manner, cytokines, vesicles, and proteases can all limit brain metastasis progression. However, these initial inflammatory steps may ultimately promote the formation of larger metastases. In the case of melanoma brain metastases, neuroinflammatory signals in the form of the cytokines cxcl10 and ccl2 from reactive astrocytes are instrumental in formation of the premetastatic niche [39].

Cancer cell–astrocyte interactions are complex. While early interactions are dominated by the largely anticancer astrocyte secretome, later interactions are defined by direct cancer–astrocyte interactions that support intracranial cancer cell growth. These interactions appear to be instrumental in the progression of metastases from subclinical micrometastases to overt macrometastases [13, 40–42]. The physical interaction between cancer cells and astrocytes depends on both protocadherin 7 (PCDH7) and connexin 43 (GJA1) [13]. Protocadherin 7 promotes the formation of connexin-43-based gap junctions with astrocytes. These interactions allow cancer cells to engage with the astrocyte gap junction network. These gap junctions enable cancer cells to exchange ions and second messengers with astrocytes [41, 42], making use of this network as a metabolic sink. In doing so, these interactions activate cancer cell Stat1/p65 signaling, enabling cancer cells to withstand both endogenous and exogenous sources of cellular stress including Fas-L and chemotherapy [13]. These molecular observations provide potential explanations for a variety of clinical phenomena associated with brain metastases, including drug resistance (beyond simple drug penetration), and lowered seizure threshold.

3.1.4 Immune Cell Evasion

Classically, the brain parenchyma has been described as enjoying a “privileged” relationship with the systemic immune system. Congruent with this, established brain metastases demonstrate a notably limited lymphocyte infiltrate [43]. However, the relationship between the systemic immune system and the central nervous system is far from well understood. Recent work has uncovered lymphatic vasculature along the sagittal dural sinuses in mice [44, 45]. Moreover,

clonal T-cell receptors against CNS-derived antigens have been detected in the cervical lymph nodes [46]. Beyond the potential importance of neutrophils in preparation of the premetastatic niche, lymphocytes may play a key role in brain metastasis pathogenesis. In the case of checkpoint blockade, mouse modeling and mechanistic work are underway concurrent with clinical trials. In the case of brain metastases, it appears that this approach may be effective, at least for a subset of melanoma patients treated with anti-CTLA4 (Ipilimumab) [47–49] or non-small cell lung cancer treated with nivolumab [50] or pembrolizumab [51].

Whereas lymphocytes are the target of a number of pharmaceuticals, macrophage comprises the majority of immune cells within parenchymal tumors [52]. These tumor-associated macrophages comprise both infiltrative bone marrow-derived macrophages as well as resident microglia [53]. Early in the infiltrative process, it is possible to identify a distinct population of bone marrow-derived macrophages. In the case of parenchymal brain tumors, recent work demonstrates that these infiltrative cells and resident macrophage display a convergent phenotype [54]. For these transcriptomic as well as functional reasons, the cells are typically referred to as tumor-associated macrophages" or TAMs. The functional role that these cells play in parenchymal brain metastasis appears to be highly context-dependent. In the case of glioma, depletion of TAMs with CSF-1R inhibition appears to result in brief dissolution of the tumor. In contrast, in parenchymal brain metastases, TAMs contribute to outgrowth and colonization of brain metastases through exploitation of a proteolytic network [55, 56].

Immune cell evasion may also occur through senescence. Tumors metastatic to the brain display hyperactive WNT/TCF signaling, a uniform property of highly metastatic subpopulations [57]. These cells appear to inhibit WNT signaling in an autocrine manner, though DKK1 [58]. In doing so, these cells express a SOX-dependent stem-like state, enabling them to evade immune surveillance and remain latent.

3.1.5 Entry into the Leptomeninges

As described above, the leptomeningeal space enjoys a privileged relationship with the systemic circulation. The leptomeninges reside behind the blood–CSF barrier, consisting of the choroid plexus epithelium. Spread of cancer cells into the leptomeningeal space is described as leptomeningeal metastasis (LM) and occurs in 5–8% of solid tumor patients and 5–15% of patients with hematological malignancies [59]. Clinical observations suggest that cancer cells may gain access to CSF compartments through four potential routes: from the venous circulation through Bateson's plexus [60] or the bridging veins [61], from the arterial circulation through the choroid plexus [62], from the spinal and cranial nerves through direct invasion, or from the brain parenchyma through penetration of the glia limitans [63]. In the case of ALL, (acute lymphoblastic leukemia), animal modeling has found support for cancer cell entry through the bridging veins of the dural sinuses via α6 integrin–laminin interactions [61]. For breast and lung cancer primaries, there is evidence in mouse models that cancer cells gain access to the leptomeningeal space through the choroid plexus [15]. In the case of medulloblastoma, CCL2 was instrumental in hematogenously disseminated cancer cell access to the leptomeningeal space [64]. It remains to be seen if evidence of these mechanisms can be found in human disease. In addition, it is unclear if the route of entry is dictated by primary tumor factors, systemic factors, or perhaps a combination of these.

3.1.6 Survival and Growth Within the Leptomeninges

Within the leptomeninges, cancer cells face additional challenges: survival within the nutrient-poor CSF and the immune infiltrate. The CSF contains minimal glucose, protein, oxygen, and other metabolic intermediates [65]. Mouse modeling experiments demonstrate that cancer cell expression of complement C3 is essential for overcoming these challenges. This component of the complement cascade leads to local generation of the split product C3a, and activation of the

choroid plexus C3aR. Once activated, signaling leads to loss of Blood–CSF Barrier integrity, and enrichment of the CSF with select plasma components; supporting cancer cell growth [15]. While the quiescent CSF is typically acellular, cancer cells enter this space accompanied by a robust immune infiltrate [66], in marked contrast with the pauci-immune environment of parenchymal brain metastases. Despite this immune infiltrate, cancer cells readily proliferate. Although one can posit a number of mechanisms whereby cancer cells might evade these immune cells, this has not yet been addressed mechanistically.

3.1.7 Invasion of Glia Limitans

Cancer cells within the leptomeningeal space may settle onto the pial surface and fill the perivascular Virchow–Robin spaces. As they invade, they may proteolytically degrade the glial limitans and thereby enter the parenchymal space. Conversely, parenchymal metastases may invade cerebral vasculature, and broach the Virchow–Robin space to enter the leptomeninges. This late stage of disease blurs the distinction between the parenchymal and leptomeningeal compartments. While observed in human disease [63], this has only rarely been observed in mouse models [11]. Cancer cell invasive process have been observed to require the cooperation of macrophage: Macrophage-derived cathepsin S supports cancer cell invasive processes within the brain parenchyma [55].

3.2 Future Directions

Our molecular understanding of metastasis to the CNS has improved a great deal over the past 10 years. Past technical revolutions in molecular biology have enabled discovery rooted in mouse modeling [67]. Given the importance of the microenvironment, transcriptome, and cancer cell heterogeneity in this process, one can envision a second revolution based on single cell technologies [68] including tissue-disruptive technologies such as inDrop [69] and Dropseq [70], as well as tissue-intact approaches such as MERFish [71, 72]. Part and parcel of this discovery approach is computational biology capable of managing such massive datasets. A number of efforts are underway to establish single-cell-based tumor atlases, including the Human Tumor Atlas Network (HTAN); parenchymal brain metastases have been included in this historic undertaking—a reflection of the community's acceptance of brain metastasis as a unique site of metastasis deserving dedicated study. Such approaches will enable use of clinical samples as tools for discovery of cancer cell–microenvironmental interactions in situ. With key cancer cell–microenvironmental pathway identified, mouse modeling and in vitro biology may be employed to determine mechanistic detail with a greater degree of certainty and granularity.

3.3 Conclusion

Metastasis to the central nervous system is governed by a complex ballet of cancer cell microenvironmental interactions that serve to first gain entry into the sequestered parenchymal and leptomeningeal environments. Indeed, the number of these interactions and the resulting intense selective pressure on these metastatic cells are reflected in the inefficiency of this process [14]. Once within these privileged spaces, microenvironmental interactions serve to evade the brains defense mechanisms and support cancer cells robust metabolic needs. These interactions depend on cooperation of genetically stable, nontransformed stromal cells. Given the apparent conserved nature of these interactions, they represent possible orthogonal approaches to prevention of CNS metastasis and targeting of established metastasis. Indeed, one can envision a future where pharmacologic targeting of genetic drivers of CNS metastases [5] is complemented by orthogonal targeting of the microenvironment [13, 73]. Continued efforts to molecularly dissect the molecular mechanisms that underlie central nervous system metastases will undoubtedly result in transformational therapeutic approaches (Table 3.1).

Table 3.1 Genes implicated in metastasis to the CNS

Extravasation into brain parenchyma		Residence within the perivascular niche		Astrocyte interactions		Immune cell evasion		Entry into the leptomeninges		Growth within leptomeninges		Invasion of the glia limitans	
AKR1B10	21	SERPINE1	12, 14	CXCL10	39	HOXB9	57	CCL2	64	C3	15	Cathepsin S	55
LRP1	22	L1CAM	12, 14, 32	CCL2	35, 39	LEF1	57	α6 Integrin	61				
ANGPTL4	11, 24	Laminin a2	34	CCL17	39	DKK	58						
COX2	11, 24	YAP	26	PCDH7	13	Wnt	56						
IL8	24	MRTF	26	GJA1	13, 41, 42								
MMP1	24	Integrin b1	32	IL-6	35								
ST6GALNAC5	11	S1P3	35	Plasmin	12								
S100A8	23												
S100A9	23												

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4 Genomic Characterization of Brain Metastases: Implications for Precision Medicine

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4.1 Introduction

Brain metastases are a devastating secondary complication of systemic cancer and account for the most common central nervous system (CNS) neoplasm in adult cancer patients [1]. Improved systemic therapies and the advancement of neuroimaging techniques have largely contributed to a longer survival of affected patients, an earlier detection of brain metastases, and therefore a rising incidence of brain metastases [1, 2]. Among all cancer types, lung cancer, breast cancer, melanoma, gastrointestinal cancers, and renal cell carcinoma have the highest propensity to cause brain metastases [3]. Affected patients face a dismal prognosis, with a median survival of 3 months up to 18 months, depending on a variety of prognostic factors such as age, Karnofsky Performance Status (KPS), primary tumor type, presence or absence of controlled systemic disease, number of brain metastases, and time to development from primary tumor diagnosis to brain metastases [4, 5]. More recently, molecular biomarkers, such as *EGFR*, *ALK*, and *HER2*, have been found to be prognostic and are being incorporated into prognostic classifications [6, 7].

Treatment options for patients with brain metastases depend on the number and size of lesions, their location as well as on the underlying primary tumor type. Historically, the mainstay of treatment for affected patients has been whole-brain radiation therapy (WBRT), in particular, if patients present with multiple lesions [8]. Alternatively, in the case of a solitary or a large symptomatic, surgically accessible lesion, patients undergo surgical resection followed by radiation [1]. The EORTC 22952-26001 study revealed that adjuvant WBRT after either surgical resection or stereotactic radiosurgery in patients with one up to three brain metastases reduces local and distant recurrence compared to observation. However, this treatment combination failed to improve overall survival as well as the duration of functional independence [9]. A recent meta-analysis found that different dose-fractionation schemes did not show a benefit in overall survival (OS) or neurological function improvement (NFI) compared to standard doses

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and that the addition of WBRT to radiosurgery did not improve OS and worsened NFI [10]. Stereotactic radiosurgery (SRS) represents a suitable treatment option for patients with smaller brain metastases (up to 3 cm in size) and oligometastatic disease of up to four brain metastases [1, 8]. SRS shows a selective survival benefit in combination with WBRT in patients with a single brain metastasis with favorable characteristics (median survival 6.5 vs. 4.5 months without SRS boost among 333 patients) [11]. However, the benefits of a SRS boost do not necessarily extend to overall survival in more than one brain metastases [12]. Similarly, the benefit of WBRT in addition to surgery is limited to reduced metastatic recurrence but not improved survival or duration of functional independence [13]. The use of WBRT in an adjuvant setting has limitations due to its effects on neurocognitive decline in this particular setting [14]. Furthermore, our ability to predict who will respond to radiation therapy remains limited and additional molecular studies (blood based and tissue based) are needed to define molecular subgroups that will most likely respond.

Systemic treatment options for patients with brain metastases are limited to date, due to the fact that most chemotherapeutic agents are not sufficiently able to cross the blood–brain barrier (BBB) and affected patients are commonly excluded from clinical trials.

In recent years, tremendous efforts have been undertaken to discover molecular characteristics of metastatic brain tumors and potentially actionable driver mutations by using next-generation sequencing techniques. The largest genomic analysis of brain metastases and matched primary tumors to date revealed that brain metastases harbor genetically actionable alterations not detecting in their underlying primary tumor, while brain metastases within the same individual were found to be genetically homogeneous [15]. Based on these findings, there is an urgent need for more brain-penetrant targeted agents that need to be specifically evaluated in prospective clinical trials in patients with brain metastases.

4.2 Lung Cancer Brain Metastases

The various histopathologic subtypes of lung cancer remain the most common form of cancer to metastasize to the brain. Several population-based studies report the incidence of brain cancer metastases in lung cancer ranges from 9 to 88% [16–20]. As overall survival (OS) of lung cancer improves, it is expected that these incidences of brain metastases will also increase with estimates of patients with lung cancer expressing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangements having an over 20% increase in brain metastases incidence with survival greater than 5 years [21].

Survival estimates following metastatic spread to the brain vary but remain quite poor, ranging from 2 to 30 months [22]. Additionally, the presence of brain metastases is associated with a significant increase in morbidity and mortality for patients with lung cancer and leads to higher healthcare costs and increased financial burden to patients [23].

4.2.1 Current Therapies of Lung Cancer Brain Metastases

Currently, the primary goal in treating brain metastases in lung cancer is palliation. Treatment strategies for brain metastases have to balance minimizing neurocognitive treatment side effects with neurocognitive side effects of metastases themselves [24].

In general, the use of systemic chemotherapy for brain metastases is limited due to the blood–brain barrier. Historically, the standard systemic therapy for non-small cell lung cancer brain metastases is platinum based, often in combination with other agents, although these regimens are often complicated by high toxicities. Fotemustine, a nitrosourea alkylating agent, in combination with cisplatin had a hematological toxicity rate of over 50% [25]. Paclitaxel, a microtubule inhibitor, in combination with cisplatin and vinorelbine, a tubulin inhibitor, or

gemcitabine, a nucleoside analog, was able to produce similar remission rates between systemic and CNS metastases [26]. Pemetrexed, a multitargeted antifolate agent, has CSF penetration and has activity in brain and leptomeningeal metastases [27].

4.2.2 Targeted Therapies for Lung Cancer Brain Metastases

4.2.2.1 Epidermal Growth Factor Receptor (EGFR)

The presence of the EGFR mutation is associated with an increased incidence of brain metastases in NSCLC though the impact of EGFR mutation status on survival with brain metastases is unclear [28, 29]. In a recently updated prognostic assessment of lung cancer brain metastases, EGFR mutations corresponded to a better prognosis [6]. EGFR-tyrosine kinase inhibitors (TKIs) may be among the most promising treatments for lung brain metastases owing to their ability to cross the blood–brain barrier. Two studies, LUX-Lung 3 and LUX-Lung 6, compared second-line EGFR-TKI, afatinib to traditional chemotherapy, cisplatin plus pemetrexed, or platinum-based chemotherapy, respectively, and found increased progression-free survival with afatinib of 8.2 vs. 5.4 months [30]. In a trial comparing EGFR-TKIs, erlotinib and gefitinib, as first-line treatment in 28 patients with NSCLC with brain metastases, 93% of patients had disease control, either partial response or stable disease, without a difference in progression or overall survival between erlotinib and gefitinib [31]. Another larger study comparing erlotinib to gefitinib as first-line treatment for NSCLC with brain metastases found that time to neurological progression was higher in the erlotinib group [32]. A comparison between all three EGFR-TKIs, gefitinib, erlotinib, and afatinib, found that afatinib had a better progression and overall free survival than gefitinib but no difference among the three TKIs in patients who had brain metastases at the start of the study [33]. A phase-II study of WBRT in combination with erlotinib for patients with NSCLC and brain metastases found that median survival was about 10 months longer in patient with EGFR mutations [34]. A meta-analysis found that WBRT in combination with gefitinib/erlotinib led to improved response rates, CNS remission, and overall survival compared to WBRT alone or WBRT plus chemotherapy [35].

4.2.2.2 ALK

The echinoderm-microtubule-associated protein-like 4 (EML4)-anaplastic lymphoma kinase (ALK) fusion was identified as another oncogene at a rate of about 6.7% of NSCLC patients, mostly younger patients who were nonsmokers with adenocarcinoma [36]. ALK abnormalities are found in approximately 5% of CNS metastases from NSCLC [37] and like EGFR mutations, correspond to a better prognosis [6]. Crizotinib was the first *ALK* tyrosine kinase inhibitor developed with an overall disease response rate of 57% [38]. Initially, there were concerns about its ability to penetrate the blood–brain barrier due to a low ratio cerebral spinal fluid (CSF) to plasma concentration [39]. Initially, case reports suggested a possible efficacy in the ability of crizotinib to treat NSCLC brain metastases and in another case efficacy with a higher dose schedule [40, 41]. The PROFILE trial showed increased progression-free survival in patients with brain metastases with crizotinib compared to chemotherapy [42]. Ceritinib is an *ALK* inhibitor that has shown increased ability to cross the blood–brain barrier and was found to have a 65% intracranial disease control rate in already *ALK*-inhibitor-treated patients [43]. Brigatinib is a newer *ALK* inhibitor which was able to produce an intracranial progression-free survival of 14.6 months in crizotinib-treated patients [44]. Current targeted treatment options in clinical use are summarized in Fig. 4.1.

4.2.3 Immunotherapies

4.2.3.1 Nivolumab

Nivolumab is a human IgG4 anti-PD-1 monoclonal antibody. The CheckMate trials evaluated the effect of nivolumab on advanced

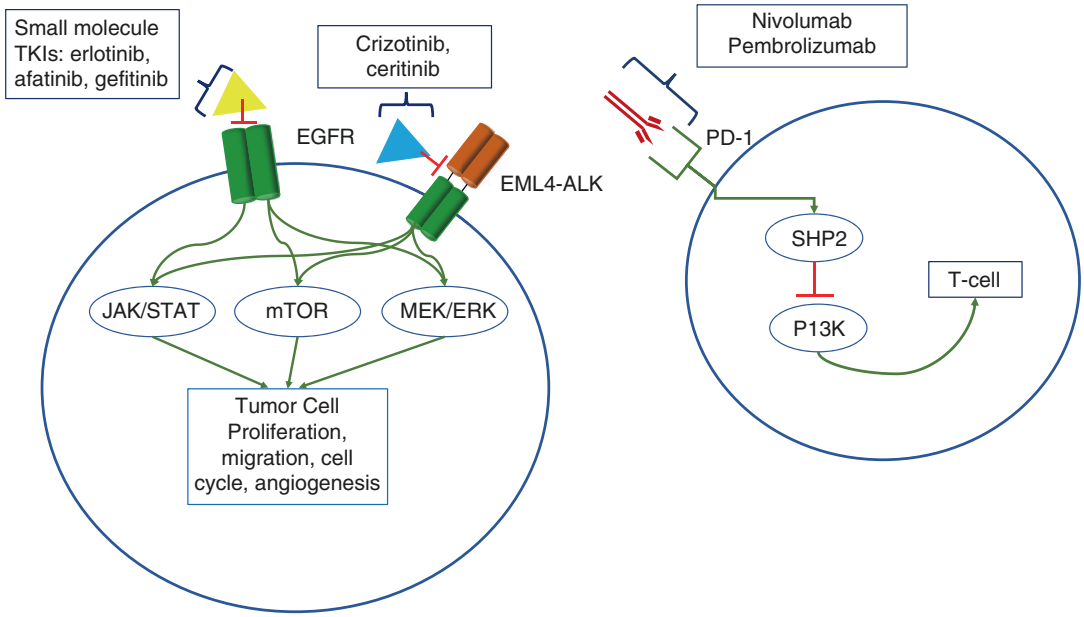

Fig. 4.1 Current targeted therapy and immunotherapies in non-small cell lung cancer in clinical use

Table 4.1 Summary of currently active and recruiting clinical trials for patients with breast cancer brain metastases

Trial number	Phase	Location	Intervention
HER2 inhibitors			
NCT02536339	II	USA	Pertuzumab + trastuzumab in patients with HER2-positive breast cancer and CNS progression after radiotherapy (WBRT/SRS)
PI3K/Akt/mTOR inhibitors			
NCT01783756	Ib/II	USA	Everolimus + lapatinib + capecitabine in patients with HER2+ breast cancer with CNS recurrence or progression after therapy with trastuzumab
CDK4/6 inhibitors			
NCT02308020	II	USA	Abemaciclib in patients with HR+, HER2± breast cancer brain metastases
NCT02774681	II	USA	Palbociclib + trastuzumab in patients with HER2+/HR− breast cancer brain metastases

NSCLC. CheckMate 017 compared the efficacy of nivolumab to docetaxel in an open-label international trial and found that nivolumab had a higher overall survival rate (42% vs. 24%) and lower risk of death than docetaxel. Among patients who had CNS metastases in this trial, the median overall survival was 5.8 months compared to 7.9 months in those without brain metastases [45]. A pooled analysis of 3 CheckMate trials showed that CNS metastases treated with nivolumab had a higher complete remission rate (28% vs. 19%) and stable disease rate (33% vs. 31%) than those treated with docetaxel and that in patients with previously treated CNS metastases, the median overall survival was longer in the nivolumab group [46].

4.2.3.2 Pembrolizumab

Pembrolizumab is a human anti-PD-1 monoclonal antibody shown to have significantly improved overall and progression-free survival compared to docetaxel in advanced NSCLC [47]. A 33% response rate has been shown in NSCLC brain metastases treated with pembrolizumab [48]. Ongoing trials of immunotherapy in lung cancer brain metastases are detailed in Table 4.1.

4.2.4 Genetics of Lung Cancer Brain Metastases

Targeted cancer therapy via molecular biomarker analysis is becoming the standard of care for cancer, and in the case of brain metastases, analysis of molecular markers of CNS metastases themselves may provide insight for more effective therapies. Various molecular studies have identified key molecular targets for future therapies. One strategy for identifying markers is to identify molecular targets critical to each step of metastases. AXL-GAS6 (a receptor tyrosine kinase inhibitor) has been identified in the epithelial to mesenchymal transition [49]. ADAM9 (a transmembrane cell adhesion protein) enables tissue plasminogen activator to stimulate promigratory proteins in mouse models allowing for increased brain metastases and was found to be at higher levels in brain metastases than in primary tumor cells [50]. Placental growth factor (PLGF) has been shown in vitro to activate endothelial growth factor receptor (EGFR) 1-Rho, which leads to disassembly of brain endothelial cell tight junctions allowing for SCLC brain metastases [51]. Mouse model studies using human-derived lung adenocarcinoma cells identified *LEF1 and HOXB9* as genes critical in the WNT/TCF pathway for extracellular matrix invasion and tumor outgrowth in the development of bone and brain metastases [52]. RT-PCR analysis of NSCLC tumor samples found that expression of CDH2 (N-cadherin) and *KIFC1* (a kinesin family protein) were positively associated brain metastases occurrence and *FALZ* (a neuronal transcriptional factor) was negatively associated with brain metastases [53]. Hypermethylation of HERC5 (a ubiquitin–protein ligase) has been shown to be associated with increased occurrence of brain metastases and decreased overall survival in NSCLC [54]. Fibroblast growth factor receptor (FGFR1) amplification were found at a five-fold higher rate in brain metastases of lung adenocarcinoma than in the primary tumor [55]. In a genomic study of matched brain metastases and primary tumors, branched genomic evolution was observed, such that brain metastases from lung cancer harbored clinically actionable alterations that were not detected in the matched primary tumors. These included alterations in the CDK pathway and PI3K pathway [15]. Another study demonstrated FGFR1 amplifications in brain metastases of lung adenocarcinoma [55]. These genes and pathways are potential targets for novel therapeutics which can be designed for the explicit purpose of reducing or treating lung cancer brain metastases.

4.3 Breast Cancer Brain Metastases

Breast cancer is the most common primary tumor occurring in women worldwide [56] and represents the second most common cause of brain metastasis in adult cancer patients [57]. The incidence of breast cancer brain metastases (BCBM) considerably varies depending on the underlying tumor subtype. Human epidermal growth factor receptor 2 (HER2)-positive and triple-negative breast cancer are more likely to cause brain metastases compared to the luminal A and B tumor subtype [7, 58], with reported incidences of BCBM ranging from 30 to 40% [59, 60]. Regarding the associated survival, patients with BCBM from triple-negative breast cancer are facing the most dismal prognosis. Hormone receptor status and HER2 status are prognostic in breast cancer brain metastases [7, 61]. According to a recent multicenter retrospective study including 1256 patients with BCBM stratified by tumor subtype, median overall survival of patients with triple-negative brain metastases was 4.9 months, compared to 9.3 and 16.5 months in patients with luminal and human epidermal growth factor (HER2)-positive brain metastases, respectively [62].

4.3.1 HER2 Receptor Status and HER2-Directed Treatment Options

In approximately 20% of all breast cancer patients, HER2 amplifications can be detected

[63]. Among those, 30–50% of affected patients will develop brain metastases during their course of disease [64]. This increased risk of developing metastatic brain disease has been attributed to the improved control of systemic disease due to treatment with the monoclonal antibody trastuzumab [65]. Regarding concordance of HER2 status in metastases and primary tumors, divergence between BCBM and their underlying matched primary tumor has been described in recent studies [66, 67]. Interestingly, a recent study analyzing a total of 182 HER2-positive primary breast cancer patients and their metastatic primary tumors demonstrated that 24% of metastatic tumors were HER2 negative [68]. This discordance of HER2 status was furthermore associated with a decreased overall survival [68]. These findings emphasize that biopsies of metastatic sites are to determine the hormone receptor status and ultimately, to direct patients to appropriate targeted therapy options.

Despite the fact that trastuzumab is an effective treatment option for patients with HER2-positive breast cancer that extends overall survival [69, 70], the role of this monoclonal antibody for the treatment of BCBM is limited depending on the condition of the BBB. A pharmacokinetic study by Stemmler et al. demonstrated that the ratio of plasma vs. cerebrospinal fluid (CSF) levels of trastuzumab in BCBM patients improves from 420:1 to 76:1 after radiotherapy. For patients with concomitant leptomeningeal disease, the plasma to CSF ratio was found to be 49:1 [71], indicating that the CNS penetration of trastuzumab improves with a partial impairment of the BBB.

In the phase-III trial CLEOPATRA, the addition of the HER2-directed monoclonal antibody pertuzumab to trastuzumab and docetaxel significantly improved the median overall survival in patients with HER2-positive breast cancer compared to the addition of placebo (56.5 months vs. 40.8 months, respectively) [72]. In a subsequent exploratory analysis of this trial, the incidence between both treatment arms was found to be similar. However, the combination of pertuzumab, trastuzumab, and docetaxel yielded a significantly longer median time to development of brain metastases compared with the combination of placebo, trastuzumab, and docetaxel (15 months vs. 11.9 months, respectively). Furthermore, the median overall survival was longer in the pertuzumab arm of this study (34.4 months vs. 26.3 months) [73]. To date, a phase-II trial is evaluating pertuzumab in combination with high-dose trastuzumab after radiotherapy (NCT02536339) in HER2-positive breast cancer brain metastasis patients.

The dual tyrosine kinase inhibitor lapatinib targets both HER2 and EGFR receptors and has been shown to cross the BBB in patients with brain metastases [74]. Unfortunately, when used as a single agent, only minor antitumor activity of lapatinib was observed in the treatment of patients with BCBM. Lapatinib monotherapy was assessed in two phase-II trials investigating its efficacy in patients with HER2-positive BCBM, but has only yielded objective response rates in the CNS of 3–6% [75, 76]. However, the addition of capecitabine to lapatinib in patients with previously untreated brain metastases led to more promising intracranial rates. The multicenter, single-arm phase-II study LANDSCAPE reported objective partial CNS response in 66% of treated patients [64]. Furthermore, promising results have been reported for the antibody-drug conjugate trastuzumab emtansine (T-DM1): A retrospective, exploratory analysis of the multicenter phase-III trial EMILIA has shown that in patients with treated asymptomatic brain metastases at baseline, T-DM1 led to a significantly improved overall survival compared to lapatinib plus capecitabine [77]. In addition, various case reports have supported a potential antitumor activity of T-DM1 in the setting of HER2-positive breast cancer brain metastasis and a partially disrupted BBB [78–84].

4.3.2 Genetics of Breast Cancer Brain Metastases: PI3K/Akt/mTOR-, CDK4/6 Pathway and Targeted Treatment Options

Activating mutations in the PI3K/AKT/mTOR and the CDK4/6 pathway frequently occur in

BCBM and open up new therapeutic strategies [15]. The mTOR-inhibitor everolimus is able to cross the BBB and might therefore be a promising treatment option for BCBM patients in the future. In two phase-III trials, the combination of everolimus either with trastuzumab and vinorelbine in patients with HER2-positive metastatic breast cancer [85] or with an aromatase inhibitor in patients with hormone receptor-positive metastatic breast cancer [86] significantly prolonged progression-free survival. A recent phase-II study of everolimus, trastuzumab, and vinorelbine for patients with progressive HER2-positive BCBM unfortunately revealed low intracranial response rates (4%, one partial response in the entire cohort) for this combination and a reported overall survival similar to a historical control [87]. The role of everolimus is currently being evaluated in combination with lapatinib and capecitabine in a phase-Ib/II single-arm trial for the treatment of HER2-positive BCBM patients with CNS progression after treatment with trastuzumab (NCT01783756).

Encouraging results have also been reported in patients with hormone receptor-positive breast cancer treated with selective CDK4/6 inhibitors targeting the D-cyclin-dependent kinase (CDK) 4/6-INK4-retinoblastoma (Rb) pathway [88]. For this reason, the effectiveness of the CDK4/6 inhibitors abemaciclib and palbociclib is currently being analyzed in clinical trials (NCT02308020, NCT02774681). Current targeted agents in breast cancer brain metastases and ongoing trials are summarized in Fig. 4.2 and Table 4.2.

4.4 Melanoma Brain Metastases

The incidence of brain metastases in patients with melanoma is exceptionally high, occurring in up to 50% of cases [89]. Melanoma is the third leading cause of death from brain metastases after lung cancer and breast cancer, and intracranial melanomas cause significant neurologic morbidities due to their high bleeding propensity. Prior to the introduction of novel therapeutic agents, patients with melanoma brain metastases had a dire prognosis. Per the original diagnosis-specific graded prognostic assessment (DS-GPA), median survival for these patients ranged between 3.4 and 13.2 months [90]. This changed

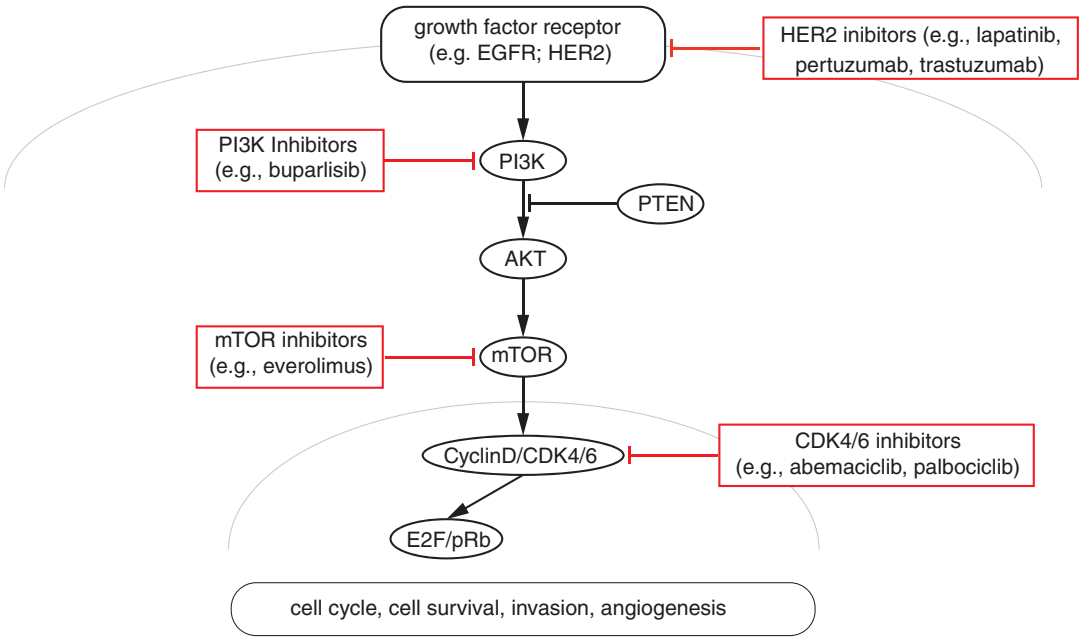

Fig. 4.2 Current targeted agents in breast cancer brain metastases

Table 4.2 Summary of currently active and recruiting clinical trials of immunotherapy for patients with non-small cell lung cancer brain metastases

Trial number	Phase	Location	Intervention
Immunotherapies			
NCT01454102	I	USA	Nivolumab in combination with gemcitabine/cisplatin, pemetrexed/cisplatin, carboplatin/paclitaxel, bevacizumab, erlotinib, ipilimumab, or as monotherapy
NCT02696993	I/II	USA	Nivolumab + SRS/WBRT± ipilimumab in patients with at least one lesion amenable to radiation therapy (SRS or WBRT)
NCT02858869	I	USA	Pembrolizumab + SRS
NCT02886585	II	USA	Pembrolizumab in patients with previously untreated or progressive brain metastases or neoplastic meningitis (various solid tumors)
NCT02085070	II	USA	Pembrolizumab (previously untreated brain metastases without need of local therapy)
NCT02681549	II	USA	Pembrolizumab + bevacizumab (previously untreated brain metastases)

drastically after targeted therapeutic agents and checkpoint blockade agents became available. The DS-GPA for melanoma was revised in 2017, with median survival now ranging between 4.9 and 34.1 months [6]. Here, we provide an introduction to these therapeutic interventions and discuss survival data, published clinical trials as well as ongoing clinical trials.

4.4.1 Targeted Agents

Approximately 40–60% of malignant melanomas were found to have mutations in the v-raf murine sarcoma viral oncogene homolog B (*BRAF*) [91]. Most of these mutations are characterized by a single amino acid substitution at codon 600 of the gene, from valine to glutamic acid (V600E). This leads to constitutive activation of the MAPK pathway through phosphorylation of MEK and subsequently ERK, which normally regulates cellular proliferation in a signal-dependent manner. BRAF-mutant tumors are exclusively dependent on the MAPK pathway for oncogenesis and are therefore highly sensitive to inhibition of this signaling cascade [92]. Prognostic classifications in brain metastases from melanoma have now incorporated BRAF mutation status, with improved survival in BRAF-positive patients [93].

4.4.1.1 Vemurafenib

Vemurafenib is a small-molecule inhibitor of mutant BRAF. It showed clinical efficacy in the BRIM-3 trial, a phase-III randomized study of 675 patients with untreated metastatic melanoma that were randomized to vemurafenib vs. dacarbazine. Six-month overall survival was 84% in the vemurafenib group vs. 64% for dacarbazine and response rate was 48% for vemurafenib vs. 5% for dacarbazine [94]. These results led to the FDA approval of vemurafenib in 2011. The subsequent co-BRIM study looked at combined inhibition of BRAF and MEK (vemurafenib and cobimetinib) in attempt to minimize acquired resistance through activation of downstream effectors of the MAPK pathway [95]. Median progression-free survival (PFS) and response rates (RR) were higher in the combination group compared to vemurafenib plus placebo (9.9 vs. 6.2 months for median PFS and 68% vs. 45% for RR). Based on this, the FDA approved this combination therapy in 2015.

Patients with untreated or recently treated (≤3 months) brain metastases were excluded from these landmark trials, and the standard of care for intracranial lesions remained a combination of surgery and radiotherapy [96]. A few studies subsequently reported safe and effective treatment of brain metastases from BRAFV600E mutant melanoma with a combination of stereotactic radiation and vemurafenib [97, 98]. A phase-II trial of vemurafenib in brain metastases was conducted between 2011 and 2016 [99]. One hundred forty-six patients were enrolled and divided into two cohorts (previously treated and untreated). Intracranial response rate was 18% in the untreated cohort, compared to 33% extracranial response. Median overall survival was

8.9 months in the untreated cohort and 9.6 months in the previously treated one. Additionally, a retrospective study of melanoma patients with brain metastases treated with a combination of BRAF and MEK inhibitors showed that there was symptomatic improvement, median PFS of 5.3 months and median OS of 9.5 months [100].

4.4.1.2 Dabrafenib

Dabrafenib is another small-molecule inhibitor of mutant BRAF that has clinical efficacy in metastatic melanoma. Contrary to vemurafenib, the initial dose escalation trials for dabrafenib included patients with untreated brain metastases [101]. The phase-III BREAK-3 trial of dabrafenib vs. dacarbazine in metastatic melanoma showed a significant PFS benefit of 5.1 vs. 2.7 months [102], which lead to the FDA approval of this agent in 2013. Similar to vemurafenib, dabrafenib was studied in combination with a MEK inhibitor, trametinib, which showed substantial improvement in PFS compared to dabrafenib alone (11.4 vs. 7.3 months) [103]. The efficacy of dabrafenib in melanoma brain metastases was assessed in dedicated phase-II trials. The BREAK-MB trial was a phase-II study of 172 patients with V600E or V600K mutant melanoma and brain metastases, either previously treated or untreated [104]. Intracranial RR was 39.2% for previously untreated patients and 30.8% for treated patients with BRAFV600E mutant tumors. RR was lower for V600K mutations. Additionally, the COMBI-MB trial is evaluating the combination of dabrafenib plus trametinib in previously treated and untreated patients and with BRAFV600E or V600D/E/K/R mutations [105]. Intracranial RR for BRAFV600E mutant tumors in previously untreated patients was 58 and 56% for previously treated ones. Median PFS was 5.6 months in the untreated group and 7.2 months in the treated group. Targeted treatment strategies and immunotherapy options for melanoma brain metastases are displayed in Fig. 4.3.

4.4.2 Immunotherapy

In addition to targeted therapy, in the past decade, immune checkpoint blockade therapy has revolutionized the management and prognosis of metastatic melanoma.

4.4.2.1 CTLA-4-Directed Therapy

Ipilimumab is a humanized monoclonal antibody against CTLA-4. Ipilimumab first showed significant clinical benefit in 2010 against the

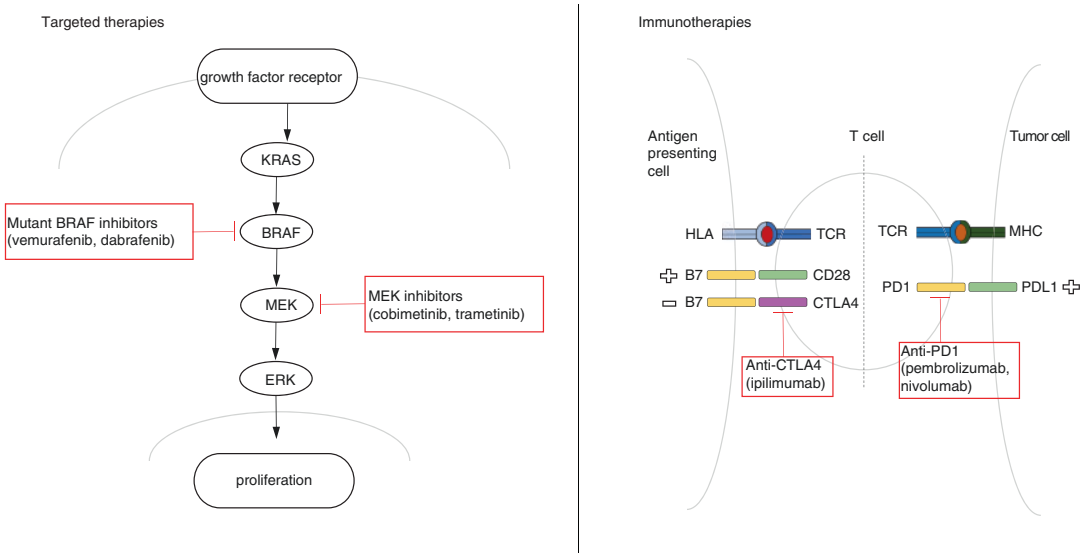

Fig. 4.3 Current targeted therapy and immunotherapies in melanoma in clinical use

gp100 vaccine in patients with unresectable stage III or IV melanoma (median OS of 10.0 vs. 6.4 months) [106] and was approved by the FDA in 2011. This trial included patients with brain metastases, most of which were previously treated, and results suggested that these patients derived a clinical benefit from ipilimumab (HR 0.7 with 95% CI 0.4–1.2). A subsequent phase-II study was conducted looking specifically at brain metastases patients [107]. Patients were divided into two cohorts based on symptoms and corticosteroid use and were given four doses of ipilimumab at 10 mg/kg. A durable response of 12 weeks or longer was observed in 24% of cases in the asymptomatic cohort (cohort A) and 5% in the symptomatic one (cohort B). Median overall survival was 7 months in cohort A and 3.7 months in cohort B. Additionally, a few studies have suggested that brain metastasis patients may derive a benefit from combining radiation and ipilimumab. A retrospective study of 77 patients treated with radiosurgery at Yale New Haven hospital with or without ipilimumab use showed that overall survival was significantly longer for patients who received ipilimumab (21.3 vs. 4.9 months) [108]. Another retrospective study of 91 patients treated with SRS showed that patients who received ipilimumab had prolonged survival of 15.1 months vs. 7.8 months for patients who did not [109].

4.4.2.2 PD-1-Directed Therapy

Pembrolizumab and Nivolumab are both humanized antibodies directed against PD-1 that were first approved for the treatment of metastatic melanoma. Pembrolizumab was compared with ipilimumab in metastatic melanoma and showed improved 6-month PFS and response rates (RR 32.9% vs. 11.9%) [110]. Nivolumab was compared with dacarbazine and showed similar results (RR 40% vs. 13.9%) [111]. Patients with active brain metastases were excluded from both of these trials. A phase-II trial was conducted to assess the efficacy of pembrolizumab in patients with untreated brain metastases from melanoma or non-small cell lung cancer. Eighteen patients with melanoma were included in this study, and intracranial RR was 22%. Safety profile was acceptable, with the majority of adverse events being grades 1–2 [48]. Long-term follow-up of this study showed that responses were durable with patients being alive 24 months post treatment initiation [112]. While no dedicated clinical trial was performed to assess the efficacy of single-agent nivolumab in melanoma brain metastases, this agent was looked at in combination with ipilimumab in a phase-II trial. The intracranial response rate was 57%, similar to extracranial responses, with a 23% rate of complete response. The rate of grade 3 or higher toxicity was 55%, similar to what was observed in patients without brain metastases.

4.4.3 Genetic Characteristics of Melanoma Brain Metastases

The studies summarized above suggest that both classes of novel therapeutic agents have activity against melanoma brain metastases and, in some cases, may be a viable alternative to radiotherapy for previously untreated patients. However, multiple questions remain to be answered before defining clear guidelines incorporating these agents into clinical practice. In the case of targeted therapies, for example, it appears that intracranial response rates are lower than systemic responses and the duration of response is short. This may be related to lower drug availability in the CNS but also to different biological drivers and mechanisms of resistance in brain metastases compared to other sites. Sequencing analysis of matched primary tumors, extracranial and intracranial metastases from the same patients revealed that intracranial lesions are often genomically distinct from primary tumors and extracranial metastatic sites, and specific cellular pathways tend to be enriched in the brain [15]. Another study showed that the PI3K/AKT pathway is hyperactive in melanoma brain metastases as opposed to other metastatic sites, and preclinical data suggest that PI3K inhibi-

tion could be an effective therapeutic strategy for these patients [113]. Future therapeutic decisions driving targeted therapies may need to be guided not only by the genomic characterization/BRAF mutation status of primary tumors but also by analysis of intracranial metastatic sites. Immunotherapies, on the other hand, appear to have similar efficacy in the brain compared to extracranial metastatic sites and they seem to induce durable responses. However, the main question remains of what patient factors and biomarkers predict response to these agents and whether these factors are the same for intracranial and extracranial metastases. Since most of the dedicated brain metastases trials only included patients who were not highly symptomatic and had small lesions, it is unclear whether patients with larger lesions would benefit or should continue to be treated with surgery and/or radiation. Lastly, the benefit of the synergistic use of immunotherapies with SRS is yet to be determined, and it is unclear whether combination therapy increases the risk of toxicity including radiation necrosis and bleeding. Multiple clinical trials are currently underway in attempt to answer these questions, a list of which can be found in Table 4.3.

4.5 Conclusion

As the incidence of metastatic brain tumors is rising, brain metastases are becoming a growing challenge in the management of cancer patients. Although substantial efforts have been undertaken to improve a variety of multimodal treatment approaches, affected patients are still facing a poor median overall survival span after initial diagnosis. Genomic analyses in the past have yielded that brain metastases may have different actionable driver mutations than their underlying primary tumor and as different metastatic sites. However, different brain metastases within the same patient seem to be rather genetically homogenous. These findings open up new therapeutic strategies but also the urgent need to address major challenges like the development of brain-penetrant targeted agents. Various clinical trials are currently ongoing to evaluate numerous targeted agents and their efficacy in brain metastases patients. Nevertheless, we still need to further improve our understanding of brain metastasis formation, the molecular background of brain metastases, potential biomarkers, and resistance mechanisms in order to effectively treat patients in the future.

Table 4.3 Summary of currently active and recruiting clinical trials for melanoma brain metastases

Trial number	Phase	Location	Intervention
Targeted therapies			
NCT03332589	I	USA	E6201 (MEK inhibitor) in BRAF- or MEK-mutant tumors
NCT03430947	II	Germany	Vemurafenib + cobimetinib after SRS in BRAF V600-mutant tumors
NCT02452294	II	Germany	Buparlisib (PI3K inhibitor) in BRAF-mutant tumors after failure of BRAF inhibitor therapy, and BRAF wild-type tumors after failure of ipilimumab
NCT02974803	II	Canada	Concurrent dabrafenib + trametinib with SRS in BRAF-mutant tumors
Immunotherapies			
NCT02858869	I	USA	Pembrolizumab ± SRS
NCT02716948	I	USA	SRS + nivolumab in newly diagnosed patients
NCT02097732	II	USA	Ipilimumab induction in patients receiving SRS
NCT02374242	II	Australia	Nivolumab ± ipilimumab
NCT03728465	II	Germany	Nivolumab + ipilimumab in patients with ≥4 symptomatic brain metastases
NCT03175432	II	USA	Bevacizumab + atezolizumab in untreated patients
NCT02460068	II	Italy	Fotemustine vs. fotemustine + ipilimumab or ipilimumab + nivolumab
NCT02681549	II	USA	Bevacizumab + pembrolizumab in untreated patients
NCT03563729	II	Denmark	Pembrolizumab or ipilimumab + nivolumab in patients in need of steroid treatment
NCT03340129	II	Australia	Ipilimumab + nivolumab + salvage radiotherapy

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5 Brain Metastases Cell Partners and Tumor Microenvironment

Pedro García-Gómez, Neibla Priego, Laura Álvaro-Espinosa, and Manuel Valiente

5.1 Brain Vasculature: Blood-Brain Barrier, Vascular Co-option, and Angiogenesis

5.1.1 Crossing the Blood-Brain Barrier

Once cancer cells reach the brain vasculature, they become physically trapped in small capillaries [1] preferably with low perfusion [2] (Fig. 5.1). Hematogenous inoculation of cancer cells indicates that the time required to cross the vascular barrier in the brain is much longer than in other organs. It takes 3–7 days to a cancer cell to extravasate through the blood-brain barrier (BBB) [1, 3, 4] but only 12 h to extravasate in the lungs [3]. The molecular requirements to cross the BBB include general mediators of extravasation (i.e., HBEGF, COX2) [5] but also other specific to the brain including cell surface modifications [5], proteases [6], and secreted growth factors as well as extracellular vesicles [6–9].

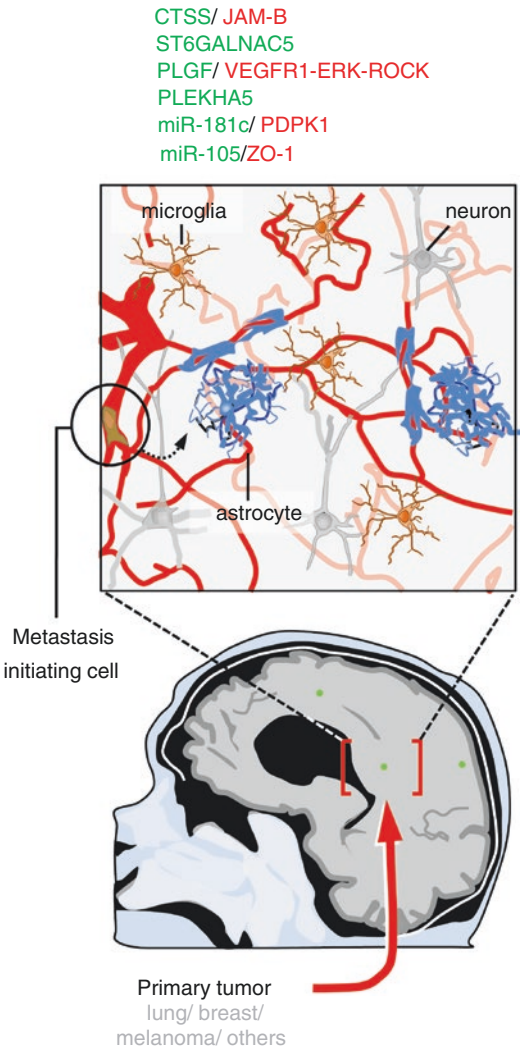

Fig. 5.1 Molecular regulation of blood-brain barrier (BBB) extravasation

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5.1.1.1 Surface Decoration

The surface of triple negative breast cancer cells requires a specific glycosylation pattern which is dependent on the sialyltransferase ST6GLNAC5. The expression of this molecule in primary breast tumors as part of a 17-gene signature (BrMS) correlates with an increased risk of brain metastasis in three independent cohorts of patients. Although the molecular mechanism by which this posttranslational modification in the membrane of metastatic cells is specifically required to transmigrate through the BBB is not known, loss of function experiments showed its importance to prevent the entry of cancer cells in the brain [5].

5.1.1.2 Proteolysis

Adherent and tight junctions are critical for the integrity of the BBB. Cathepsin S (CTSS) cleaves junctional adhesion molecules (JAMs), occludins and claudins, all of which are important for cell adhesion [6]. Among them, JAM-B is specifically expressed in brain endothelial cells. Proteolysis of JAM-B-dependent junctional adhesions of brain endothelial cells by cancer cell-derived CTSS increases the transmigration in an in vitro BBB model as well as in brain metastasis assays in vivo [6]. High expression levels of CTSS at the primary site correlates with decreased metastasis-free survival in the brain but not in bone or lungs.

5.1.1.3 Secreted Components

PLFG (placental growth factor) is a secreted molecule required for SCLC cancer cells to cross the BBB. Extracellular PLGF binds to the endothelial *VEGF* receptor-1 (VEGFR-1) that leads to the activation of ERK and Rho kinase (ROCK) activities. The activation of this signalling pathway in brain endothelial cells induces the disruption of occludin and ZO-1 dependent junctions, thus compromising BBB integrity [7]. Elevated levels of PLGF in the blood of patients with small cell lung cancer (SCLC) correlates with the development of brain metastasis [7].

Extracellular vesicles regulate different aspects of cancer [10, 11], including cell-to-cell communication [12]. MicroRNAs contained in extracellular vesicles produced by cancer cells located in the primary tumor influence the integrity of the BBB to facilitate extravasation of circulating tumor cells (CTCs). The microRNA miR-181c contained in cancer cell-derived extracellular vesicles is transferred to brain endothelial cells where it downregulates the expression of *PDPK1*, an essential factor for actin dynamics by its regulatory effect on cofilin phosphorylation. Defective actin dynamics impairs intracellular trafficking of multiple proteins required for the maintenance of brain endothelial cell intercellular junctions such as tight junction proteins, actin filaments, and N-cadherin [8]. Similarly, miR-105 contained in extracellular vesicles impaired the integrity of the BBB through an alternative mechanism involving the negative regulation of ZO-1 expression [9]. Consequently, the uptake of extracellular vesicles loaded with these miRNAs facilitates extravasation of CTCs through the BBB [8] and other vascular barriers [9]. Circulating extracellular vesicles containing miR-181c and miR-105 were more abundant in the serum of patients with metastatic breast cancer, including the brain [8, 9].

5.1.1.4 Other Mediators

Additional mediators of extravasation through the BBB that have been validated in patients includes PLEKHA5, which has been described in melanoma brain metastasis [13]. However, the mechanism by which this molecule facilitates transmigration of metastatic cells through the BBB remains to be solved.

5.1.1.5 Importance of Identifying Mediators of BBB Extravasation

The main interest lies on their potential as biomarkers to predict the risk of developing brain metastasis from the primary tumor [5–9, 13]. Although metastatic cells might have completed extravasation by the time the primary tumor is diagnosed, having determined the risk of metastasis might facilitate clinical decisions of future therapies aimed at preventing the development of symptomatic metastases.

5.1.2 Using Preexisting Vessels: Vascular Co-option

After completing extravasation, metastasis-initiating cells remain located at the perivascular niche [1–4, 14]. The physical interaction with the preexisting brain capillaries, termed vascular co-option [15], does not involve angiogenesis and mimics the cellular and molecular behavior of pericytes [3]. Vascular co-option has been described both clinically and experimentally in lung cancer, breast cancer, melanoma, colorectal cancer, and renal cancer metastasis in multiple secondary organs including the brain [1, 4, 14, 16–19]. The perivascular location gives cancer cells preferential access to oxygen, nutrients, and angiocrine factors produced by endothelial cells [4, 14, 20] (Fig. 5.2). The implications of vascular co-option include both aggressive growth but also states of latency and immune evasion [21, 22].

5.1.2.1 Dormancy/Latency and Immune Evasion

Breast cancer metastasis could be manifested many months and even years after the removal of the primary tumor [23]. Under these circumstances disseminated tumor cells (DTCs) enter in a state of dormancy until they start to re-grow secondary tumors [24]. The perivascular niche regulates dormancy of metastatic cells by different mechanisms. Thrombospondin-1 (*TSP-1*) has been described as an important angiocrine factor reducing tumor growth and angiogenesis [25, 26]. In brain metastasis, *TSP-1* induces dormancy of metastatic cells in the brain and other organs such as the bone and the lungs. Expression of *TSP-1* occurred in stable non-angiogenic brain endothelium that induces dormancy in cancer cells that are in the vicinity. On the contrary, downregulation of the expression of *TSP-1* and enhanced expression of the pro-tumor factors *TGF-β1* and periostin (*POSTN*), which

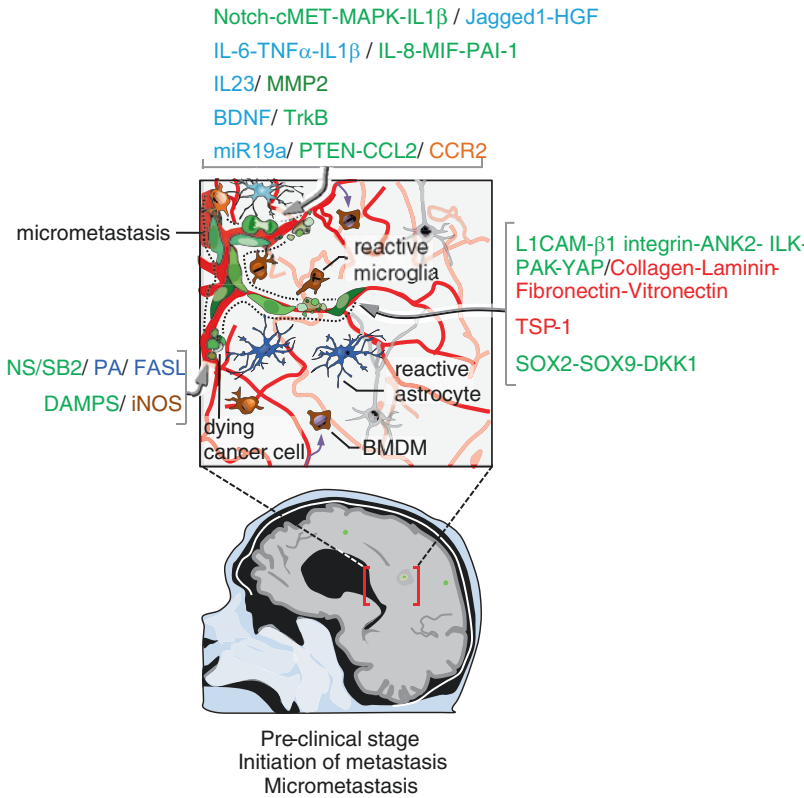

Fig. 5.2 Early stages of brain colonization

preferentially occurs in sprouting endothelial cells, favors tumor cell growth [22].

In contrast to a prolonged period of inactive cancer cell proliferation (dormancy), metastatic cells could develop transient states of active proliferation intermingled with periods of quiescence. This latency program is driven by the transcription factors SOX2 and SOX9 in combination with the inhibition of WNT signaling. When DTCs are latent, they downregulate the NK cell ligands UL16-binding proteins, PVR/CD155, FAS, and TRAILR, which allow them to avoid the action of the immune system and remain viable [21].

5.1.2.2 Molecular Regulation of Vascular Co-option

In spite of the involvement of the perivascular niche in latency or dormancy, the ability of metastasis-initiating cells to interact with preexisting capillaries is required for their outgrowth [1, 3, 4, 14]. Two cell adhesion molecules are key during this process including β1-integrin and L1CAM [4, 14]. Targeting them in cancer cells impairs the initial stages of metastasis colonization from breast, lung, renal, and colorectal cancer, melanoma, and lymphoma and prevents the development of macrometastases [3, 4, 14].

β1-integrin-mediated anchorage of cancer cells to components of the basal lamina (collagen I and IV, fibronectin, laminin, and vitronectin) of preexisting capillaries induces phosphorylation of focal adhesion kinase (FAK) leading to ERK1/2 activation, which is translated into an important survival signal that allows metastatic cells to resume proliferation in secondary organs [14]. L1CAM further promotes β1-integrin downstream signaling increasing the potency of its activation in an ankirin2-dependent manner, which leads to increased PAK1/2 phosphorylation and enhanced formation of filamentous actin. Increased actin filament formation induces cancer cell spreading along capillaries activating YAP-mediated mechanotransduction upon its nuclear translocation, which drives downstream gene expression reactivating proliferation [3].

5.1.2.3 Implications of Vascular Co-option

Although our knowledge on the interaction between metastasis-initiating cells and preexisting capillaries is very limited, the fact that known targets located at the cellular surface are critical to multi-organ metastasis from highly prevalent cancer types suggests an important therapeutic opportunity to prevent the development of metastasis, even if cancer cells have already disseminated out of the primary tumor.

5.1.3 Brain Metastasis-Associated Angiogenesis

5.1.3.1 Regulation of Brain Metastasis-Associated Angiogenesis

Neo-angiogenic vessels could be easily found in brain metastasis derived from non-small cell lung cancer [1, 27], where it is required to support the transition from micrometastasis to macrometastasis [1] (Fig. 5.3). However, this dependency might not apply to other cancer types such as melanoma, which continues to rely on co-optive growth along the vessels rather than in angiogenesis [1]. In breast cancer, the importance of angiogenesis in brain metastasis has been also reported [28, 29].

The expression of vascular endothelial growth factor (*VEGF*) by cancer cells is a major component to activate the angiogenic program in endothelial cells [30]. *VEGF* expression in breast cancer cells with tropism to the brain is increased compared to their parental counterparts [28], and its expression correlates with enlarged brain blood vessels and growth of brain metastasis from colon and lung adenocarcinoma [27]. Lower *VEGF* expression or the use of VEGFR inhibitors give rise to a reduction of angiogenesis subsequently limiting tumor growth in the brain [27, 28].

VEGF regulation is dependent on hypoxia, where *VEGF* is potently induced by the activation of the transcription factor HIF-1α [31]. Additionally, under normoxic conditions, activation of $\alpha_v\beta_3$ in cancer cells upon phosphorylation and inactivation of the translation repressor 4E-BP1 also enables *VEGF* expression and tumor angiogenesis [31].

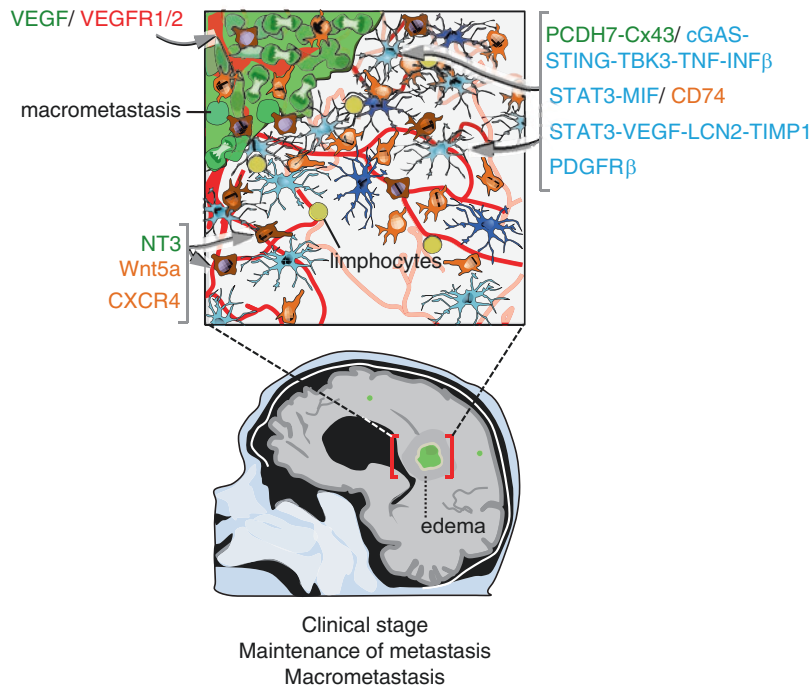

Fig. 5.3 Advanced stages of brain colonization

5.1.3.2 Therapeutic Approaches

More than 40 molecules have been identified to play a role in the formation of new blood vessels; however, almost all studies focused on VEFG and its receptors as it is the most potent angiogenic molecule. Actually, since 2004, ten drugs have been approved to target *VEGF* or its receptors [32]. Apart from *VEGF*, few studies focused on other angiogenic molecules in brain metastasis [33, 34]. Targeting neo-angiogenesis using anti-*VEGF* therapeutic antibodies was frequently used to treat brain metastasis; however, clinical trials did not report decreased incidence of brain metastasis or increased overall survival in patients [27, 29, 35–37]. Pre-clinical research suggests that anti-angiogenic approaches generate superior therapeutic responses when combined. For instance, drugs targeting VEGFR2 and HER2 in HER2-amplified breast cancer brain metastasis or inhibition of *VEGF* together with inhibitors against angiopoetin-2 work better than monotherapies [29, 38]. Alternatively, anti-angiogenic inhibitors can be used to impair the switch from micrometastasis to macrometastasis. This preventive scenario has been successfully validated in experimental models of lung cancer brain metastasis using anti-*VEGF* inhibitors that increased overall survival [35].

Inefficacy of anti-angiogenic drugs might involve the induction of a hypoxic environment that increases invasiveness and resistance to therapy. However, a higher proportion of mature vasculature compared to the primary cancer site may explain why brain metastasis is not so dependent on angiogenesis [37]. Alternatively, a c-Met/β1-integrin complex with pro-metastatic functions has been found to be blocked by the binding of *VEGF* to VEGFR2. This competitive negative regulation preventing the binding of c-Met to β1-integrin is suppressed by the use of *VEGF* inhibitors, explaining the increased cancer cell aggressiveness after anti-angiogenic therapy [33].

5.1.4 Influence of Brain Vessels on Anti-cancer Therapy in the Brain

The blood-brain barrier (BBB) acts as a barrier also for drugs and thus adds a significant caveat for the treatment of brain disorders [39, 40]. Even

if the brain is affected by multiple metastases, the BBB is not completely disrupted. Experimental evidences have probed that there is a high degree of inter-lesion heterogeneity regarding the compromise of the BBB integrity since only 10% of brain metastases reach therapeutic levels of non-permeable drugs [41, 42]. Thus BBB-permeable drugs seem to be the best strategy to target brain metastasis as suggested by pre-clinical approaches [42]. Alternatively, other efforts have been performed to overcome the impedance of some drugs to penetrate into the brain [43]. Pioneer studies addressing the similarities and differences regarding inter-lesion heterogeneity of the BBB have found pericytes as major contributors, where Desmin^{+} pericytes are enriched in highly permeable lesions [41, 44].

5.2 Astrocytes

Astrocytes are the most abundant glial cell type in the brain. They encounter and interact with metastatic cells during the process of brain colonization. When this interaction happens astrocytes become reactive, a cellular state induced when damage or injury is sensed by this cell type [45]. Cell-to-cell communication between cancer cells and reactive astrocytes includes direct physical contact but also interactions mediated by secreted molecules and vesicles. This crosstalk could have anti- or pro-metastatic consequences. The complex behavior of astrocytes surrounding brain metastasis could derive from the intrinsic heterogeneity of this cell type (Figs. 5.2 and 5.3).

5.2.1 Communication Through Secreted Molecules

5.2.1.1 Cancer Cells to Reactive Astrocytes

Secreted molecules can act as paracrine signals between cancer cells and reactive astrocytes. Cancer cells from breast cancer brain metastasis produce IL-1β upon c-Met and MAPK activation [46]. Cancer cell-secreted IL-1β upregulates the expression of Jagged 1 in astrocytes, which signals back to metastatic cells activating Notch pathway promoting self-renewal of metastasis stem cells [47]. Additionally, cancer cell-derived IL-1β induced the production of HGF by reactive astrocytes, which increases c-Met activation in metastatic cells in a feed-forward mechanism [47]. Accordingly, BBB-permeable Notch inhibitor compound E or c-Met inhibitor pterostilbene decreased experimental breast cancer brain metastasis [46, 47].

5.2.1.2 Reactive Astrocytes to Cancer Cells

Astrocyte-secreted molecules influence brain metastatic cells. Some of these secreted factors are found additionally in neuroinflammation, suggesting that the same molecular pathways that are induced during brain injury could be involved in brain metastasis. Lung cancer brain metastasis co-cultured with astrocytes influence the brain cell type through the production of IL-8, MIF, and PAI-1. Activated astrocytes respond to the cancer cell secretome producing IL-6, TNF-α, and IL-1β that stimulate tumor cell proliferation [48]. Moreover, astrocytes produce the neurotrophin BDNF that binds to TrkB receptor in HER2+ cancer cells supporting the colonization of the brain. Combined inhibition of HER2 with lapatinib and TrkB with cyclotraxin B reduces survival of HER2+ breast cancer brain metastatic cells more efficiently than each compound individually [49]. Other pro-tumorigenic signal produced by reactive astrocytes includes MMP-9 that promotes cancer cell invasion by degrading undetermined components of the extracellular matrix (ECM) and neo-angiogenesis by releasing *VEGF* from the surrounding matrix [18]. Melanoma brain metastatic cells induce the expression of different pro-inflammatory factors in reactive astrocytes including IL-23 [50, 51]. IL-23 produced by brain metastasis-associated reactive astrocytes induce the upregulation and secretion of MMP2 in cancer cells, which promote their migratory and invasive behavior [50]. Secreted MMP2/9 from reactive astrocytes can also increase cancer cell migration and modulate organization of actin stress fibers on ECM proteins (type I collagen, fibronectin, and laminin substrates) [52].

5.2.2 Other Types of Interactions

5.2.2.1 Direct Physical Contact: Gap Junctions

Astrocytes and cancer cells from melanoma, lung cancer, and breast cancer form gap junctions that support brain metastasis growth and contribute to their resistance to various chemotherapies by inducing key survival genes [53, 54]. Brain tropic cancer cells are enriched in PCDH7, which interacts with the same protocadherin in astrocytes to assemble Cx43-dependent gap junctions. Metastatic cells use these intercellular channels to transfer dsDNA and cGAMP, which are generated in high amounts in cancer cells secondary to proliferative or therapeutic stress, to astrocytes. In reactive astrocytes, cGAMP binds to STING triggering the expression of the inflammatory cytokines IFNα and TNF in a TBK1/IRF3-dependent manner. Secreted cytokines activate STAT1 and NF-κB pathways in brain metastatic cells that increase their resistance to chemotherapy [55]. The use of the gap junction inhibitors tonabersat or meclofenamate sensitizes brain metastasis to chemotherapy.

5.2.2.2 Extracellular Vesicles

The high secretory nature of reactive astrocytes includes the production of extracellular vesicles. Reactive astrocyte-derived exosomes contain miRNAs that are incorporated by tumor cells. miRNAs contained in the miR-17~92 cluster epigenetically downregulate *PTEN* expression in brain metastatic cells, leading to a deregulation of NF-κB that increases the secretion of CCL2. Cancer cell-derived CCL2 recruits Iba1^{+}-myeloid cells, which promotes proliferation and reduces apoptosis of metastatic cells [56].

5.2.3 Are Reactive Astrocytes Only Pro-metastatic?

Reactive astrocytes can also play an anti-tumor role effectively compromising the viability of breast and lung cancer brain metastasis-initiating cells [4] (Fig. 5.2). Plasminogen-activator (PA) secreted by reactive astrocytes surrounding micrometastasis converts neuronal-derived plasminogen into plasmin. Plasmin is lethal to cancer cells not adapted to this microenvironment by its action on solubilizing FASL, which acts as a paracrine death signal for cancer cells, and inactivating L1CAM, a cell adhesion molecule required for vascular co-option of cancer cells (see "Molecular Regulation of Vascular Co-option"). Serpins, especially neuroserpin and serpin B2, expressed in some metastatic cells allow them to block astrocyte-derived PA, thus protecting cancer cells from plasmin-mediated death [4].

5.2.4 Evidences of Reactive Astrocyte Heterogeneity

Astrocyte heterogeneity is not merely restricted to the functional aspects discussed above, but also to different molecular profiles. For instance, nestin is only present in some reactive astrocytes in the vicinity of brain metastatic cells [18]. Similarly, PDGFRβ^{+} reactive astrocytes were found intermingle with PDGFRβ^{-} ones in breast cancer brain metastasis [57]. The importance of dissecting astrocyte heterogeneity to understand the biology of brain metastasis has been confirmed by the transcription factor STAT3. STAT3 is present in a subpopulation of brain metastasis-associated reactive astrocytes from different primary origins. This subpopulation of reactive astrocytes is key for the viability of metastasis in experimental models and in patients [58]. Drugs targeting subpopulations of reactive glial cells have resulted in effective strategies to challenge brain metastases [57, 58].

5.3 Macrophages

5.3.1 Macrophages in the Brain

Brain metastasis-associated macrophages (BMAM) include those resident cells generated during embryonic stages (non-parenchymal macrophages and microglia) as well as blood-borne-derived monocytes, which only enter the

brain under pathological situations and generate bone-marrow-derived macrophages (BMDM) [59, 60]. Although detailed characterization of each subtype exists [60], they have not been studied as such in most reports from the literature. Reactive microglia and macrophages frequently display an ameboid morphology [61] and increased expression of F4/80, CD68, and Iba-1 and are frequently found surrounding and infiltrating metastases from lung, breast, melanoma, and colorectal cancer in patients and mouse models [18, 60, 62–66]. Differential CD45 expression levels can discriminate microglia ($CD45^{low}$) from BMDM ($CD45^{high}$) in mouse models but not in human brain tumors [60]. Tmem119 is enriched in both human and mouse brain metastasis-associated microglia, while CD49D/ITGA4 is only expressed in BMDMs [60, 67]. Future studies will benefit from the possibility of dissecting the specific contribution of each population of BMAM to brain metastasis.

5.3.2 Functional Contributions of BMAM

BMAM are not only variable in number, ranging from 4 to 70% of all cells within human brain metastases [68] or 5–30% in experimental metastases from breast cancer models [69, 70] but also regarding the functional contribution to metastasis. Both anti-metastatic as well as pro-metastatic functions have been described, similar to other glial components (see "Evidences of Reactive Astrocyte Heterogeneity") (Figs. 5.2 and 5.3).

Microglia cells surround cancer cells just after they extravasate, being one of the earliest responders to metastatic colonization [18]. Such behavior might reflect the protective role of microglia also described in other brain disorders. In fact, their ability to produce nitric oxide upon stimulation with danger-associated molecular patterns (DAMPs) eliminates metastatic cells in the brain [70, 71]. However, as reported also in other non-cancer-related brain insults [72], brain macrophages can contribute to aggravate pathological conditions. Metastatic cells avoid the anti-tumor behavior of BMAM by producing NT-3, an inhibitor of microglia activation [73], which favors brain colonization [70]. Pro-tumorigenic $CCR2^{+}$ macrophages are attracted to tumor cells in a CCL2-dependent manner, which is produced by cancer cells with reduced *PTEN* levels, facilitating the growth of brain metastases in vitro, ex vivo [74] and in vivo [56].

Instead of behaving as passive brain components, BMAM could promote brain metastasis invasion by producing Wnt5a [64]. Consequently, the use of Wnt pathway inhibitors could block the invasive capacity of cancer cells in the brain [64]. In addition to the crosstalk from BMAM to metastatic cells, the former alters gene expression in macrophages. Specifically, BMAM increase CXCR4 expression upon interaction with cancer cells [64]. Use of AMD3100 to disrupt CXCR4 signaling in macrophages negatively impacts cancer cell-mediated invasion in brain slice organotypic cultures [75]. At advanced stages of brain metastasis, BMAM use proteolytic activity of cathepsin S (CTSS) to support brain colonization. Targeting the protease genetically or with the inhibitor VBY-999 impairs brain metastasis formation. Interestingly, expression of CTSS is only enriched in BMAM at advanced stages of colonization while early on is produced by cancer cells [6].

5.3.3 Identification and Contribution of Subpopulations of BMAM to Brain Metastasis

Intrinsic differences between different types of BMAM are likely to be important to understand the variety of behaviors reported. Although limited, studies that have addressed this heterogeneity have noticed important aspects. Non-parenchymal BMAM that are located in the meninges are less sensitive to be reprogrammed into pro-tumor cells in comparison with those located within the brain parenchyma when both are under the influence of metastatic cells. Furthermore, flow cytometry analysis reveals superior activation state and antigen-presenting potential of the non-parenchymal BMAM [69].

Consequently, the existing ties between the location of brain macrophages and their ontogeny [76] might help to dissect their phenotypic complexity in brain metastasis. In addition, the sustained growth of cancer cells during brain colonization modifies the microenvironment inducing new signaling networks. Reactive astrocytes modified by the presence of cancer cells increase their production of MIF, which promotes the expansion of the $CD74^+$ pro-tumor BMAM. Targeting MIF-CD74 signaling with the BBB-permeable drug ibudilast impairs the growth of brain metastasis in organotypic cultures [58].

5.4 Adaptive Immune System in Brain Metastasis

5.4.1 Mechanism of Immune Evasion in Brain Metastasis

In spite of being an organ with limited lymphocyte infiltration, when metastases affect the brain this situation changes. Experimental brain metastases are infiltrated by activated $CD69^+$ or $CD25^+$ $CD8^+$ and $CD4^+$ T cells, $FoxP3^+CD4^+$ regulatory T cells and NK cells as detected by immunohistochemical analysis and flow cytometry [77–80] (Fig. 5.3). Myeloid-derived suppressor cells (MDSCs) and neutrophils also infiltrate brain metastasis lesions and interact with components of the adaptive immune system [81].

However, in spite of the presence of potential anti-tumor components, brain metastases have been reported to avoid immune attack. Initiation of the adaptive immune response involves antigen recognition. Brain metastasis cells from breast cancer and melanoma modulate the expression of components of the HLA class I antigen processing pathway to escape from $CD8^+$ T cell recognition. In fact, spontaneous brain metastasis could be increased by targeting *TAP1*, a component of the HLA class I antigen processing machinery (APM), since tumor cells become less susceptible to cytotoxic-mediated lysis by T cells [82]. Additional mechanisms to escape anti-tumor immunity have been described with the use of CpG oligodeoxynucleotides (ODN). The potent immunomodulatory activity of CpG ODN requires the activation of TLR9 that has to be strongly expressed by tumor cells in order to induce cell death and amplify the immune response. However, TLR9 levels in brain metastatic cells from breast cancer are not sufficient to initiate this mechanism in vitro upon treatment with CpG ODN, and thus metastasis in the brain are not as sensitive as cancer cells in primary tumors [77]. In addition to antigen presentation or the presence of other cell surface receptors, cancer cells modify the local brain microenvironment to impair anti-tumor adaptive immunity. Activation of the transcription factor STAT3 in reactive astrocytes induced by the metastatic cell secretome drives a paracrine mechanism by which PD-L1 expression but also secretion of molecules with immunosuppressive properties as well as components of the extracellular matrix (ECM) would be responsible for decreasing the activation state and cytotoxic activity of $CD8^+$ T lymphocytes surrounding established brain metastases [58].

5.4.2 Experimental Immunotherapies in Brain Metastasis

5.4.2.1 Immune Checkpoint Inhibitors

The immune system can be used to challenge the viability of metastatic cells in the brain of experimental models. Neutralizing antibodies targeting the immune checkpoint T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) are effective against melanoma brain metastasis. In order to achieve therapeutic benefit in the brain, the presence of concurrent extracranial disease is required. PD-1/CTLA-4 blockade increases T cell infiltration in the brain after a systemic expansion of $CD44^+CD62L^-$ effector $CD8^+$ T cells. Extracranial disease is needed to induce ICAM-1/VCAM-1 expression on brain capillaries to allow efficient extravasation through the BBB of incoming $CD8^+$ T cells [83]. In a mouse model of osteosarcoma brain metastasis, combined treatment of radiotherapy applied to the primary tumor and anti-PD-1 immune checkpoint blockade produced a strong

systemic anti-tumor response. In this model, increased numbers of $CD4^+$ and $CD8^+$ T cells and decreased MDSCs in peripheral blood were sufficient to reduce tumor burden in the brain [78]. Combination of locally applied radiation with anti-PD-1 antibody also increased $CD4^+$ and $CD8^+$ T cell infiltration in the brain and reduced regulatory T cells in the metastatic lesions [78].

5.4.2.2 Vaccines

In vitro irradiated B16 murine melanoma engineered to produce GM-CSF could be used as a vaccine when implanted subcutaneously in mice. Even if brain tumors are already established, the enhanced effector response induced on $CD8^+$ T cells is sufficient to prolong mice survival [79]. Similarly, vaccines based on lyophilized High Five™ insect cells engineered to produce IFNβ confers tumor-specific immune protection mediated by $CD4^+$ and $CD8^+$ T cells that home into the brain targeting melanoma brain metastasis [80].

5.4.2.3 Viruses

A retroviral replicating vector encoding cytosine deaminase and 5-FC induces systemic anti-tumor immunity by stimulating immune memory and decreasing MDSCs. When applied to a colorectal cancer brain metastasis model, this immune-based strategy increased mice survival [81]. Adenoviruses can also be used to transduce dendritic cells to express specific tumor antigens. The melanoma-associated antigen MART-l effectively activates cytotoxic T lymphocytes that target melanoma brain metastasis [84].

5.4.2.4 CAR T Cells

Chimeric antigen receptor-engineered T cells against HER2 (HER2-CAR T cells) delivered in the brain have a strong in vivo antitumor activity in orthotopically implanted breast cancer xenografts. When administered in the cerebral ventricles, HER2-CAR T cells are able to target multiple metastatic foci in the brain parenchyma as well as leptomeningeal deposits. Optimal CAR T cell responses against brain metastasis require different co-stimulatory signaling domains. The 4-1 BB co-stimulatory domain is more effective than the CD28 domain since it achieves superior T cells cytolytic activity, limits T-cell exhaustion, and promotes T cell proliferation [85].

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Liquid Biopsy Diagnosis of CNS Metastases

6

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Abbreviations

BCAAs	Branched-chain amino acids
cfDNA	Cell-free DNA
cfRNA	Cell-free RNA
circRNA	Circular RNA
CNAs	Circulating nucleic acids
CNS	Central nervous system
CNV	Copy number variation
CPs	Circulating proteins
CSF	Cerebrospinal fluid
CTC	Circulating tumor cell
ctDNA	Circulating tumor-derived DNA
CUP	Carcinoma of unknown primary
ddPCR	Digital droplet PCR
dsDNA	Double-stranded DNA
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EMT	Epithelial to mesenchymal transition
EpCAM	Epithelial cell adhesion molecule
ESMO	European Society of Medical Oncology
EVs	Extracellular vesicles
FC	Flow cytometry
FDA	US Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
HER2	Human epidermal growth factor receptor
IVD	Diagnostic medical device
LDH	Lactate dehydrogenases
LM	Leptomeningeal metastases
lncRNA	Long non-coding RNA
LOH	Loss of heterozygosity
miRNA	Micro-RNA
mRNA	Messenger RNA
NGS	Next-generation sequencing
NSCLC	Non-small cell lung cancer
PCR	Polymerase chain reaction
PPV	Positive predictive value
PSO	Particle swarm optimization
ssDNA	Single-stranded DNA
TEPs	Tumor-educated platelets
TME	Tumor microenvironment
WES	Whole-exome sequencing
WGS	Whole-genome sequencing

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6.1 Introduction

Central nervous system (CNS) metastases represent a major cause of morbidity and mortality in patients with solid tumors. Based on several studies, the occurrence is estimated to be between 9 and 17%, although the exact frequency might be higher [1–4]. The reported frequency of detection of CNS metastases is increasing. This can partly be explained by the development of more accurate methods that allow for earlier detection of CNS metastases [4, 5]. Another contributing factor may be the more efficacious treatment of cancer outside the CNS. As 25–30% of the CNS metastases are at first clinically asymptomatic [4], awareness of risk factors for their development should be taken into consideration for further screening of patients. For instance, lung cancer, breast cancer, and melanoma are tumors well known to have relatively high propensity to metastasize to the brain [6].

Neuroimaging is a very powerful diagnostic tool for further exploration of presence/absence of CNS metastases in case neurological symptoms develop or for screening of cancer patients. Also, this diagnostic tool allows for monitoring tumor progression and treatment response. An important disadvantage of neuroimaging techniques is that (at least so far) it is difficult to generate information on molecular characteristics of the tumor, while such information is increasingly important for optimal diagnosis and treatment.

Tissue biopsy remains the most definitive test to obtain detailed (histopathologic and molecular) information about the tumor [4]. Of note, the pathological analysis of a single biopsy provides "snap-shot" information, reflecting the tumor in a specific moment in time and not necessarily revealing all relevant information on, e.g., intratumoral (molecular) heterogeneity. Also, in a patient with multiple CNS metastases, often only one lesion is biopsied/resected. Not infrequently, information obtained in the primary tumor is extrapolated because the benefits of obtaining material of the CNS metastases itself are considered to not outweigh the costs including the negative side effects of the surgical procedure. For the same reason, repetitive sampling of CNS metastases for pathological analysis is generally avoided [4, 7, 8].

Several body fluids (especially blood and CSF) have been shown to carry tumor-derived material, analysis of which may provide valuable information for diagnostic, prognostic, predictive, and/or therapy monitoring purposes [9]. Liquid biopsy is a minimally invasive diagnostic approach that is based on the analysis of such tumor-derived information in "biofluids" and theoretically allows for real-time and repetitive assessment of, e.g., molecular features. Thereby, liquid biopsies have the potential to provide information in patients with (suspected) CNS metastases that is complementary to the neuroimaging and tissue analysis findings. Inclusion of liquid biopsy analysis as diagnostic tool may overcome some of the limitations of aforementioned diagnostic platforms currently implemented in the clinic.

6.2 Biosources in Liquid Biopsies

Several biofluids can be considered for a liquid biopsy, namely, serum or plasma (both from whole blood samples), CSF, urine, saliva, pleural effusion fluids, and bronchial washings. From these biofluids, different biosources can be analyzed that may contain information regarding the disease state of the sample's donor. The analysis of specific proteins, metabolites and electrolytes and of tumor cells in biofluids has already been performed since the nineteenth century in the realm of what is known as clinical biochemistry and cytopathology, respectively. In this respect, liquid biopsies are thus not that new. However, the liquid biopsy is nowadays generally understood as a term that includes a much broader spectrum of analyses. In cancer patients, biosources that are being investigated in liquid biopsies (Fig. 6.1) thus not only encompass circulating proteins (CPs), metabolites, and circulating tumor cells (CTCs) but also circulating nucleic acids (CNAs), extracellular vesicles (EVs), and tumor-educated platelets (TEPs).

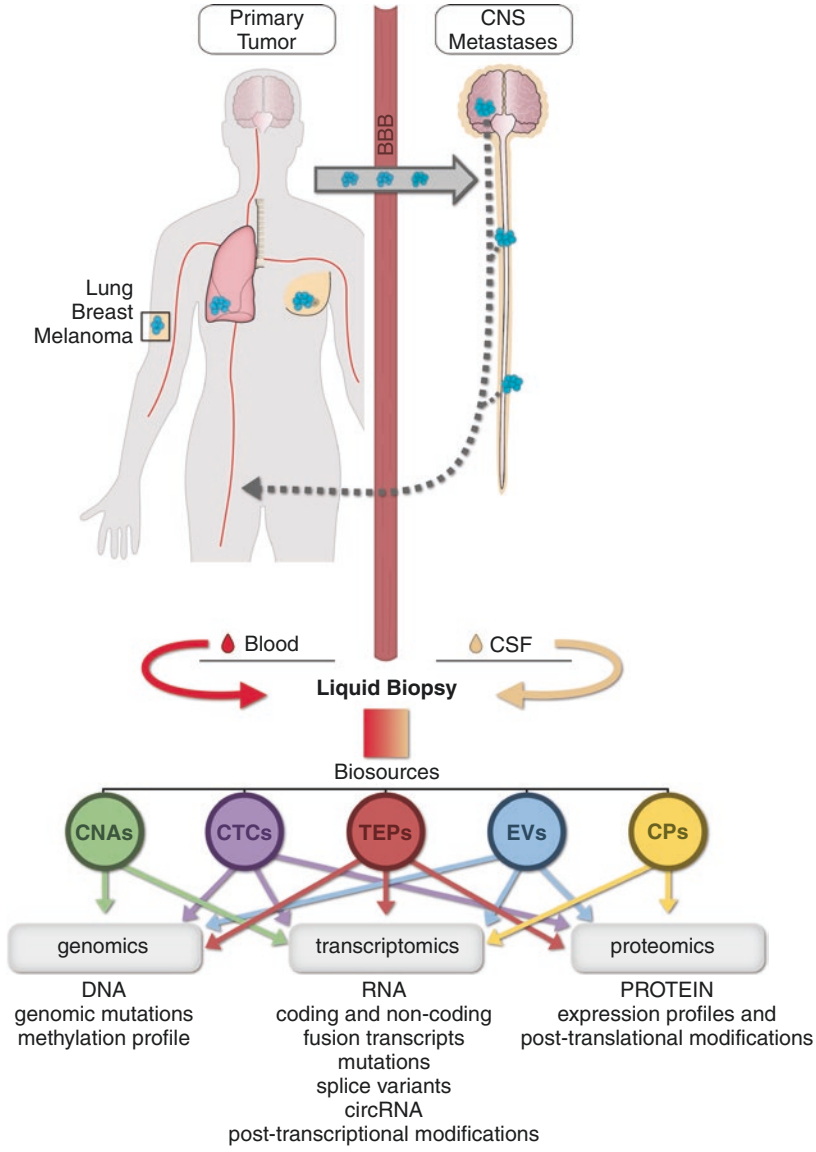

Fig. 6.1 Liquid biopsy in blood and CSF. Cells from primary tumors such as lung cancer, breast cancer, and melanoma can get released into the blood circulation and disseminate to the CNS (*arrow*), where they may form metastases in different compartments (intraaxial/CNS parenchyma, leptomeningeal, dura) and/or circulate in the CSF. Liquid biopsies for the diagnosis of these CNS metastases can be improved by thorough sampling and examination of bodily fluids (*depicted biofluids are CSF* (*yellow*) *and blood* (*red*)). After isolation of CNAs, CTCs, TEPs, EVs, or CPs (*grouped as biosources*) from these fluids, subsequent genomic, transcriptomic, and/or proteomic analysis (*each biosource is connected to the analysis approach by an arrow*) provides the information that can indeed be used for clinical purposes. Obviously, repeated CSF examination is more cumbersome for the patient than serial blood sampling. However, CSF is derived from the intradural compartment and thus in closer contact with CNS metastases than blood. The quality and quantity of tumor-derived information that is "seeping" from the intradural compartment into the blood circulation (*dashed arrow*) is likely highly variable and dependent on factors like nature, extent, and exact location of the metastases and further influenced by the degree of blood-brain barrier disruption. It is presently unclear how reliably such information in the blood can be used for the clinical diagnosis of CNS metastasis. Importantly, especially in patients in which the primary tumor and/or extradural metastases are still present, it can be expected to be very difficult to designate signals in the blood as being derived from the CNS metastatic disease. CSF may therefore continue to represent the more informative biofluid for liquid biopsy diagnosis of CNS metastasis

6.2.1 Circulating Tumor Cells

Primary and metastatic tumors often release some cells into the bloodstream, the so-called CTCs [10]. Thomas Ashworth is reported to be the first to describe the presence of CTCs in blood and their resemblance to the tumors from which they originated [11]. Obviously, detailed analysis of these CTCs may provide useful information about the neoplasms from which they are derived. Indeed, CTCs are now widely recognized as important not just because of their role in the metastatic process but also as a source of biomarkers when aiming for liquid biopsy diagnostics. While most CTCs circulate as single cells, microemboli containing clusters of CTCs have also been observed and exhibit distinct phenotypic and molecular characteristics in comparison to single CTCs [12–14]. Due to the short life of CTCs combined with the harsh conditions in the bloodstream, generally only a limited number of CTCs can be isolated from a blood sample [15]. However once captured the CTCs provide a unique source of tumor/cancer-derived biomarkers such as DNA, RNA, and proteins.

As summarized by Alix-Panabières and Pantel [16], CTCs can be harvested by different assays that use their biologic and physiologic properties. CTC assays generally start with an enrichment step that increases the concentration of CTCs and thereby facilitates their detection. The enrichment can be done by using particular antibodies, selecting cells from the blood using antibodies for epithelial markers (such as epithelial cell adhesion molecule (EpCAM)) or for mesenchymal markers. Furthermore, in order to remove different types of leucocytes from the samples, antibodies against CD45 can be used. Examples of techniques using the antibody positive selection approach are (ex vivo) CellSearch® system, MagSweeper™, EPHESIA CTC-chip, and Velcro-like device and (in vivo) CellCollector® and photoacoustic nanodetector [16]. Other assays exploit the physical properties of CTCs by using, e.g., filtration, Ficoll gradient, electric field, and/or single spiral microchannel.

After enrichment, several techniques can be used to further characterize CTCs:

1. Immunological technologies, using, e.g., anti-epithelial, anti-mesenchymal, anti-tissue-type-specific, and/or anti-tumor-marker antibodies. These immunocytochemical approaches can be applied using technologies like flow cytometry, CellSearch® system, and DEPArray®. The CellSearch system (Menarini Silicon Biosystems) is an FDA (US Food and Drug Administration)-approved detector for CTCs expressing EpCAM in patients with metastatic breast, prostate, or colorectal cancer. Until now, however, this technology is not very widely used because the test reveals prognostic rather than predictive information and does not (yet) have a major impact on therapeutic management.
2. Molecular RNA-based technologies, such as multiplexed reverse transcription (RT)-PCR combined with liquid bead array, allow simultaneous amplification and detection of multiple transcripts, using multi-parameter RT-quantitative PCR (RT-qPCR). Recent introduction of next-generation sequencing (NGS) techniques (e.g., RNA sequencing) will further advance to the molecular (transcriptomic) analysis and characterization of captured CTCs.
3. Functional assays: In vitro, viable CTCs can be detected by using the fluoro-EPISPOT technology which consists in the capture of proteins secreted by the CTCs by matrix-bound antibody at the bottom of the culture dish, followed by a second fluorochrome-conjugated antibody or by performing an invasion assay using CTC secreted molecules captured by the matrix (fluorescents). In vivo, xeno-transplantation of CTCs with stem cell properties to an immune-deficient murine host can subsequently give rise to tumor growth. However, this approach has limitations as it is highly dependent of factors such as the mouse strain [16] and the time needed to develop detectable tumor. Although these CTC-based functional assays so far lack robustness required for clinical implementation, their use in experimental settings is important for further elucidation of the tumor cell biology in a more representative way than in vitro.

6.2.2 Circulating Nucleic Acids

CNAs are extracellular nucleic acids (DNA, RNA) present in plasma, serum, lymphatic fluid, and CSF. Recent advances in molecular assays development such as NGS have significantly increased sensitivity and specificity of tests for identification of CNAs in liquid biopsy. Indeed, the detection of CNAs is nowadays a common diagnostic test for the diagnosis of fetal disorders and increasingly applied for molecular testing of samples from patients with cancer [17]. Relatively high concentrations of CNAs are related to cell apoptosis and can be detected in the plasma of cancer patients. CNAs encompass:

1. Circulating DNA: Cell-free DNA (cfDNA), including circulating tumor-derived DNA (ctDNA)
2. Circulating RNA: Cell-free RNA (cfRNA), including messenger RNA (mRNA), microRNA (miRNA), and circular RNA (circRNA)

ctDNA can be released by (primary and metastatic) tumors directly into the circulation as well as by CTCs. Most of the ctDNA fragments are considered to be released by apoptotic and necrotic cells. Non-malignant cells also release cfDNA. This has been identified as a confounding factor as in the circulation of cancer patients the ctDNA ratio is low compared to the total cfDNA [18]. The half-life of ctDNA in circulation is reported to be between 16 min and 2.5 h [19, 20]. Sensitive and specific technologies such as BEAMing, Safe-SeqS, TamSeq, and digital droplet PCR (ddPCR) have recently been introduced as approaches for the detection of ctDNA including the detection of point mutations. These technologies aim for detection of mutations in a set of predefined genes, like *KRAS* in the context of epidermal growth factor receptor (EGFR) blockade by antibodies. Also, untargeted approaches like array-CGH or whole-exome sequencing/whole-genome sequencing (WES/WGS) can be used. These latter technologies enable to screen the genome, establish copy-number changes, and discover new genomic aberrations, like those that confer resistance to a specific targeted therapy [21].

To date, there are two FDA-approved cfDNA-based tests: the cobas *EGFR* mutation Test v2 (Roche Molecular Diagnostics), which is a real-time PCR test for the qualitative detection and identification of mutations in exons 18, 19, 20, and 21 of *EGFR* in DNA derived from formalin-fixed paraffin-embedded (FFPE) tumor tissue or from plasma of patients with non-small cell lung cancer (NSCLC), and Epi proColon (Epigenomics AG), a qualitative assay for PCR detection of methylated Septin9 DNA, the presence of which is associated with colorectal cancer [22–24]. For these two tests, clinical utility has already been demonstrated.

Recent study by Mouliere and coworkers exploited the endogenous biological properties of cfDNA to reveal characteristic differences in fragment lengths of circulating DNA [25]. The analysis shows an enrichment of ctDNA in fragment sizes between 90 and 150 base pairs. By focusing on the size-selected cfDNA, they identified clinically actionable mutations and copy number alterations that were otherwise not detected. This interesting new approach could be exploited to further enhance sensitivity for detecting the presence of ctDNA in liquid biopsies [25].

Furthermore, studies addressing the methylation profiles of ctDNA from blood samples and matched tumor tissue of several cancers have shown that DNA methylation patterns of ctDNA and tumor tissue are well correlated [26]. Recently, new assays utilizing the enrichment of methylated ctDNA by immunoprecipitation-based protocol in combination with lower sequencing depth (i.e., cfMeDIP–seq) can greatly improve detection of ctDNA in small quantities of circulating DNA pool. This approach exhibited a robust performance in cancer detection and classification across an extensive collection of plasma samples from patients with several tumor types [27].

While clinical translation of ctDNA detection for cancer diagnosis has been attracting much attention, the analysis of circulating "free" RNA is difficult as plasma contains potent ribonucleases (i.e., RNases) that, in principle, destroy any free RNA. Nevertheless, tumor-derived extracellular RNAs are detectable in plasma and serum and

appear to be protected from degradation through formation of the protein-bound RNA complexes [28] and by RNA inclusion within EVs [29–31].

6.2.3 Extracellular Vesicles

EVs encompass two major classes: exosomes and shed microvesicles (sMVs). EVs are derived from endosomal multivesicular bodies. sMVs are larger than exosomes, and they are formed by direct outward budding of cytoplasmic protrusions [32]. EVs can be found in virtually all bodily fluids including blood, CSF, saliva, and urine [33]. Tumor cells have been shown to secrete more exosomes than normal cells [34]. The interest in EVs as a source of diagnostic information has rapidly increased by discovery that EVs have specific profiles based on the content of RNA (messenger RNA (mRNA), long non-coding RNAs (lncRNA), and miRNA), DNA (both double- and single-stranded DNA (dsDNA and ssDNA)), and proteins, thereby reflecting their cell of origin [35]. circRNAs have been also demonstrated to be enriched in exosomes [36]. Additionally, the pattern of integrins (i.e., transmembrane receptor proteins) on the surface of exosomes derived from tumor cells may provide insight into the organotropism of (future) metastatic behavior [37]. Altogether, this makes especially the "cargo," but maybe also the "package" of EVs interesting candidates for biomarkers for clinical cancer diagnostics.

6.2.4 Tumor-Educated Platelets

Platelets are anucleated cells derived from megakaryocytes in the bone marrow and lung [38]. These cells lack a nucleus; however they contain pre-mRNAs, miRNA, lncRNA, circRNA, mitochondrial DNA, a functional spliceosome, and a protein translation machinery [39, 40]. Platelets have a life span of approximately 7–10 days, after which they travel to the spleen and are degraded. Platelets interact with cancer cells in the tumor microenvironment (TME) and with CTCs that have entered the bloodstream. This interaction can alter the RNA expression of platelets and result in their "education," which can be detected with RNA sequencing or digital PCR. The potential of TEPs as a noninvasive biomarker for RNA biomarker panels was relatively recently advocated. In 2015 it was reported that RNA analysis of TEPs allows for discrimination of cancer patients from healthy individuals with high accuracy [41]. Two years later, high-accuracy performance of the test was reported when using a particle swarm optimization algorithm (PSO) for detection of cancer [42]. Analysis of tumor-derived biomarkers in platelets by digital PCR can also be exploited to predict therapy response [43].

However, larger series of patients, including those with early-stage cancer and with inflammatory or other non-neoplastic diseases, need to be analyzed in order to further assess the value of such a test for clinical practice.

6.2.5 Circulating Proteins and Metabolites

In the processes related to cancer development, growth, and metastases, proteins have a crucial role and represent the link between genotype and phenotype. Already for a long time, a lot of effort has been put into the discovery of protein-based biomarkers with clinical utility [44–47]. Because the majority of targeted therapies are directed against proteins, there is a strong focus in biomarker discovery on the measurement of such molecules [29]. Regardless of these efforts, so far only a few serum protein-based biomarkers (e.g., PSA, CEA, CA125, or CA19–9) were approved by the FDA for clinical use [29, 48].

Current advances in the development of multiplex technologies for proteomics discovery are enabling systematic analysis of a complete proteome as an integrated system. In particular, mass-spectrometry-based proteomics have generated comprehensive protein maps of all frag-

mented peptides obtained from a sample. Subsequent bioinformatics approaches, such as machine learning tools, have generated high-quality protein association maps providing insight into the composition, structure, and function of the proteome as a whole [49]. It is anticipated that these advances will greatly contribute to the fields of cancer diagnostic and precision medicine.

In addition to proteins, during tumor growth the metabolism of the cancer patient is altered and metabolite levels in circulation can potentially serve as biomarkers [50]. Examples are the levels of glycogen, branched-chain amino acids (BCAAs), pyruvate, insulin, and fatty acids. Based on a study on early development of pancreatic cancer, it was reported that currently unknown signals may induce cessation of long-term protein storage, thereby resulting in an increase of BCAAs in circulation [51]. In contrast, NSCLCs may rapidly take up BCAAs, causing a decreased BCAA levels in plasma [52]. Such studies suggest that more detailed analysis in liquid biopsies of proteins and metabolites may indeed be of additional value for the clinical diagnosis of cancer patients.

6.3 Liquid Biopsy Diagnosis of CNS Metastases

6.3.1 CSF Cytology

CSF represents a relatively easily accessible body fluid and a rich source of cancer-related biomarkers which indeed have already been exploited to some degree for the detection of CNS malignancies [53–55]. Abnormalities on routine CSF analysis are observed in more than 90% of the leptomeningeal metastasis (LM) patients. These include increased opening pressure (>200 m H_2O), increase of the number of leucocytes (>4/mm^3), elevated total protein amount (>50 mg/dL) and lactate dehydrogenases (LDH), and decrease of glucose concentration (<60 mg/dL) [56, 57]. Although the abnormal cell count and altered biochemical parameters in CSF may seem associated with LM, these alterations lack specificity for LM diagnosis as they can be found also in other neurological disease [58, 59].

For decades, CSF cytology has been the "gold standard" technique for the diagnosis of LM [60, 61]. According to the recently published guidelines of the European Society of Medical Oncology (ESMO), the results of this analysis are ideally reported as "positive" in the presence of malignant cells in CSF, "equivocal" when only suspicious or atypical cells are detected, or "negative" in the absence of malignant, equivocal, and atypical cells [56]. This assay has high specificity (>95%) but low sensitivity (<50%), which may lead to under-diagnosis of LM [62]. The volume of CSF sample is reported to have impact on the sensitivity of the assay: with a larger volume of CFS (>10 mL), the sensitivity may rise to 80–90% [55, 56, 58, 62–64]. After obtaining CSF, it is very important to process the sample as quickly as possible in order to avoid suboptimal preservation of cells [62]. The sensitivity of CSF cytology can be further increased by using Thinprep, which is a liquid-based cytology method. It ensures the collection of most of the cells in the CSF samples with minimal distortion and therefore permits an adequate preservation of the cellular and subcellular structure [65].

As CSF cytology is a non-quantitative method with relatively low sensitivity, it does not readily allow for monitoring disease burden. New technologies, such as flow cytometry (FC) and genetic analysis, may help to more accurately diagnose and monitor CNS metastatic disease. FC is a highly sensitive cytological technique, able to detect malignant cell in a small volume of CSF. It exploits fluorescent antibodies to identify expression of particular proteins on the surface of CTCs [55, 62]. FC is a fast and automated method which allows a more objective determination of CNS tumor burden [55, 66]. This assay can be performed by using standard FC equipment, facilitating its introduction in clinical analysis. FC has been shown to be very effective for detection of CTCs with epithelial origin in CSF by

using antibodies against EpCAM. One study even reported a sensitivity and specificity of up to 100% for the diagnosis of LM in patients with carcinoma, albeit in a small series. This EpCAM-based FC assay enabled detection of CTCs even in case of a cell count below 50 cells/ml (i.e., a situation in which the traditional cytology analysis is often negative) [58]. The CellSearch assay is a similar, EpCAM-based detection method. CellSearch is a FDA-approved assay for detection of CTCs in blood from solid tumors and has recently been modified for CSF analysis. EpCAM+ CTC detection by CellSearch was reported to have a sensitivity between 76 and 100% for the diagnosis of LM in patients with carcinomas such as lung and breast cancer [67–69]. CellSearch was also exploited for the detection and enumeration of CTCs in the CSF of melanoma patients with LM using particular melanoma cell markers. Again, the assay was reported to allow for quantitative analysis of CTCs, even in samples with a low number of malignant cells [70].

These new assays for detection of CTCs are not only more sensitive, specific, and quantitative than conventional CSF cytology but also can provide more detailed molecular information that may give new knowledge of the metastatic process in CNS. However, standardization of the procedures and proper validation studies with larger cohorts of patients and adequate control groups are needed for definitive assessment of these tests. Also, it is important to realize that (metastatic) carcinoma cells may lose EpCAM expression, e.g., in the course of epithelial to mesenchymal transition (EMT) [71]. This phenomenon may explain why in some cases EpCAM-based FC results were negative while traditional CSF cytology analysis was clearly positive.

6.3.2 Other CSF Biosources

CTCs are not the only cancer-related biosource in CSF in patients with CNS metastases. Cell-free circulating tumor DNA (ctDNA) is present in CSF as well and represents another useful source to obtain genetic information about (presence/absence of) metastases. Unlike CTCs, which require an isolation method based on protein surface markers, cell-free DNA can be easily isolated by centrifugation. Comparative studies using massive parallel sequencing showed that detection of CSF ctDNA has a higher sensitivity than analysis of ctDNA from plasma for the diagnosis of CNS metastases. Importantly, detection of CSF ctDNA complements the diagnosis of leptomeningeal carcinomatosis (confirmed by autopsy) where the results further show that the CSF ctDNA analysis provides detection of disease at a level not measurable by cytologic analysis [54, 72].

Genomic alterations present in CSF ctDNA of patients with known or suspected CNS metastases are generally consistent with the molecular profile that has been found in the primary tumor and/or plasma, but they also may encompass unique alterations [53, 73, 74]. For example, using NGS, Li et al. analyzed genetic alterations in primary EGFR-mutant NSCLCs of patients with LM as well as ctDNA in CSF and plasma of these patients. They found that unique genetic profiles of driver and resistance genes of LM, as CNVs of MET, KRAS and ERBB2, and LOH of TP53, were captured in CSF ctDNA [74]. Sequencing of CSF-derived ctDNA can also be used to obtain genetic information from patients with CNS metastatic disease of carcinoma of unknown primary (CUP) that indicates the origin of the tumor and thereby facilitates tailored management of the patient [75].

Changes in the molecular profile of CSF ctDNA may reveal changes of CNS tumor burden during treatment [72, 75–77]. Exploiting polymerase chain reaction (PCR) analysis to evaluate specific *EGFR* mutations in CSF, ctDNA may allow improved assessment of the efficacy of EGFR tyrosine kinase inhibitor treatment in patients with LM and/or brain metastases [76, 77]. Genetic analysis of CSF-derived ctDNA has also been reported to be useful in the follow-up of the treatment of patients with human epidermal

growth factor receptor (HER2) positive breast cancer metastatic to the CNS. Recently, Siravegna and coworkers emphasized the need for a paired analysis of plasma and CSF ctDNA in the management of such patients [72].

The measurement of tumor markers such as CAE, CA15.3, CA125, and CA19.9 in CSF is already used for quite some time for diagnosing CNS metastases in patients (suspect) to have cancer [55, 78, 79]. More recently, proteomic profiles in CSF were investigated as a potential biomarker source for this diagnosis. In particular high level of adhesion molecules (VCAM1 and ICAM 1), cytokines (IL-8, IL-18, PRAC, and IP-10), and other proteins (VEGF and SDF-1) were reported to have a potential diagnostic utility for discriminating cancer patients without LM and with LM [57, 79, 80]. Similarly, information on peptides derived from proteins involved in host-disease interaction, inflammation, and immune defense (serotransferrin, alpha1-antichymotrypsin, hemopexin, haptoglobin, and transthyretin) has been associated with presence of cancer [66].

Abnormal metabolic state of (CNS) cancer cells leads to an altered release of metabolites in the CSF. Mass spectrometry analysis has identified an elevated level of 20 and 5 metabolites in the CSF of patients with metastatic breast and lung cancer, respectively [81]. In addition, the microRNA signature may represent another source of biomarkers in CSF. Using Nanostring technology, Drusco et al. [82] investigated CSF total RNA in different groups of individuals/patients ("normal," benign tumor, glioblastoma, medulloblastoma, and lymphoma) and found differential expression of has-miR451, has-miR711, has-miR935, has-miR223, and has-miR125b among the groups. Teplyuk et al. [83] reported elevated levels of miR-10b and miR-21 in CSF of patients with brain metastases of breast and lung cancer and glioblastoma. In the same study, a signature of 7 microRNAs enabled discrimination between metastatic brain tumor and glioblastoma with an accuracy of over 90%. Additionally, overexpression of lung and breast cancer miRNAs that belong to the miR-200 family and their detection in CSF may hold the potential to discriminate between primary (e.g., glioblastoma) and metastatic brain tumors [83].

CSF thus represents a biofluid with a lot of potential for improved liquid biopsy diagnosis of CNS metastases. Obviously, CSF is derived from the intradural compartment and thus in closer contact with CNS metastases than blood. The quality and quantity of tumor-derived information that is "seeping" from the intradural compartment into the blood circulation is likely highly variable and dependent on factors like nature, extent, and exact location of the metastases and the degree of blood-brain barrier disruption [54, 72]. However, there is variable clinical reluctance to perform lumbar punctures for diagnostic reasons, partly because such a puncture may be cumbersome for the patients, and in particular if there is a strong concern of inducing brain herniation due to the presence of an intracranial mass.

6.3.3 Blood

As an alternative and much more easily accessible biofluid than CSF, blood should be considered. A study by Lohr et al. [84] demonstrated that up to 90% of mutations present in prostate cancer could be detected in blood samples using exome sequencing of immune-purified CTC in patients with metastatic prostate cancer. Furthermore, tumor-specific mRNA and miRNA could be detected in serum exosome preparations obtained from patients with glioblastoma [85]. Several early phase studies have been performed using blood for liquid biopsy diagnosis in patients with several types of cancers including CNS tumors [86]. Such findings suggest that indeed blood may be a potent liquid biopsy source for molecular diagnostics of metastatic disease. Importantly, however, especially in patients in which the primary tumor and/or extradural metastases are still present, it may be difficult to unequivocally designate signals in the blood as being derived from the CNS metastatic disease.

To establish the utility of blood-based liquid biopsy for detection of CNS metastases would require the analysis of longitudinal blood sample collection which will allow for not only the discovery of molecular biomarkers for CNS metastases but also for monitoring treatment response and distinguishing tumor recurrence from pseudoprogression. Furthermore, such studies may boost the identification of blood-derived biosources indicative of organ-specific pre-metastatic process [34]. Theoretically and ideally, for patients with HER2-positive breast cancer, melanoma, or non-small cell lung cancer (NSCLC) who have the highest risk of developing brain metastases, the major breakthrough would come from the design of therapeutic strategies that prevent CNS metastasis occurrence. Improved understanding of the molecular mechanisms that drive organotropism of metastases in combination with using blood as liquid biopsy source for early detection of (imminent) metastatic dissemination could ultimately even allow prevention of CNS metastases to occur.

6.4 Conclusions and Future Perspectives

Current standard approaches for the diagnosis and monitoring of CNS metastases, such as neuroimaging and tumor tissue analysis, suffer from several limitations. Neuroimaging does not (yet) provide molecular information and especially for the diagnosis of LM may have suboptimal accuracy. Surgical biopsies of the CNS can be challenging, and such a biopsy may not fully capture intratumoral heterogeneity [81]. Integrated analysis of CTCs, CNAs, EVs, TEPs, CPs, and metabolites can potentially help characterizing the global tumor genome and transcriptome. At the moment CTCs and ctDNA are the biosources most commonly studied in the context of liquid biopsies, with CSF and blood as "biofluids" in patients with CNS metastatic disease.

Minimally invasive procedures for sampling bodily fluids open the possibility for frequent "biopsies" and longitudinal follow-up of patients, thereby monitoring treatment efficacy and allowing for early detection of disease progression and timely adjustment of therapeutic management. Indeed, several studies have recently reported the usefulness of CSF sampling for detection of CNS metastases and treatment monitoring [53]. While CSF may be a more optimal source for detection of CNS metastasis-derived nucleic acids (ctDNA and RNA) and CTCs, it has the disadvantage that lumbar puncture is a more invasive procedure than drawing a blood sample by venipuncture.

It is still unclear which liquid biopsy biosource is best suited for early detection of CNS (micro)metastases. Also, the potential of liquid biopsy-based analysis on determining the exact location (intraaxial/CNS parenchyma, leptomeningeal, dura) and the extent of CNS metastases is currently unclear. Although several challenges remain, standardization and validation of currently available techniques (Table 6.1) is crucial for moving liquid biopsies towards clinical application for early detection of CNS metastases.

Additional pre-clinical studies addressing the biology of information obtained by liquid biopsies on, e.g., organotropism are required. Exosomes from "CNS-tropic" tumor cells were reported to fuse preferentially with brain endothelial cells. This indicates that the exosomal integrins pattern can potentially be used to predict organ-specific metastases [37]. Integrated analysis of both blood- and CSF-derived EVs may hold the information necessary to predict or to determine the location of metastases within the CNS. In addition, the work by Cohen and coworkers [87, 88] has emphasized the molecular power of combining ctDNA and protein biomarkers which significantly improved tumor detection accuracy. Integration of the data derived from different biosources may help to overcome the issue of low levels of individual molecular biomarkers and pave the way for

Table 6.1 Summary of methods and assays currently used for the detection and analysis of liquid biopsy (LB) biosources: CTCs, ctDNA/ctRNA, proteins, metabolites, EVs, and TEPs; methods to isolate and analyze blood-derived biosources for cancer detection and from CSF for CNS metastases detection

Biosource	LB methods/assays used for detection of cancer in blood	LB methods/assays used for detection of CNS metastases in CSF
CTCs	Ex vivo: • Flow cytometry • CellSearch® • MagSweeper™ • EPHESIA • CTC-chip • Velcro-like device • BEAMing PCR In vivo: • CellCollector® • Photoacoustic nanodetector In vitro: • EPISPOT	• Cytology • Flow cytometry • CellSearch®
ctDNA/ ctRNA	• NGS • Real-time PCR; cobas EGFR mutation Test v2 (Roche Molecular Diagnostics) • qPCR: Epi proColon (Epigenomics AG) • BEAMing • Safe-SeqS • TamSeq • Digital droplet PCR (ddPCR) • WGS • Array-CGH • Exome sequencing	• NGS • ddPCR • WES • CellMax cutting-edge SMSEQ • ARMS PCR • Real-time PCR • Nanostring
Proteins	• ELISA • Immunoassays	• MI-Assay • Radioimmunoassay • ELISA • Modular Analytics SWA MALDI-TOF/FTICR
Metabolites	• Mass spectrometry	• Mass spectrometry
EVs	• EVs number and size: Tunable Resistive Pulse Sensing and Nanoparticle Tracking Analysis • Antibody-based assays • Nano FC: Apogee	(*Not implemented for CNS metastases detection*)
TEPs	• ThromboSeq	(*Not tested in CSF*)

Assays recently approved by FDA for detection and analysis of liquid biopsy biosources are in bold

blood-based liquid biopsy diagnostics for CNS metastases as well.

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Preclinical Models of Brain Metastases

7

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Abbreviations

BBB	Blood-brain barrier
BLI	Bioluminescence
BTB	Blood-tumor barrier
ECM	Extracellular matrix
GEMM	Genetically engineered mouse model
GFAP	Glial fibrillary acidic protein
GFP	Green fluorescent protein
HER2	Human epidermal growth factor receptor 2
MRI	Magnetic resonance imaging
NOD	Non-obese diabetic
NSG	NOD-SCID-gamma
PDX	Patient-derived xenograft
SCID	Severe combined immune deficiency
TRD	Texas Red dextran

7.1 Introduction

Preclinical models are paramount to decipher molecular mechanisms of brain metastases and to develop new therapeutic options. The metastatic process, the movement to and progressive colonization of distant sites by tumor cells, comprises convoluted and dynamic stages: (1) the tumor cells migrate away from the primary tumor; (2) acquire the capacity to intravasate and survive in the vasculature; (3) extravasate at a distant organ to finally survive, potentially through a dormancy phase; (4) and proliferate [1]. At each stage, tumor cells need to circumvent immune surveillance and adapt to each new microenvironment [2]. In parallel, tumor-secreted factors and extracellular vesicles may actively prepare the distant organ, forming the premetastatic niche, to lodge and promote the growth of the arriving tumor cells [3]. Brain metastases evolve in a unique environment, composed of brain-resident cells, such as microglia and astrocytes, and insulated by the blood-brain barrier (BBB), a multicellular dynamic structure regulating exchanges between the blood and the central nervous system [4]. A neuroinflammatory response, consisting of reactive microglia and astrogliosis, is observed around the metastatic lesions [5], as well as infiltrated lymphocytes [6–8]. While parenchymal metastases are the most prevalent, cancer cells can also grow along the meninges, tissues covering the brain and spinal cord, and inside the cerebrospinal fluid, forming leptomeningeal metastases [9, 10]. As the cancer cells co-opt the brain vasculature [11] and proliferate, the BBB develops into the blood-tumor barrier (BTB) [12, 13]. Due to the complexity of the metastatic cascade and the singularity of the brain microenvironment, in vitro models are inadequate and

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limiting. Progress in understanding the brain metastatic process depends on the development of relevant animal models, mirroring the clinical observations and recapitulating the metastatic cascade in its dynamic milieus.

Judicious choices of animal models combined with appropriate quantitative tools are crucial to answering scientific questions. In this chapter, the first part will present the animal models and analytical technologies. While essentially murine, the animal models differ by the primary tumor of origin (lung vs. breast vs. melanoma); the species of the tumor cells (human vs. mouse), which will determine the immunocompetence of the host; and the injection/implantation site of the cancer cells. A description of the available quantitative and imaging technologies will subsequently follow. This first part will end with an overview of non-rodent in vivo models. Each model presents some advantages and inconveniences, determined by the scientific questions. In the second part of the chapter, we will review three main research questions: (1) understanding the biological underpinning of the metastatic progression, (2) identifying the bi-directional communication between the immune system and the tumor cells, and (3) evaluating therapeutic compounds. For each research question, the relevant animal models and experimental designs will be discussed.

7.2 From Technical Perspectives: Overview of What Is Available

7.2.1 Rodent Models

Mice are the most commonly used animals for brain metastasis research. Few genetically engineered mouse models (GEMM) efficiently form brain metastases [14–16]. Therefore, most studies have relied on allograft or xenograft models, i.e., injection of cancer cells into the animal (Fig. 7.1a). Historically, the earliest mouse models of brain metastasis were developed by injecting cancer cells directly into one of the carotid arteries. Following blood flow, the cancer cells are arrested in the brain vasculature where they can extravasate to form brain metastases. When injected in this manner, many cancer cell lines will efficiently form brain metastases even with-

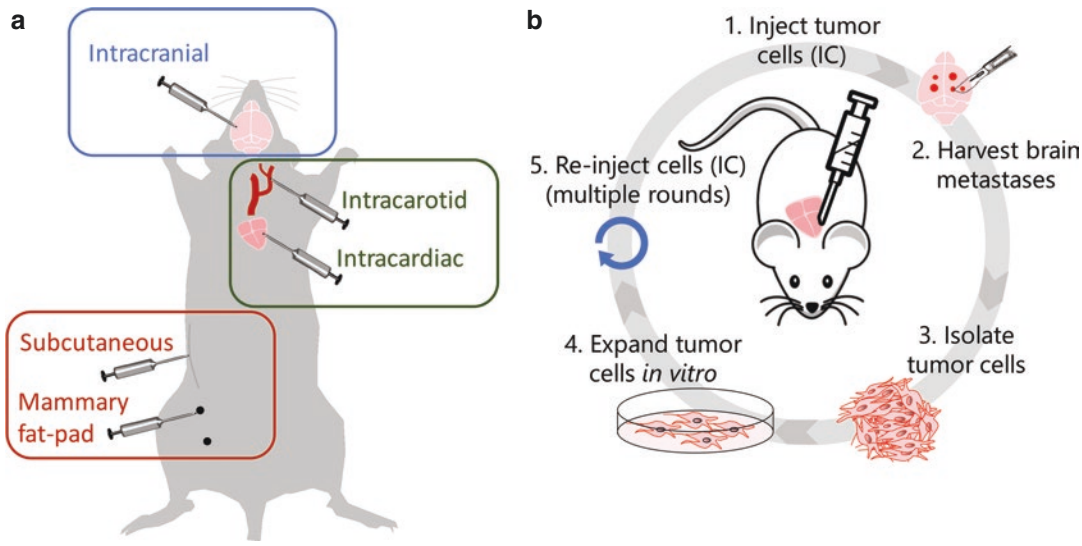

Fig. 7.1 Generation of brain-tropic cancer cells. (**a**) Various routes of administering cancer cells in rodents to study metastasis. (**b**) Establishment of brain metastatic variants by repeated cycles of cancer cell injection and brain dissection (I.C.: Intracardiac)

out prior in vivo selection for brain-seeking capacity (see below and Fig. 7.1b). The major advantage of intracarotid injections is that there is usually a high incidence of brain metastases without significant extracranial diseases. The majority of brain metastases will be found in the brain hemisphere closest to the injection site and the contralateral hemisphere can serve as a control. However, intracarotid injections are difficult and invasive. Mice must be deeply anesthetized during the entire procedure, which involves making an incision in the neck, blunt dissecting out the carotid artery from surrounding muscles, and then ligating the carotid artery after injection to prevent bleeding [17].

An alternative and less invasive method to introduce cancer cells into the arterial circulation is to inject cancer cells into the left cardiac ventricle. Under deep anesthesia, a needle is inserted through the chest wall and into the left ventricle of the heart. Although not necessary, injections may be performed with aid of ultrasound to increase success rate [18–20]. Cancer cells injected into the left cardiac ventricle are carried by circulation and distributed throughout the entire body. This route of injection is useful for determining the tropism of a cell line to specific organs. However, for poorly brain-tropic model systems, in addition to brain metastases, there is often significant metastatic tumor burden in visceral organs (e.g., lungs, liver, gut) and bone.

To increase brain metastasis incidence and burden, researchers have established variants of cancer cell lines with increased capacity to form brain metastases [11, 12, 21–32]. These cells were derived by first injecting mice with cancer cells via the carotid artery or left cardiac ventricle and then recovering the cancer cells that have colonized the brain. The recovered cells were expanded in culture and re-injected into another cohort of mice. This process of in vivo selection was repeated multiple times (Fig. 7.1b). When injected into circulation, these "brain-seeking" variants produce multifocal lesions of micro- and macro-metastases in the brain with varying histology. There are often fewer extracranial metastases due to increased tropism to the brain.

Similar methods have been used to develop a limited number of models of leptomeningeal metastases [25]. These models were developed by injecting cancer cells into the cisterna magna and then recovering cancer cells from the meninges of moribund mice. The recovered cells were injected into another cohort of mice and the process was repeated multiple times, with a last round of injection into the left cardiac ventricle. The resulting cancer cell variants show increased propensity to develop leptomeningeal metastases.

Both intracarotid and intracardiac injection models can only be used to study the latter part of the metastasis cascade. An ideal experimental model of brain metastasis would be one where cancer cells are injected orthotopically, such as in the mouse mammary fat pad for breast cancer or subdermal for melanoma. Unfortunately, few cancer cell lines metastasize efficiently to the brain from the primary site. Mice often succumb to extracranial morbidities before quantifiable lesions are present in the brain. Therefore, brain metastasis incidence and burden are usually low. These same limitations apply to GEMMs.

One method that is frequently used to generate models with high brain tumor burden is by direct injection of cancer cells into the brain. These intracranial models do not faithfully model brain metastasis because the cancer cells do not have to extravasate through the blood-brain barrier. However, they may be useful for studying how cancer cells interact with the brain parenchyma.

A hybrid orthotopic-intracranial model could be a powerful tool to dissect the role of extracranial tumors on intracranial metastatic tumor progression and response to therapy [33].

The past few decades have seen a dramatic increase in the number of mouse models of brain metastasis. Some of these models for breast, lung, and melanoma are listed in Tables 7.1, 7.2, and 7.3, respectively. Most brain

Table 7.1 Mouse models of breast cancer brain metastasis

Route of injection	Cell line[a]	Description	Species	Mouse strain	References
Intracarotid	MDA-MB-231	Triple negative breast cancer cell line derived from the pleural effusion of a women with metastatic breast cancer	Human	Athymic nude	[84]
	MDA-MB-231-Br3	A subline of triple negative MDA-MB-231 breast cancer cells that was selected in vivo (3 rounds intracarotid) for brain metastatic capacity	Human	Athymic nude	[21]
	BT474.Br	A subline of HER2+ BT474.m1 breast cancer cells that was selected in vivo (2–3 rounds, intracarotid) for brain metastatic capacity	Human	Athymic nude	[85]
	4T1	Breast cancer cells isolated from a spontaneous tumor in BALB/C mouse	Mouse	BALB/C	[86]
	4T1-Par3	A subline of 4T1 breast cancer cells that was selected in vivo (3 rounds, intracarotid) for capacity to form parenchyma metastases	Mouse	BALB/C	[22]
	4T1-Dura3	A subline of 4T1 breast cancer cells that was selected in vivo (3 rounds, intracarotid) for capacity to form dural metastases	Mouse	BALB/C	[22]
Intracardiac	COH-BBM1	HER2+ breast cancer cells isolated from resected brain metastases of a breast cancer patient at the City of Hope	Human	NOD/SCID	[87]
	CN34-BrM2	ER− breast cancer cells isolated from the pleural effusion of a patient at MSKCC that were subsequently selected in vivo (2 rounds, intracardiac) for brain metastatic capacity	Human	Beige nude	[23]
	MDA-MB-231-BrM2	A subline of triple negative MDA-MB-231 breast cancer cells that was selected in vivo (2 rounds, intracardiac) for brain metastatic capacity	Human	Athymic nude	[23]
	MDA-MB-231-BR	A subline of triple negative MDA-MB-231 breast cancer cells that was selected in vivo (at least 5 rounds, intracardiac) for brain metastatic capacity	Human	Athymic nude	[24]

Table 7.1 (continued)

Route of injection	Cell line[a]	Description	Species	Mouse strain	References
	MDA-MB-231-LeptoM	A subline of MDA-MB-231 triple negative breast cancer cells that was selected in vivo (first 3 rounds of injection into cisterna magna, then 1 round intracardiac) for capacity to form leptomeningeal metastases	Human	Athymic nude	[25]
	HCC1954-BrM	Subline of HER2+ HCC1954 breast cancer cells selected in vivo for capacity to form brain metastases	Human	Athymic nude	[25]
	HCC1954-LeptoM	Subline of HER2+ HCC1954 breast cancer cells selected in vivo (first 3 rounds of injection into cisterna magna, then 1 round intracardiac) for capacity to form leptomeningeal metastases	Human	Athymic nude	[25]
	231-Br-eGFP HER2/vector	MDA-MB-231-BR cells transduced with viral vector to overexpress human HER2	Human	Athymic nude	[35]
	MCF7-HER2-BR	A subline of MCF7-HER2 cells (originally from Dr. Dennis Slamon) that was selected in vivo (3 rounds, intracardiac) for brain metastatic capacity	Human	Athymic nude	[26]
	JIMT-1-BR	A subline of the HER2+ JIMT-1 breast cancer cells, which were originally derived from a patient that was resistant to trastuzumab. These cells were selected in vivo (3 rounds, intracardiac) for brain metastatic capacity	Human	Athymic nude	[27]
	SUM190-BR	A subline of HER2+ SUM190 inflammatory breast cancer cells that was selected in vivo (3 rounds, intracardiac) for brain metastatic capacity	Human	Athymic nude	[12]
	E22-1	A patient-derived xenograft (PDX) model developed by implanting a brain metastasis from a patient with triple negative breast cancer into NSG mice. Cells from the dissociated PDX tumor was then injected into mice	Human	NSG	[73]

(continued)

Table 7.1 (continued)

Route of injection	Cell line[a]	Description	Species	Mouse strain	References
	MDA-MB-231	Triple negative breast cancer cell line derived from the pleural effusion of a women with metastatic breast cancer	Human	NSG	[72]
	PyMT-BrM	A subline of TS1 cells that was derived from the primary tumor of a MMTV-PyMT transgenic mouse. These cells were selected in vivo for brain metastatic capacity	Mouse	FVB	[28]
	99LN-BrM	A subline of 99LN cells, which were derived from a lymph node metastasis in MMTV-PyMT transgenic mouse. These cells were selected in vivo for brain metastatic capacity	Mouse	C57BL/6	[29]
	ErbB2-BrM2	Cells isolated from a mammary tumor in an *ErbB2* transgenic mouse was selected in vivo (2 rounds, intracardiac) for brain metastatic capacity	Mouse	FVB	[11]
	4T1-BR5	4T1 breast cancer cells selected in vivo (5 rounds, intracardiac) for capacity to form brain metastases	Mouse	BALB/C	[30]
Orthotopic (mammary fat pad)	COH-BBM1	HER2+ breast cancer cells isolated from resected brain metastases of a breast cancer patient at the City of Hope	Human	NOD/SCID	[87]
	CN34-BrM2	ER- breast cancer cells isolated from the pleural effusion of a patient at MSKCC that were subsequently selected in vivo (2 rounds, intracardiac) for brain metastatic capacity	Human	Beige nude	[23]
	CN34-BrM2	ER- breast cancer cells isolated from the pleural effusion of a patient at MSKCC that were subsequently selected in vivo (2 rounds, intracardiac) for brain metastatic capacity	Human	NSG	[72]
	MDA-MB-231	Triple negative breast cancer cell line derived from the pleural effusion of a women with metastatic breast cancer	Human	NSG	[72]
	MDA-MB-231-Br3	A subline of triple negative MDA-MB-231 breast cancer cells that was selected in vivo (3 rounds intracarotid) for brain metastatic capacity	Human	Athymic nude	[86]

Table 7.1 (continued)

Route of injection	Cell line[a]	Description	Species	Mouse strain	References
	MDA-MB-453	Breast cancer cells isolated from the pericardial effusion of a breast cancer patient. These cells are weakly HER2+	Human	Rag2−/−Il2rg−/−	[88]
	4T1-Br4	4T1 breast cancer cells selected in vivo (4 rounds) for capacity to spontaneously metastasize from the primary mammary fat pad tumor to brain	Mouse	BALB/C	[31]
	4T1-BR5	4T1 breast cancer cells selected in vivo (5 rounds, intracardiac) for capacity to form brain metastases	Mouse	BALB/C	[89]
Intracranial	COH-BBM1	HER2+ breast cancer cells isolated from resected brain metastases of a breast cancer patient at the City of Hope	Human	NOD/SCID	[87]
	COH-BBM2	HER2+ breast cancer cells isolated from resected brain metastases of a breast cancer patient at the City of Hope	Human	NOD/SCID	[87]
	4T1	Breast cancer cells isolated from a spontaneous tumor in BALB/C mouse	Mouse	BALB/C	[90]

[a]Cells may be transduced with a viral vector to express a gene of interest, a reporter protein (e.g., GFP, luciferase) or shRNA

Table 7.2 Mouse models of lung cancer brain metastasis

Route of injection	Cell line[a]	Description	Species	Mouse strain	References
Intracarotid	NCI-H250	Small cell lung cancer cell line isolated from brain metastasis of lung cancer patient	Human	Athymic nude	[91]
	PC14-PE6	Cells isolated from pleural effusions of nude mice injected with PC-14 non-small lung cancer cells	Human	Athymic nude	[92]
	PC14Br (also Br4)	Subline of PC-14 non-small cell lung cancer cells isolated from brain metastases in immunodeficient mice	Human	Athymic nude	[92, 93]
	PC14	Non-small cell lung cancer cell line derived from a lymph node metastasis of a lung cancer patient	Human	Athymic nude	[84]

(continued)

Table 7.2 (continued)

Route of injection	Cell line[a]	Description	Species	Mouse strain	References
Intracardiac	H2030-BrM3	Subline of H2030 non-small lung cancer cells selected in vivo (3 rounds, intracardiac) for capacity to form brain metastases	Human	NOD/SCID or Athymic nude	[32]
	PC9-BrM3	Subline of PC9 non-small cell lung cancer cells that were selected in vivo (3 rounds, intracardiac) for capacity to form brain metastases	Human	NOD/SCID or athymic nude	[32]
	PC9-LeptoM	Subline of PC9 non-small cell lung cancer cells that were selected in vivo for capacity to form leptomeningeal metastases	Human	Athymic nude	[25]
	PC14-PE6 pGF1 Br2	PC14-PE6 lung cancer cells selected in vivo (2 rounds, intracardiac) for capacity to form brain metastases	Human	NOD/SCID	[94]
	Kras/ p53-393N1 (other less brain metastatic lines: -482N1, 2691N1)	Cell lines derived from lymph node metastases of GEMM that have lung adenocarcinomas with KRAS G12D mutation and loss of p53	Mouse	B6129SF1/J	[11, 95]
	LLC-BrM	Lewis lung cancer (LLC) cells selected in vivo (intracardiac) for capacity to form brain metastases	Mouse	C57BL/6	[25, 95]
	LLC-LeptoM	Lewis lung cancer (LLC) cells selected in vivo for capacity to form leptomeningeal metastases	Mouse	C57BL/6	[25]
Orthotopic (lung)	A549	Non-small cell lung cancer cell line derived from the lung adenocarcinoma of a 58-year-old patient	Human	Athymic nude	[96]
Intracranial	PC9	Non-small cell lung cancer cell line derived from a lymph node metastasis of a lung cancer patient	Human	Athymic nude	[97]

[a]Cells may be transduced with a viral vector to express a gene of interest, a reporter protein (e.g., GFP, luciferase) or shRNA

Table 7.3 Mouse models of melanoma brain metastasis

Route of injection	Cell line[a]	Description	Species	Mouse strain	References
Intracarotid	A375-Br	A subline of A375 melanoma cells that was *selected* in vivo (~3 rounds intracarotid) for brain metastatic capacity	Human	Athymic nude	[98]
	B16-BL6	Highly metastatic subline of B16 melanoma cells	Mouse	C57BL/6	[36, 59]
	K-1735 C4	Clone 4 of K-1735 cells derived from melanoma in C3H/HeN mouse induced by UV light and croton oil	Mouse	C3H/HeN	[36, 59]
Intracardiac	H1_DL2	GFP/luciferase-expressing subline of H1 cells originally isolated from a brain metastasis of a melanoma patient	Human	NOD/SCID	[44, 99, 100]
	B16-F10	Metastatic subline of B16 melanoma cells	Mouse	C57BL/6	[20]
	131/5B1	Cell line derived from brain metastases of mice injected with a lung metastatic variant of human WM239A cells	Human	Athymic nude	[20]
Orthotopic (subdermal)	131/4-5B1	Cell line derived from brain metastases of mice injected with a lung metastatic variant of human WM239A cells	Human	SCID	[101]
	131/4-5B2	Cell line derived from brain metastases of mice injected with a lung metastatic variant of human WM239A cells	Human	SCID	[101]
	RMS	Cells isolated from a spontaneous tumor in a Ret transgenic mouse	Mouse	C57BL/6	[57]
Intracranial	B16/Fluc/OVA	Subline of B16 melanoma cells expressing luciferase or ovalbumin (OVA)	Mouse	C57BL/6	[33]
	RMS	Cells isolated from a spontaneous tumor in a Ret transgenic mouse	Mouse	C57BL/6	[33]

[a]Cells may be transduced with a viral vector to express a gene of interest, a reporter protein (e.g., GFP, luciferase) or shRNA

metastasis models are xenografts of human cancer cells in immunodeficient mice such as the athymic nude, NOD/SCID, or NOD-SCID-gamma (NSG). The latter is widely used for patient-derived xenografts (PDX), in which tumor pieces of a patient are directly engrafted into mice [34]. Among xenograft models, most are triple-negative and HER2+ breast cancer, which are the two subtypes with the highest risk of brain metastases in breast cancer patients. Contrasting the breadth of brain metastasis models for breast cancer, there are few models for lung cancer and melanoma. Consistent across all cancer types is the lack of good immunocompetent models in which mouse cancer cells are injected into syngeneic mice. For example, nearly all breast cancer brain metastasis studies in immunocompetent mice use the parental or in vivo selected sublines of 4T1 mouse breast cancer cells in BALB/c mice.

The different models are very heterogeneous in their disease presentation. The duration from inoculation to morbidity can vary widely between models, ranging from weeks (e.g., 4T1-BR) to months (e.g., SUM190-BR). Further, the histology is very different. MDA-MB-231-BR (231-BR) [35] produce multiple metastatic clusters of micro- and macro-metastases at brain anatomical sites comparable to that found in human [5], SUM190-BR [12] produce multiple oval-shaped metastases, and MCF-7-HER2-BR [26] mainly produce a single massive lesion, which can form either leptomeningeal or intraparenchymal metastases. When injected into the carotid artery, B16-BL6 mouse melanoma cells almost exclusively form leptomeningeal metastases, whereas K-1735-C4 melanoma cells mainly form parenchyma metastases [36]. Each model should be viewed as one patient, and as such, multiple models should be used to validate an observation. Ultimately, the choice of model must be driven by the research question.

7.2.2 Procedures and Technologies for Quantitative Analyses of Metastatic Processes in Animal Models

Following the choice of the animal models comes the development of accurate and reproducible methods of evaluation and quantitation. Whether we want to investigate the different stages of the metastatic cascade, understand the interaction with the microenvironment, identify oncogenic drivers, or evaluate drug efficacy, preclinical evaluation requires a combination of histopathological procedures, advanced imaging technologies, and molecular biological approaches.

To analyze the metastatic burden at a specific time point, the gold standard procedure is to dissect the brain, perform step sections throughout the brain (Fig. 7.2a), and stain with hematoxylin and eosin (H&E). The metastatic lesions appear as cell clusters with large nuclei and darker cytoplasm (Fig. 7.2b 231-BR, 7.2c, SUM190-BR). In addition, imaging technologies provide an easy and fast evaluation of the metastatic burden. By transfecting the cancer cells with luciferase, the size of the metastases can be inferred by quantifying the bioluminescent (BLI) intensity (Fig. 7.2d). Expression of green fluorescent protein allows an estimation of metastatic involvement ex vivo, i.e., after dissection of the brain (Fig. 7.2e).

Multiple biological phenomena can be examined using fluorescent markers and immunostaining of brain tissues. The cancer cells can be manipulated to express a fluorescent protein, as described above; however expression of exogenous genes remains an issue in immunocompetent models. The blood vasculature can be visualized by injecting high molecular weight dye into the circulation, just before euthanasia. The integrity of the BTB is evaluated by injecting lower molecular weight fluorescent dyes, followed by the perfusion of the animal to wash

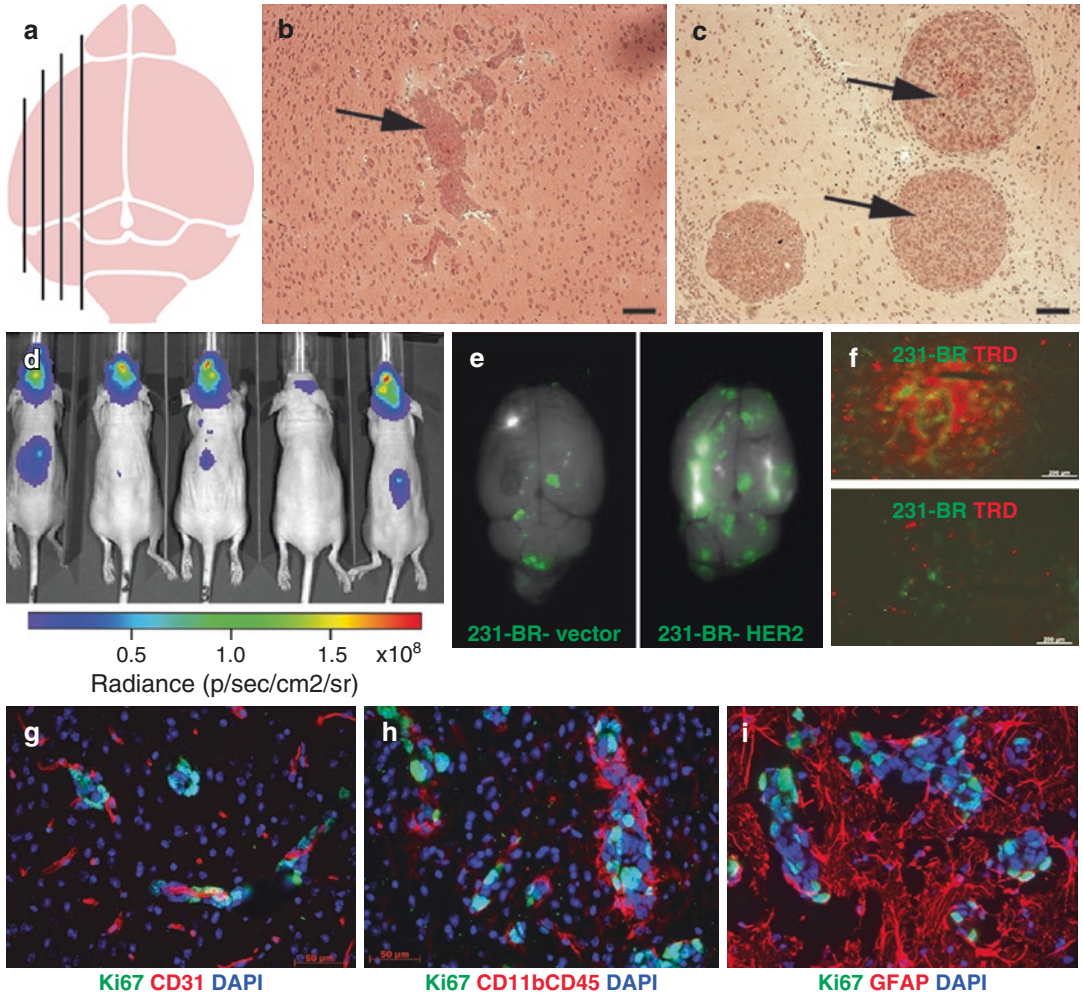

Fig. 7.2 Quantitative analyses of brain metastases in mouse models. (**a**) Schema of step section of the brain. (**b**) Hematoxylin and eosin staining of a brain slice from a mouse developing 231-BR metastatic lesions (black arrow indicates a large lesion among a metastatic cluster). (**c**) Hematoxylin and eosin staining of a brain slice from a mouse developing SUM190-BR metastatic lesions (black arrows). (**d**) Bioluminescence imaging of mice injected with tumor cells expressing luciferase. (**e**) Ex vivo imaging of mouse brains with metastatic lesions visualized in green. Left panel: brain colonized by the 231-BR-vector. Right panel: brain colonized by the Her2 overexpressing variant of the 231-BR. (**f**) Blood-Tumor Barrier (BTB) disruption evaluated with Texas Red dextran (TRD) diffusion. Mice with 231-BR brain metastases were injected with TRD (red) 10 minutes before euthanasia. The mice were perfused to remove the dye from the vasculature. Examples of metastatic lesions with highly (upper panel) and poorly (lower panel) permeable BTB. (**g–i**) Immunofluorescence staining of mouse brain tissue sections with metastatic lesions (clusteres of blue nuclei stained with DAPI). Proliferating cancer cells are stained with Ki67 (green). Metastatic cancer cells grew around (**g**) CD31+ blood vessels (red) and are associated with (**h**) CD45+/CD11b+ reactive microglia (red) and (**i**) GFAP+ reactive astrocytes (red)

out the vasculature. The permeability of the BTB is measured by quantifying the amount of dye exudation in the brain parenchyma. Figure 7.2f shows two different metastatic lesions, visualized by green fluorescent protein: extensive diffusion of Texas Red dextran (TRD) (3 kDa) is observed in the top panel and limited TRD diffusion in the bottom panel. Immunostaining of brain slices provides a snapshot of the metastatic process, allowing molecular characterization of the cancer cells and the microenvironment. In the three panels of Fig. 7.2g–i, the cancer cells appear as clusters of blue nuclei (DAPI staining); about 50% of the cancer cells proliferate, per Ki67 staining, in green. Different components of the microenvironment are highlighted in red: in Fig. 7.2g the cancer cells grow along the blood vasculature (CD31), and in Fig. 7.2h, i, activated microglia (CD11b/CD45) and activated astrocytes (GFAP), respectively, congregate around the metastatic clusters [5, 37]. For unbiased investigations, brain tissues can be analyzed through omics approaches, such as microarrays, RNA sequencing, single cell sequencing, or proteomics, providing exploratory endpoints through the analysis of large volumes of data.

In addition to in vivo imaging modalities, such as BLI as described above, intravital microscopy, magnetic resonance imaging (MRI), or nuclear imaging technologies such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) [38], offer the unique feature to perform longitudinal observations by collecting data over time in live animals. Intravital microscopy uses multiphoton laser-scanning microscopy through a cranial window implant, allowing visualization of cancer cell extravasation and outgrowth in the brain [39]. Similar to ex vivo investigations, the metastatic cells are visualized through the expression of a fluorophore and fluorescent markers can be injected in the live animal to highlight the vasculature. This technology can investigate different phenomena over time: (1) dormancy [40], i.e., the metastatic cells persist as a single cell or small micro-metastases but do not proliferate, (2) blood-tumor barrier (BTB) permeability [41, 42], and (3) drug efficacy by measuring tumor growth and regression [41]. For magnetic resonance imaging (MRI) technique, a contrast agent is required. To visualize metastases growth and/or dormancy, cancer cells are labeled with superparamagnetic iron oxide nanoparticles (SPION) or micron-sized iron oxide particles (MPIO) [43–45]. The vasculature permeability can be assessed by gadolinium diffusion [46].

Finally, to measure functional mechanisms of a gene candidate, the gene or molecular pathway of interest needs to be targeted, either using compounds to activate or prevent the gene function or using molecular biology to overexpress or downregulate the gene (e.g., RNA interference, knockout, or knock-in). Genetically engineered mouse models (GEMM) allow investigation of genes in the microenvironment, while manipulations of cancer cell lines provide a tool to elucidate tumor-specific mechanisms. Genetic manipulations are becoming more and more sophisticated with spatial (using a promoter expressed only on specific cells) and temporal (i.e., using a promoter regulated by a drug) control. The field is constantly evolving to create more sophisticated tools for better mechanistic evaluation of biological phenomena.

7.2.3 Non-rodent In Vivo Models

While several rodent models have been established as described previously, additional in vivo models can bring important insights into the metastatic processes. The zebrafish (*Danio rerio*) is a powerful model to study this biological phenomenon, as it is easily scalable, simpler to generate transgenics, ideal for in vivo imaging, and suitable for high-throughput drug screening. Zebrafish proves to be an ideal model system to study metastasis, owing to the transparency of embryos as well as adult animals (*casper* strain) [47], allowing tracing of even a single cancer cell through various stages of metastasis. Cancer cells face an extra hurdle of crossing the blood-brain barrier (BBB) while metastasizing to the brain. Transmission electron microscopy analysis and functional studies using fluorescent markers revealed that maturation of BBB in zebrafish

occurs between 3 and 10 days post-fertilization [48]. Accumulating evidences reveal histological, ultrastructural, and functional similarities between the mammalian and zebrafish BBB [49].

Of interest, a spontaneous model of melanoma brain metastasis has been developed. Melanocyte-specific expression of mutant $BRAF^{V600E}$ under the control of the *mitfa* promoter in *p53* mutant background led to 100% incidence of melanoma in zebrafish [50]. Using these animals, Heilmann et al. [51] generated fluorescently tagged zebrafish cell line (ZMEL1) that can be transplanted in transparent adult fish, and each step of the metastasis can be studied at single-cell resolution. They observed formation of metastases in various organs including the head. Stoletov et al. [52] showed that when 4T1 breast cancer cells were injected, Cx43 expression was necessary for extravasation and metastasis formation in the zebrafish brain.

Stoletov et al. [52] also used a chicken embryo model to study breast cancer and melanoma cell metastasis to the brain. They reported formation of multiple metastatic microtumors in the brain. In another study, human melanoma cells, transplanted in developing hindbrain of chicken embryos formed loose tumors within 4 days [53].

Overall, although non-rodent models for studying human cancer and metastasis pose a few major challenges such as they grow at a suboptimal temperature of 28 °C (in case of zebrafish) and exhibit significant anatomical/physiological differences compared to human, they come with advantages such as low cost, easy maintenance, simpler process of creating transgenics, and possibility of noninvasive high-resolution imaging.

7.3 Optimizing Experimental Designs Based on the Scientific Questions

Some general considerations apply to any experimental designs. Metastatic models are notoriously heterogeneous. Accounting for this variability, power analyses, need to be performed to define the minimum number of animals required to achieve statistical power. To avoid unconscious bias altering the evaluation process, the researcher performing the quantitative analysis needs to be blinded to the treatment groups. Ultimately, for any scientific question, the animal model needs to model the clinical manifestation.

7.3.1 Investigating the Metastatic Processes

Cancer cells from primary tumors disseminate and subsequently seed a new tumor in a distant tissue through a multi-step metastatic process. Initially, the tumor cells need to lose their cell-cell adhesion, acquire motility and ability to degrade the matrix to get into the circulation. In blood, the tumor cells that can evade shear stress, anoikis (programmed cell death induced by lack of cell/ECM attachment) and host's immune response, survive and home-in at secondary sites. Here, cells extravasate and, based on microenvironmental cues, either remain dormant or proliferate and colonize, to give rise to metastases. In case of brain metastasis, the cancer cells need to overcome an additional hurdle, where cells need to cross the BBB that protects the brain. Current preclinical models enable us to address various stages of metastasis independently.

The routinely used hematogenous models, in which cancer cells are directly injected into the circulation, do not allow studying initial stages of metastasis, such as primary tumor invasion and intravasation into the circulation. The genetically engineered mouse models (GEMM) and orthotopic models can be useful for studying earlier metastatic events. GEMMs show de novo tumor and metastasis formation, usually in an immune-competent animal, thus enabling us to model the whole process of metastasis. Unfortunately, most GEMMs exhibit low incidence of metastatic spread [54], and there are a very few GEMM models that metastasize to brain [14, 15]. In orthotopic models, the cancer cell lines or patient-derived tissue/cells are implanted into the same organ, such as mammary fat pad in the case of breast cancer [31, 55], lungs in the case of lung cancer [56], and

subcutaneous tissue in the case of melanoma [57, 58]; however, again, the incidence of brain metastasis is abysmal.

For investigating the late steps of brain metastasis, such as extravasation of tumor cells across the blood-brain barrier and colonization in brain parenchyma, numerous preclinical models are available. Various breast cancer [24, 27, 35], lung cancer [32], and melanoma [36, 59] mouse models have been reported, where tumor cells are injected directly into the blood (generally via intracardiac or intracarotid injection), which form brain metastases. These hematogenous models have been used extensively to study extravasation at blood-brain barrier [23, 60], tumor cell interactions with the microenvironment during colonization [28, 61], blood-tumor barrier modification [12, 13], and drug efficacy on established metastases [26, 62]. For assessing final events in brain metastasis, intracranial models, where cancer cell lines or patient-derived tissue/cells are implanted directly into the brain, have been utilized [63]. The intracranial models using tissue biopsies provide tumor characteristics closer to the patient as the tissue microenvironment remains partially intact. However, they recapitulate only the last sept of metastatic cascade. Finally, the premetastatic niche is a favorable environment at a secondary site, established by the primary tumor where it will subsequently metastasize [64]. Orthotopic [65] and hematogenous models [66] have been used to understand the establishment of premetastatic niches in the brain. It may be possible to provide a premetastatic niche by forming an orthotopic primary tumor in advance of hematogenous injection of tumor cells.

7.3.2 Characterizing Immune Response

There has been a renewed interest in studying the role of immunity in brain metastasis. This is partly due to the impressive response observed in some melanoma patients treated with checkpoint immunotherapy [67–69] and due to a growing body of data demonstrating that T cells are present in most brain metastases [6–8]. The choice of which mouse model to use depends on the specific immune subset one would like to study. Most brain metastasis models are xenografts of human cancer cells in immunocompromised mice. However, even immunocompromised mice have different severities of immunodeficiency. Nude mice lack functional T cells but the innate immunity is largely intact [70]. Therefore, they may be used to study innate immune cells such as microglia, macrophages, and natural killer (NK) cells. NSG mice not only lack immune cells of adaptive immunity (T- and B-cells), but they also have a defective innate immunity, most notably an absence of functional NK cells [71]. This may be one reason why tumor models that are poorly metastatic in nude mice can metastasize efficiently to the brain when injected into NSG mice [72]. The NSG mice may be particularly useful for modeling the entire metastasis cascade since cancer cells will spontaneously metastasize to the brain even from the primary site [72]. They are also useful for patient-derived xenografts [73], but because they are severely immunocompromised, there is very little contribution of the immune response to tumor progression. If the goal is to study the adaptive immune response such as to test novel combinations of immunotherapies, then immunocompetent mice must be used. Currently, syngeneic models are the only option since brain metastasis incidence and burden are too low in GEMMs. There are few syngeneic models but there is hope that more immunocompetent models will be developed. For example, there are now "humanized" mouse models in which immunodeficient mice are engrafted with human hematopoietic stem cells or peripheral blood mononuclear cells to develop a functional human immune system [71, 74–76]. These mice are prohibitively expensive, and, although untested, they may be useful for brain metastasis studies.

7.3.3 Preforming Experimental Therapeutics

Mouse models have been intensively utilized to evaluate drug efficacy [77]. In addition, radiation therapy is another treatment modality investigated in mouse models [78, 79]. Important considerations are needed to perform experimental therapeutics in models that are accurate, reproducible, quantifiable, and translatable to the clinical scenario. Experimental models, in which the cancer cells are injected into the heart or carotid artery, are often the models of choice as they allow brain metastasis development in 100% of the animals injected and provide sufficient tumor burden allowing quantification. Conventionally measurable endpoints are metastasis burden and survival. However, survival may result from brain metastasis involvement as well as from additional systemic metastases. Cognitive deficiency and systemic toxicity are also important endpoints that should be evaluated. Injection timing defines the clinical setting. In a prevention setting, the compounds are injected before the formation of micro-metastases, targeting single cells to prevent outgrowth, while a treatment setting aims at reducing established metastases [2]. The activity of a compound relies on its absorption, distribution, metabolism, and excretion (ADME). The physiology of the mice being different from the human's, especially in terms of metabolic enzymes processing the compounds, the pharmacokinetics need to be evaluated in mice and compared to clinical data. The drug concentrations need to be achievable in human. Drug formulation, modality of injection, and treatment schedule need to consider not only the pharmacodynamic properties of the compounds but also the clinical feasibility. For example, in the context of chronic daily treatment, oral gavage should be favored over intravenous injection. Through their renewal potential and stability in expressing human tissue features, patient-derived xenograft (PDX) models represent the ultimate efforts to mirror the clinical phenomena of general cancer and metastasis progression [34, 80]. Remarkably, PDX models were shown to recapitulate drug sensitivity/resistance patterns observed in the clinic, in the corresponding patient, highlighting the predictive value of the model. While the development of PDX models for brain metastases is still in its infancy [73, 81, 82], it is hoped that progress in the field will lead to brain metastasis PDX able to predict patient treatment response.

7.4 Conclusion

Animal models are invaluable tools to decipher complex physiological mechanisms. Preclinical models and imaging technologies are continuously evolving, such as improving patient samples engraftment in mice or humanizing the immune system of the mice [71, 74–76]. However, no single model can recapitulate perfectly the human disease. Success in understanding the clinical metastatic process lies in the multiplicity of models and approaches, using different metastatic lines and xenografts in different genetic backgrounds of the host. In vitro and ex vivo (e.g., brain tissue slices [83]) models can complement animal studies to refine specific mechanisms or perform high-throughput screenings. To ensure the predictive value of the animal models, validation with clinical specimens or correlation with epidemiological data should be regularly performed. Progress will be generated by collaborative efforts integrating different expertise and academic disciplines, orchestrating a bi-directional communication between the bench and the clinic.

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Part II

Clinical/Radiological Presentation and Management

8 Clinical Presentation of Brain Metastases

Annette Compter and Dieta Brandsma

8.1 Introduction

Brain metastases can result in a large variety of focal and nonfocal neurological symptoms. The clinical presentation of brain metastases is affected by the location, size and growth rate of the tumour. Any new neurological symptom or change in behaviour or cognition in a patient with cancer warrants further investigations for brain metastases. Focal neurological symptoms, like hemiparesis and dysphasia, can be caused by a direct effect of the brain metastasis or the surrounding oedema on the brain tissue or other neural structures. Most of these neurological symptoms occur within days to weeks, although an intratumoural haemorrhage can result in an acute onset of symptoms. Epileptic seizures occur in 10–20% of patients with brain metastases.

Nonfocal symptoms, like headache, nausea and disturbance of consciousness, can arise from increased intracranial pressure. When the tumour obstructs the flow of the cerebrospinal fluid (CSF), a hydrocephalus can develop, resulting in headache, nausea, sleepiness and an unsteady gate. The mass effect of brain metastases can lead to cerebral herniation. This may result in reduced consciousness and ultimately to death due to brainstem compression, unless high doses of Dexamethasone for surrounding oedema are given.

8.2 Focal Neurological Deficits

The presentation of patients with brain metastases varies widely, and symptoms can be either focal or nonfocal. There is a large variety in symptoms based on the location of the brain metastases. Most patients present with neurological symptoms with a subacute onset within days to weeks due to an increasing mass effect of the tumour on the brain and the surrounding oedema. An intratumoural haemorrhage can result in a sudden onset of headache, nausea, focal neurological symptoms and sometimes decreased consciousness. Melanoma, choriocarcinoma, thyroid and renal carcinoma brain metastases have a relatively high bleeding risk [1]. Furthermore, patients with brain metastases have a slightly increased risk of stroke due to vascular compromise by the tumour, venous sinus thrombosis and the hypercoagulable state of patients with a metastatic tumour.

Supratentorial brain metastases can result in motor, sensory, language or visual impairments depending on the size and location of the tumour. Hemiparesis results from a tumour in the motor cortex, internal capsule, corona radiata or brainstem. Tumours in the sensory cortex

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Table 8.1 Presenting clinical features in 1013 patients with brain metastases

Symptoms and signs	Percentage of brain metastases patients with symptoms or signs
Cognitive or mental status change	34
Headache	31
Weakness/paresis	24
Seizure	19
Ataxia	11
Visual symptoms	5
Nausea or vomiting	4
Other (e.g. bulbar symptoms, dizziness and syncope)	4
Sensory symptoms	2
Papilloedema	0.5
None	9

Adapted from Lassman, De Angelis. Brain metastases. Neurol Clin 2003 [2]

and thalamus usually give rise to sensory disturbances. Tumours in the dominant frontal and temporal lobe can cause aphasia. Compression of the midbrain by a metastasis can result in the Parinaud syndrome with an impaired upward gaze, light-near dissociation, convergence nystagmus and eyelid retraction. Common focal and nonfocal presenting neurological symptoms are shown in Table 8.1 [2]. Unfortunately, neither absence of focal symptoms nor a normal neurological examination does rule out brain metastases.

8.3 Nonfocal Symptoms

8.3.1 Symptoms of Increased Intracranial Pressure

Brain metastases can give rise to an increased intracranial pressure in various ways. Often mass effect on the brain is caused by the tumour itself and its surrounding vasogenic oedema. In addition, obstruction of the CSF flow, for example, due to mass effect of the brain metastasis on the third or fourth ventricle, can lead to hydrocephalus. Brain metastases can cause cerebral herniation, which is the shift of cerebral tissue from its normal location into an adjacent intracranial space as a result of mass effect. This displacement may result in reduced consciousness by direct or indirect pressure of the brainstem.

Patients with an increased intracranial pressure usually have symptoms of headache, vomiting, decreased vision due to papillary oedema and sometimes reduced consciousness due to compression on the brainstem or both hemispheres. When the intracranial pressure is very high, patients can experience ‘plateau waves’, a sudden rise in intracranial pressure that leads to headache or an altered consciousness for 5–20 min.

8.3.1.1 Headaches

Headaches in patients with systemic cancer can be caused by the antitumour treatment (e.g. hormone therapy), psychological factors, a preexisting headache syndrome (tension type headache or migraine) or can be due to cerebral or leptomeningeal metastases. Approximately 30% of patients with cerebral metastases present with headache. Tumours located in the posterior fossa and in the midline are more often associated with headache, probably partly due to the disturbance of the CSF flow. Other factors that are associated with tumour-related headache are the size of the tumour and the extent of cerebral oedema [1].

Classically, headaches associated with brain metastases are described as occurring at night or early in the morning, and pain tends to increase after Valsalva manoeuvres, such as sneezing or coughing. Headache can be positional with an increase in headache while bending over or standing up. Unfortunately, the majority of patients with brain metastases does not present with these classical headache symptoms, and often it is not possible to differentiate between tension-type headache, migraine or brain metastases based on the clinical characteristics of the headache in patients with systemic cancer.

In patients with brain metastases, headaches are often accompanied by other symptoms, in particular nausea and vomiting. In a prospective study of 68 patients with systemic cancer without known brain metastases, evaluation for headache showed brain metastases in 32% of patients.

Headache duration <10 weeks, emesis and pain not compatible with the tension-type all significantly predicted the presence of brain metastases [3]. In a more recent prospective study, 54 patients with systemic cancer with new headache or a change in pattern of an existing headache were evaluated; 54% were found to have brain metastases. Clinical predictors of brain metastases were emesis, gait instability and extensor plantar response at neurological examination [4].

8.3.1.2 Vomiting

Vomiting is most frequent in tumours of the posterior fossa, especially when there is extension in or compression of the fourth ventricle. Some patients may experience unexpected vomiting without preceding nausea, 'projectile vomiting'. In case of increased intracranial pressure due to brain metastases, vomiting often occurs in the morning.

8.3.1.3 Visual Symptoms

Patient can present with different visual symptoms due to the increased intracranial pressure. Papillary oedema can lead to complaints of reduced vision in one or both eyes. In case of high intracranial pressure from brain metastases, diplopia can result from compression on the third, fourth or sixth cranial nerve. Due to its length, the sixth cranial nerve is most often affected.

8.3.1.4 Reduced Consciousness

Reduced consciousness in brain tumour patients is mostly caused by obstructive hydrocephalus and cerebral herniation.

An obstructive or noncommunicating hydrocephalus in patients with brain metastases is caused by obstruction of the CSF flow in the ventricles from the mass effect of the tumour and surrounding oedema. Common places for obstruction of CSF flow in patients with brain metastases are obstruction of the fourth ventricle from mass effect in the posterior fossa and obstruction of the Sylvian aqueduct from supratentorial mass effect. The presentation of patients will depend on the speed of onset of the obstruction of the CSF. In an acute obstruction resulting from an intratumoural haemorrhage or rapidly growing metastasis, patients may present with subacute headache, nausea, blurred vision from papillary oedema and reduced consciousness. In a gradually progressive hydrocephalus, symptoms may be mild, including mild cognitive complaints and ataxia, while imaging shows a clear dilatation of the ventricles.

A communicating hydrocephalus is caused by obstruction of CSF flow through the subarachnoid spaces or impaired absorption at the arachnoid granules. In patients with brain metastases, a communicating hydrocephalus is mainly seen in patients with altered CSF composition by malignant cells or/and high protein content. This is mostly caused by concomitant leptomeningeal metastases or an intraventricular haemorrhage from brain metastases adjoining the ependyma. Figure 8.1 shows examples of (non) communicating hydrocephalus in patients with metastases of the central nervous system.

Cerebral herniation is the shift or herniation of brain tissue from one dural compartment in an adjacent compartment due to an increased pressure from a space-occupying mass (Fig. 8.2). Four well-known forms of herniation are subfalcine, transtentorial, central and tonsillar herniation. In subfalcine herniation, the cingulate gyrus is pushed under the falx. This is a common form of herniation that usually does not directly give rise to neurological symptoms. Seldom a frontal lobe infarction is seen due to the occlusion of the anterior cerebral artery that runs in close proximity to the falx. Transtentorial, or uncal herniation, leads to the displacement of the uncus, the mesial temporal lobe, over the tentorial edge. Patients with transtentorial herniation may present with a fixed and dilated ipsilateral pupil due to ipsilateral oculomotor nerve compression. Herniation of the uncus into the posterior fossa and the midbrain can result in impaired consciousness and contralateral hemiparesis by compression on the corticospinal tract. Compression on the posterior cerebral artery from transtentorial herniation can cause a cerebral infarction in the occipital lobe. In central

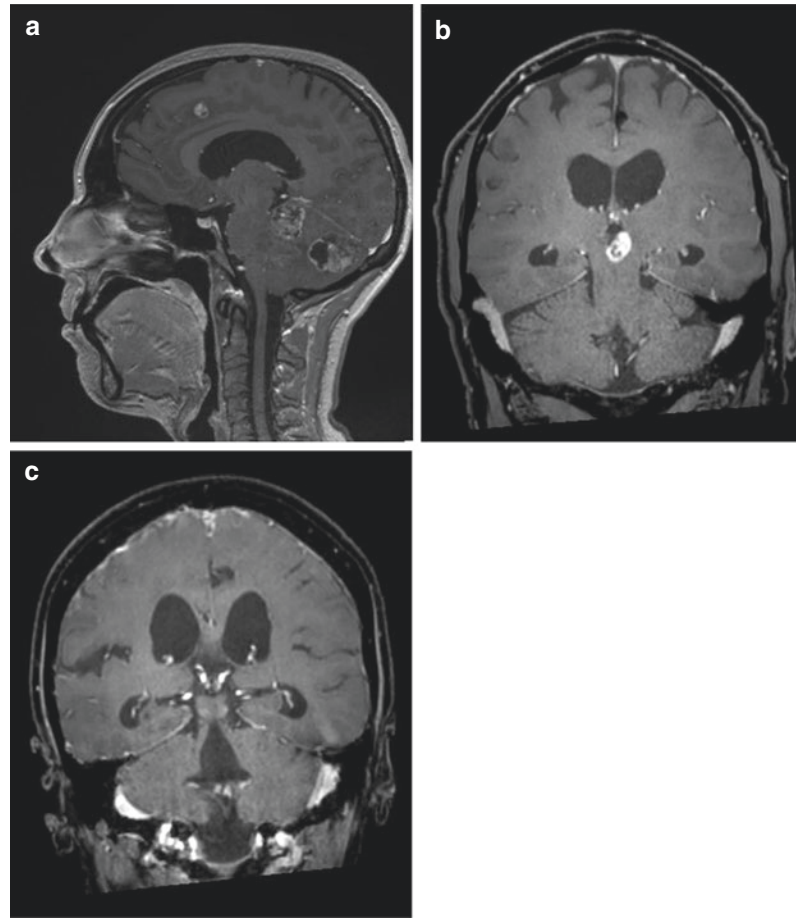

Fig. 8.1 Examples of (non)communicating hydrocephalus in patients with central nervous system metastases: noncommunicating hydrocephalus due to compression of the fourth ventricle caused by cerebellar metastases (**a**), noncommunicating hydrocephalus due to compression of the fourth ventricle caused by a brain metastasis in the mesencephalon (**b**) and communicating hydrocephalus in patient with both brain metastases (not shown on MRI) and cytology proven leptomeningeal metastases (**c**)

transtentorial herniation, the entire midbrain is herniated downwards due to generalized cerebral mass effect. Cerebellar-foramen magnum herniation, or tonsillar herniation, is the downwards displacement of the cerebellar hemispheres through the foramen magnum leading to compression on the caudal medulla. Clinical manifestations can be episodic tonic extension and arching of the neck, respiratory disturbances, cardiac irregularity and impaired consciousness and ultimately death.

8.3.2 Cognitive Symptoms

Cognitive symptoms and mental status change are common presenting symptoms in patients with brain metastases and are mainly depending on the location and size of the brain metastases [5]. The volume of brain metastases is stronger correlated with cognitive dysfunction than the number of brain metastases [6].

Cognitive dysfunction, including memory problems and mood or personality changes, is found in 65–90% of patients with brain metastases [7–9]. Most often multiple cognitive domains are affected, particularly in larger tumours affecting multiple brain regions.

Cognitive symptoms in patients with brain metastases are generally in line with the traditional understanding of functional neuroanatomy of the brain. Tumours in the frontal lobe may cause executive function disorders, resulting in difficulties in planning, inappropriate behaviour and affect. Patients with tumours in the dominant posterior frontal lobe can have an expressive aphasia due to involvement of the Broca area. Tumours in the dominant temporal lobe can result

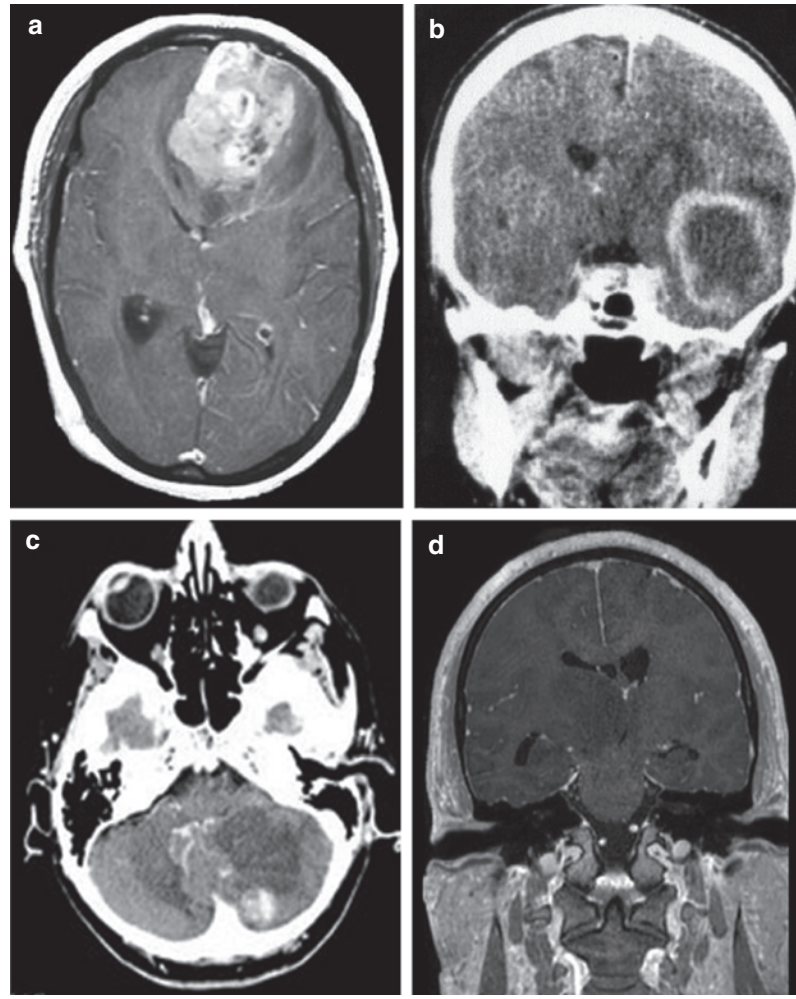

Fig. 8.2 Different forms of herniation caused by a brain tumour and surrounding oedema: subfalcine herniation of the cingulate gyrus under the falx (**a**), central herniation (tumour not visible on MRI shown, only cerebral oedema) (**b**), transtentorial herniation of the uncus of the temporal lobe over the tentorial edge, central herniation (tumour not visible on MRI shown, only cerebral oedema (**c**) and tonsillar herniation of cerebellar hemispheres through the foramen magnum (**d**)

in different language problems, including word-finding difficulties and understanding of speech and written text. Temporal lobe tumours in the non-dominant hemisphere can lead to problems in intonation and perceiving and expressing emotion in speech. Apraxia, dyscalculia and dyslexia can occur in patients with tumours in the parietal lobe. These patients can also have spatial orientation problems. Patients with tumours in the occipital lobe, especially in the non-primary visual cortex, may show difficulties in visual perception and memory of objects. Cerebellar tumours might also cause the so-called cerebellar cognitive affective syndrome, with disturbances in executive functioning, language deficits and personality changes.

8.4 Epilepsy

An epileptic seizure is among the most common presenting symptoms of brain metastases and has a significant impact on quality of life. Around 10–20% of patients with brain metastases present with an epileptic seizure [10–13]. Up to 35% of patients with brain metastases experience at least one epileptic seizure during the course of their disease [14]. The incidence of epilepsy in patients with brain metastases is lower than in patients with a primary brain tumour, probably due to the less-infiltrative growth of brain metastases and the inability to influence neuronal excitability biochemically [15]. Patients with brain metastases and an epileptic seizure have a high

risk of recurrence. Therefore, start of anti-epileptic drugs is advocated after a first epileptic seizure [15, 16]. Prophylactic use of anti-epileptic drugs in patients with brain metastases who never had an epileptic seizure is not recommended.

Epilepsy mainly results from supratentorial brain metastases, with the highest risk of epilepsy in cortical metastases. Patients with metastases in the frontal lobe, temporal lobe or insula have a higher risk of epilepsy than patients with metastases in other brain regions [17]. Incidence of epilepsy seems to vary by the underlying primary tumour, with the highest incidence in melanoma patients (67%) and lung cancer patients (29%) [18]. Induction of epilepsy is thought to result from tissue damage in brain metastases, such as necrosis and deposition of haemosiderin [19]. New-onset seizures in patients with known brain metastases may indicate progression of tumour or associated oedema or an intratumoural haemorrhage.

In patients with brain metastases, almost all epileptic seizures are symptomatic, and the ictal signs depend on the location of the metastasis. Most generalized tonic clonic seizures are secondary seizures with a focal onset.

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Epilepsy in CNS Metastases

9

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9.1 Introduction

Seizures represent one of the most frequent symptoms among patients with brain tumors being the highest incidence observed in lower-grade gliomas (up to 80–90%) [1]. Conversely, the incidence of seizures in brain metastasis is lower [2], ranging from 24% to 34% of patients in old series [3, 4], which were mostly CT-based, to 14.6% in a recent review performed on patients diagnosed in the MRI era [5]. This reduced incidence may be attributed to the higher sensitivity of MRI in detecting brain metastases at an earlier time point, when the lesions are smaller and the patients asymptomatic.

Most patients develop seizures at the time of presentation (78%), while 22% develop seizures later in the course of the disease [5]. The most common types of seizures are simple partial seizures, while complex partial seizures are less frequent (also in comparison to gliomas). Status epilepticus is rare.

Some studies have reported a tendency toward a better prognosis in patients with gliomas who have seizures [6, 7]; however, few data are available concerning the potential prognostic role of the presence of seizures in patients with brain metastases. In a recent paper [8] which has collected 823 patients with both primary and secondary brain tumors (518 metastases), no survival differences were observed among brain metastasis patients with or without seizures.

9.2 Risk Factors and Pathogenesis

Primary tumor type and tumor location are the most important factors associated with the risk of seizures in brain metastases [9]. Among the most frequent tumor types, the highest rate for seizures is observed in melanoma (between 11% and 33%) [10–12], followed by lung (12.5%) [13, 14]. Among less frequent primary tumors, seizure risk seems relatively high for ovarian cancers (15.3%) [15] and low for colorectal (7.7%) [16] and prostate cancers (4.9%) [17].

The incidence is higher for patients with metastases involving or adjacent to brain regions with high epileptogenicity, such as motor cortex and temporal lobe. Other factors associated with the risk of seizures are multiplicity of lesions and presenting headaches or cognitive deficits [18].

Very few is known concerning the pathogenesis of epilepsy in brain metastases [9]. Intracranial metastases tend to be well circumscribed compared to primary brain tumors which are more infiltrative in nature: given this difference in growth pattern, it is commonly thought that brain metastases are less likely to

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induce seizures than primary tumors. However, the mechanisms of epilepsy in brain metastases are poorly understood. Alterations in peritumoral microenvironment of the cortex, including inflammation, hypoxia, and acidosis, induce swelling and cell damage together with deregulation of sodium and calcium influx with generations of discharges. Brain metastases could cause disturbances in the metabolism of amino acid neurotransmitters in peritumoral areas and disrupt the balance between excitatory and inhibitory compounds. Moreover, brain metastasis induces local microcirculation impairment, thus leading to ischemia and seizures. Conversely, the mechanism of a denervation hypersensitivity seems to be more related to a chronic epilepsy as in slow-growing gliomas.

9.3 The Role of AEDs for Prophylaxis

Whether prophylactic use of anticonvulsants may be useful in patients with brain metastases is a matter of debate. Published series focusing on this topic have included patients with both primary and secondary brain tumors [19, 20] drawing the conclusion that for adult patients with brain tumors, who have not experienced a seizure, routine prophylactic use of anticonvulsants is not recommended.

In 2010 Mikkelsen et al. [21] performed a systematic review on the role of prophylactic anticonvulsants in the management of brain metastases. The literature search resulted in 16966 papers; however, four studies only were subject to full text screening, and three of them were further excluded as they lacked baseline data for brain metastases patients. Ultimately, one study [22] met the eligibility criteria and reported a randomized controlled study comparing anticonvulsants versus no anticonvulsants in 100 patients with newly diagnosed brain tumors. Sixty patients had brain metastases of whom 26 were treated with anticonvulsants (25 phenytoin and 1 phenobarbital) while 34 received no anticonvulsants. The trial was terminated early because the seizure rate in patients who did not receive prophylactic treatment was only 10%, and there was no significant difference between those who received anticonvulsants and those who did not.

In 2013, Wu et al. [23] conducted a prospective, randomized trial examining the use of phenytoin for postoperative seizure prophylaxis in patients with supratentorial brain metastases or gliomas undergoing surgical resection. At the time of trial closure, 123 patients were randomized and 77 were metastases. The incidence of seizures was 18% in the observational group compared with 24% in the prophylaxis group ($p = 0.51$). Moreover, routine phenytoin administration was associated with a significant drug-related morbidity. The authors concluded that the low baseline rates of perioperative seizures in patients with brain tumors raise concern about the routine use of prophylactic phenytoin in this patient population.

Both the American Academy of Neurology (AAN) [19] and the Association of Neurological Surgeons (AANS) [21] recommended against routine prophylaxis with antiepileptic drugs for patients with primary brain tumors or brain metastases without a history of seizures. More recently, the European Association of Neuro-Oncology (EANO) has reported in the Guidelines on Brain Metastases the same statement [24].

Despite the wide agreement within the scientific community, some open issues still remain, such as the potential benefit of seizure prophylaxis in some subgroups of patients at higher risk and the impact of prophylaxis employing newer antiepileptic drugs. In this regard, Goldlust et al. [12] reviewed the records of all melanoma patients with brain metastases treated at Memorial Sloan-Kettering between May 2006 and October 2008. They collected 109 patients: seizures led to diagnosis of brain metastases in 13% (14/109), while 20% of patients (22/109) developed seizures during the disease course. Risk of seizures in this subgroup of patients

was significantly increased in case of hemorrhagic or multiple supratentorial lesions or brain metastases. Patients on prophylaxis with antiepileptic drugs, consisting of monotherapy with levetiracetam in most of patients, had a 0% risk of developing seizures by 3 months, while patients who did not receive prophylaxis had a 17% risk. These data suggest that, at least in this subgroup of patients, prophylaxis with a newer antiepileptic drug may have a role in the prevention of seizures, but prospective studies on a larger patient population are needed.

9.4 The Role of AEDs for Treatment

Limited data are available concerning the efficacy and safety of older and newer antiepileptic drugs in patients with brain metastases and seizures. More in general, there is no evidence that a specific antiepileptic drug is more effective than another, and randomized trials are lacking. The availability of new classes of antiepileptic drugs, which are better tolerated and result in a better compliance, has increased the spectrum of pharmacotherapy.

Table 9.1 summarizes the main studies on the use of antiepileptic drugs (mostly on levetiracetam) performed more in general in brain tumors in the last 10 years. Series are heterogeneous in terms of histology, combining primary and secondary brain tumors, different phases of the disease and different types of seizures. Overall, the number of patients with brain metastases is limited in each series (from 2 to 30); moreover, the rate of seizure response and seizure-free is extremely wide, ranging from 20% to 100% and from 27% to 77%, respectively [25–28].

To date, two small series only have been published focused on the use of antiepileptic drugs in a selected population of patients with brain metastases. Newton et al. [26] analyzed in a retrospective series of 13 patients with brain metastases (6 from breast, 5 from lung, and 2 from melanoma) the efficacy and tolerability of levetiracetam. The median dose was 1000 mg/day. Seizure frequency was reduced to less than 50% compared to baseline in 100% of the patients, and in 77% of patients a complete response was observed. The most common side effects were somnolence and headache. In a more recent, prospective small series, Maschio et al. [28] reported the results in terms of efficacy and tolerability of three different AEDs (levetiracetam, oxcarbazepine, topiramate) employed in monotherapy in 30 patients with brain metastases. With a median follow-up of

Table 9.1 Studies reporting the efficacy of new AEDs in brain metastases

Study	AEDs		Study design	No.	Histology	Rate of responders (%)	Seizure freedom (%)
Newton et al. J Neurooncol 2006	Levetiracetam	Add-on Mono	Retrospective	41	12 GBM 13 AA 7 MTS 7 LGGs 2 PCNSL	90	58.5
Newton et al. J Neurooncol 2007	Levetiracetam	Add-on Mono	Retrospective	13	13 MTS	100	77
Maschio et al. J Neurooncol 2010	Levetiracetam Oxcarbazepine Topiramate	Mono	Prospective	30	30 MTS	100	63.3
Maschio et al. J Neurooncol 2008	Topiramate	Add-on Mono	Prospective	47	28 HGGs 13 LGGs 4 MEN 2 MTS	20	56

6 months, the authors reported a significant reduction in the mean monthly seizure frequency in all treated patients, with 19 patients (63.3%) obtaining a complete seizure control. The efficacy was similar for the three AEDs, and the incidence of side effects was low, probably due to the fact that all patients were treated in monotherapy.

No data are available concerning the potential pharmacoresistance of epilepsy due to brain metastases. Overall, in the absence of specific guidelines on the use of antiepileptic drugs in this population of patients, the AED choice is primarily based on type of epilepsy, age, comorbidity, and concomitant treatments (see "Interactions"). Epilepsy in patients with brain tumors in general, including brain metastases, belongs to the type of focal epilepsy, either with or without generalization. For this type of seizure, the International League Against Epilepsy (ILAE) suggested, as the most appropriate AEDs, levetiracetam, carbamazepine, phenytoin, and zonisamide (level A), being valproate the only level B [29].

Carbamazepine and phenytoin, as enzyme-inducing drugs, may accelerate the metabolism of many chemotherapeutic agents or targeted therapies, and compromise their antitumor efficacy; conversely, the use of zonisamide has not been the subject of any study in brain metastases. For these reasons, in case of symptomatic management of brain tumor-related epilepsy, brain metastases included, levetiracetam followed by valproic acid are considered the most appropriate AEDs [30]. No data are available on the impact on seizures in brain metastases of the newer AEDs, such as lacosamide, perampanel, or brivaracetam.

9.5 Interactions

The risk of interactions between AEDs and anticancer agents is a major concern. Enzyme-inducing AEDs, such as carbamazepine, phenytoin, barbiturates, and to a lesser extent oxcarbazepine, stimulate the activity of drug-metabolizing enzymes, thus enhancing the metabolic clearance of many concomitant drugs, including corticosteroids and many chemotherapeutic or targeted agents [31, 32]. The strongest interactions of carbamazepine, phenytoin, and phenobarbital are seen with cyclophosphamide, camptothecin derivates, taxanes, and topoisomerase inhibitors [30, 33].

Combined use of EI-AEDs and mTOR inhibitors produces a diminished systemic exposure to temsirolimus, everolimus, and sirolimus [34, 35].

With the concurrent use of CYP3A4-inducing AEDs, a substantial number of tyrosine-kinase inhibitors (crizotinib, dasatinib, imatinib, lapatinib, etc.) have showed a significant faster metabolism [36]. Moreover, a number of anticancer agents, including targeted agents, may increase or decrease the serum concentration of AEDs, suggesting the need for a more accurate monitoring of serum level of AEDs in cancer patient receiving antineoplastic agents [37, 38].

9.6 The Potential Antineoplastic Role of AEDs

The issue concerning the potential antineoplastic role of some AEDs has been longer discussed. The activity of valproic acid as a histone deacetylase inhibitor has gained attention for antitumor effects. In the last 10 years, some retrospective analyses have reported that glioma patients, both in children and adult, exposed to valproic acid have a better outcome [39–41]. Other enzyme-inducing AEDs, notably carbamazepine, have been suggested in small studies to play a role in prolonging survival in GBM [42, 43]. Levetiracetam may inhibit transcription of the O6-methylguanine-methyltransferase repair protein gene, leading to the hypothesis of a potential role in prolonging survival in GBM. Happold et al. [44] performed a pooled analysis of four

randomized clinical trials in newly diagnosed glioblastomas (AVAGLIO, CENTRIC,CORE, RTOG 0825) and did not observe any significant difference in outcome (PFS and OS) between patients taking valproate and patients naïve. Similarly, no association with improved outcome was observed for levetiracetam use.

Few data are available on this topic concerning brain metastases. Reddy et al. [45] performed a study with the aim to investigate the effects of VPA on outcome in a population of patients with brain metastases from breast cancer treated with whole brain radiotherapy. The rationale of this study was based on the previous observation in preclinical studies that VPA had radiosensitizing effects in differentiated mammary cells. Patients receiving VPA had a median OS of 11 months as compared to 5 months for those not receiving VPA. Moreover, median OS was 9 months for patients taking any AEDs versus 4 months for those not taking AEDs. Thus, this study suggests that the use of AEDs, including VPA, is associated with a better outcome in patients with brain metastases from breast treated with whole brain radiotherapy.

9.7 The Influence of Antineoplastic Treatments on Seizures

Surgical resection allows seizure control in many patients with primary brain tumors, particularly in low-grade gliomas, including those with pharmacoresistant epilepsy: the percentage of seizure-free patients in the major series ranges from 65% to 82% [46, 47]. Across all studies, the most significant factors associated with seizure freedom are completeness of tumor resection and short preoperative duration of tumor-associated epilepsy. In addition to the well-known impact of surgical resection, there are increasing data regarding the role of radiotherapy and chemotherapy in reducing seizure frequency in patients with gliomas [48, 49].

Thus far, there are few data regarding the impact of antineoplastic treatments on seizures in brain metastases. Total surgical removal could be effective in allowing seizure control: in a large retrospective series of brain metastases receiving surgery, radiation, and chemotherapy, a subtotal resection (as compared to total resection) has been associated with a higher probability of losing seizure control in the follow-up [18]. However, there are no data on the impact on seizures of the individual treatment modalities, i.e., surgery, WBRT, SRS, and chemotherapy.

Conversely, seizures may represent an adverse effect of high-dose focal radiotherapy. Stereotactic radiosurgery, either as a boost of WBRT or alone, is associated with early seizures occurrence in 2–12.4% of patients [14, 50]. Moreover, ^{131}Cs brachytherapy implants after surgery has resulted in a 4.3% incidence rate or seizures [51]. In general, there is need that studies on the effects of SRS of brain metastases from different solid primaries will prospectively collect data on the rate and risk factors for seizure developments following treatment.

Epilepsy is a dose-limiting toxicity in phase I and II clinical trials of some anticancer drugs. Seizures may occur in patients undergoing treatment for cancer, especially at high-drug doses. Moreover, renal or hepatic disorders may affect drug clearance and lead to seizures. Some cytotoxic agents, which are used in patients with or without brain metastases in patients with NSCLC, breast cancer, or colorectal cancer, may rarely give rise to seizures. Cisplatin-induced seizures are a manifestation of an acute toxic encephalopathy, generally appearing during or soon after the administration [52]. Generalized tonic-clonic seizures are the most common type and may be combined to cortical blindness, aphasia, hemiparesis, or acute confusional state. Seizures are associated with cisplatin-induced hypokalemia, hyponatremia, and hypomagnesemia. Seizure most frequently

appear during or soon after paclitaxel administration [53]. Previous brain surgery and/or WBRT may increase the risk of seizures, as the damage of the BB can facilitate seizures or encephalopathy. 5-Fluoracil-induced seizures are uncommon in patients receiving high doses or continuous infusion [54].

In most cases, drug-induced seizures arise spontaneously after drug withdrawal. The usefulness of neuroprotective agents (amifostine, glutathione, vitamin E) has not been proven.

Targeted agents and immunotherapy with checkpoint inhibitors are not considered a risk factors for seizures thus far (Figs. 9.1, 9.2, and 9.3).

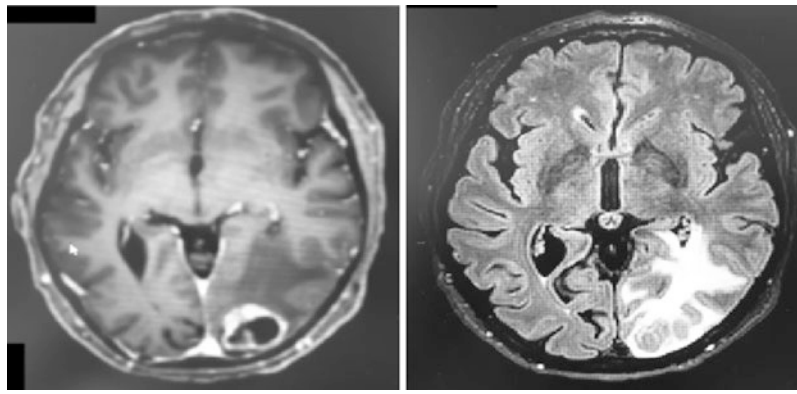

Fig. 9.1 Sixty-four-year-old male, with a diagnosis of renal carcinoma treated with surgery alone. After 1 year from diagnosis of the primary tumor, he developed partial seizures with visual disturbances in the right field, and levetiracetam 2000 mg/day was started. MRI with gadolinium showed a single lesion in the left occipital lobe, with a ring enhancement and edema. Patient underwent surgery with a gross total removal of the lesion with a histological diagnosis of metastasis from renal carcinoma. Then stereotactic radiosurgery to the surgical bed was performed

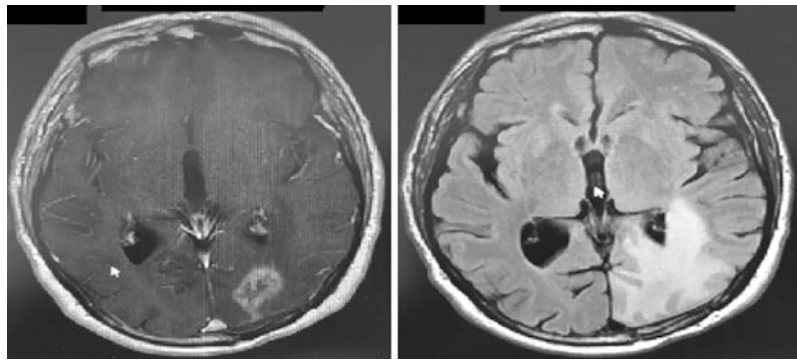

Fig. 9.2 After 6 months from radiotherapy, while he was taken levetiracetam 2000 mg/day, the patient experienced a generalized seizure and MRI displayed a "nodular" enhancement with increase of edema in the site of the previous surgery. Carbamazepine was given as add-on treatment. Patient underwent a second surgery, and a diagnosis of radionecrosis was obtained

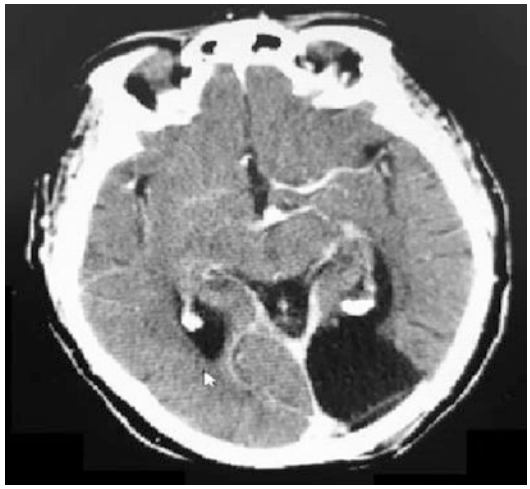

Fig. 9.3 Postoperative CT documented a gross total resection, and the patient remained seizure-free for 3 years

9.8 Conclusions

Epilepsy in brain metastases is an emerging issue, also due to the increasing number of long-surviving patients with solid cancer who are at risk of relapse into the brain. The risk of seizures for patients with brain metastases is lower as compared to gliomas, but the pathogenesis could probably differ, and novel clinical and preclinical studies are needed. Randomized trials should investigate the role of new AEDs in those subgroups of patients at high risk of seizures, such as those with hemorrhagic or multiple brain metastases from melanoma. With the increasing use of stereotactic radiosurgery, risk factors for the development of seizures will be welcome.

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Safety, Tolerability, and Use of Steroids

10

Fabian Wolpert and Patrick Roth

10.1 Background

Steroid treatment for patients with brain metastases was established in the 1950s [1, 2] and remains the primary choice for the treatment of peritumoral brain edema. The anti-edema effects of steroids provide quick and reliable, though transient, relief from intracranial mass effect and associated symptoms. In this chapter, an overview on the pathomechanism of tumor-related edema as well as the effects, pharmacokinetics, and most important side effects of steroids will be provided.

10.2 Pathomechanisms Underlying the Peritumoral Edema

The origin of peritumoral edema is vasogenic, which is a result of an impaired function of ependymal tight junctions at the blood-brain barrier. Its increased permeability results in fluid redistribution toward the extracellular space and edema with an increase of intracranial pressure [3, 4]. Several molecules that are crucial for tight junction function, including occludins, claudins, and zona occludens proteins, are downregulated in tumor blood vessels [5, 6]. Aquaporins, another class of molecules crucial for renal fluid retention and regulation, are upregulated in cells from primary brain tumors and brain metastasis [7] and may further contribute to edema formation. Whether the leakage of the blood-brain barrier is primarily mediated by antitumor inflammatory responses or is a direct result of the action of cytokines which are released from tumor cells has not yet been definitively clarified for brain metastases. The multiple actions of corticosteroids, however, can target both pathways, since they limit inflammation by direct inhibition and apoptosis of immune cells [8–10] and result in a decreased release of cytokines such as vascular endothelial growth factor (VEGF) in vitro and in vivo [11, 12]. The VEGF pathway contributes to edema formation and can be targeted therapeutically with antibodies such as bevacizumab.

10.3 Steroid Types: Pharmacological Properties and Relevant Drug Interactions

Natural steroid hormones produced in the adrenal glands comprise mineralocorticoids and glucocorticoids. Glucocorticoids like cortisol are catabolic hormones that regulate blood sugar levels, but exert also anti-inflammatory as

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well as immune regulatory effects and mediate vasoconstriction [13]. Immunosuppression and vasoconstriction are in part desired and needed for the anti-edema properties of steroids. In contrast, increased blood sugar levels or worsening of a pre-existing diabetes is a major challenge in patients treated with steroids [14], which will be outlined later in this chapter.

Aldosterone, the most prominent mineralocorticoid, is involved in the regulation of electrolyte and water homeostasis. This explains increased fluid retention and a subsequent increase of arterial blood pressure, as well as electrolyte disbalances (increase of sodium and decrease of potassium levels) which may occur upon therapeutic administration of steroids with mineralocorticoid activity. These effects may subsequently induce cardial and neurocognitive deficits and lower the threshold for epileptic seizures [14]. As a consequence, several synthetic corticosteroids have been designed in the past decades in order to maximize their anti-inflammatory and anti-edema potential while minimizing mineralocorticoid effects. Table 10.1 provides an overview on the most relevant synthetic corticosteroids that are used in neuro-oncology.

In contrast to side effects, which can be mostly attributed to mineralocorticoid and glucocorticoid properties, it is only partially understood how steroids decrease tumor-associated edema. In brief, free glucocorticoids permeate the cellular membrane and bind to the cytosolic glucocorticoid receptor. Binding to this receptor initiates several transcriptional and posttranscriptional changes: receptor-bound glucocorticoids are translocated to the nucleus involving heat-shock proteins. Here, the glucocorticoid receptor binds to specific sequences, depicted as glucocorticoid response elements (GRE) that initiate downstream signaling. Subsequently, the expression of several interleukins and other pro-inflammatory chemo- and cytokines is suppressed. Here, synthetic steroids such as dexamethasone or methylprednisolone are superior to the physiologically occurring cortisol due to their higher binding affinity to GRE. Furthermore, steroid signaling affects the expression of various genes and transcription factors such as NF-κB [16–18]. Direct anti-edema effects involve an upregulation of tight-junction proteins like occludins and claudins which are crucial for the integrity of the blood-brain barrier. Its restoration reduces transependymal fluid permeability and the extent of edema, and local vasoconstriction decreases intracranial pressure and improves drainage of extracellular fluid [3, 14, 17, 19].

There are several significant interactions of steroids with other drugs. Effects of oral anticoagulants can be enhanced and result in an increased bleeding risk [20]. Corticosteroid levels can be reduced by enzyme-inducing anticonvulsants like phenobarbital, phenytoin, and carbamazepine [21–24]. The same might account for other inducers of the cytochrome P450 system, e.g., rifampicin [25]. Furthermore, corticosteroids tend to interact with antidiabetic drugs, antibiotics, diuretics, and antiviral as well as antifungal medications.

In addition to an improvement of clinical symptoms related to the mass effect of a tumor, steroids also have antiemetic effects and are therefore included in many chemotherapy protocols as a premedication. These effects are explained by several humoral, anti-inflammatory, and direct actions on CNS structures including the area postrema in a serotonin-dependent manner [26].

10.4 Clinical Control of Edema

In contrast to its widespread use, there is only limited evidence from clinical trials regarding the quantification of edema reduction by corticosteroids, and the available data rely mostly on reports with a low number of patients, mainly from the 1960s to the 1990s. First clinical and basic research reports attributed the antiedema effects of corticosteroids to an improvement of cerebral blood flow as well as a restoration of vasal autoregulation and blood brain barrier function [19, 27–30]. Further studies from the MRI era suggested a significant size reduction of contrast-enhancing tumor parts and the surrounding edema, but not of cerebral blood volume or flow [31–33]. However, these studies are limited

Table 10.1 Properties of selected corticosteroids (Adapted from [13, 15])

Agent	Cortisol equivalent (mg)	Relative glucocorticoid potency	Relative mineralocorticoid potency	Fluorinated	Biological half-life (h)	Usual dose range (mg)	Cushing threshold (mg)	Clinical remarks
Hydrocortisone	1	1	1	No	8–12	20–30	30	Primarily cortisol replacement therapy
Cortisone	1.25	0.8	0.8	No	8–12	–	40	
Prednisone	0.25	4	0.6	No	12–36	5–60	7.5	High glucocorticoid action, first alternative to dexamethasone
Methylprednisolone	0.2	5	–	No	12–36	500–1000	6	Anti-inflammatory/immunosuppressive, intravenous, and orally available
Dexamethasone	0.04	30	–	Yes	36–72	2–24	1.5	Anti-inflammatory/immunosuppressive; minimal mineralocorticoid activity and fluid retention; high potency and long duration of action
Budesonide	n.a.	>30	n.a.	No	36–72	400–1600	n.a.	Primarily inhalative treatment

by their small sample size and focus on primary brain tumors such as gliomas and meningiomas, and it remains elusive if these findings also fully apply to patients with brain metastases. To date, there are no data from clinical studies with a significant sample size available that quantified the effect of steroids in a meaningful number of patients.

Several orally available steroids were mainly developed in the 1950s and 1960s of the last century, most importantly dexamethasone and prednisone. No data from dedicated trials are available that compared the activity of different synthetic corticosteroids. Because of its high glucocorticoid potential (30-fold stronger than that of endogenous cortisol), favorable pharmacokinetic profile with low mineralocorticoid potential, long half-life of approximately 48 h that allows a dosing schedule of once daily, and lower tendency to induce delirium or psychotic disturbances, dexamethasone has been used most frequently at many neuro-oncological centers (see Table 10.1 for pharmacological properties).

Clinical responses to steroid administration are in the range of 30–70% [4, 14]. However, relief from intracranial pressure and neurological deficits is typically obtained for only a few weeks.

10.5 Side Effects and Frequent Complications Associated with Steroid Administration

The following section summarizes the most important side effects of steroid treatment (Table 10.2). For many complications and their prevention, the level of evidence is low, and comprehensive guidelines are lacking.

Cardiovascular side effects belong to the most significant complications during steroid therapy, most importantly arterial hypertension which is frequently observed in a dose-dependent manner [34]. This is explained by fluid restriction and vascular constriction mediated by steroids [35].

Furthermore, steroid medication is a confirmed independent risk factor for venous thromboembolic events [36, 37]. Steroids probably contribute to endothelial dysfunction and hypercoagulability by overexpression of prothrombotic factors, including factors VIII, IX, and von Willebrand factor as well as increased plasminogen activator inhibitor 1, an endogenous inhibitor of fibrinolysis [36]. Furthermore, venous stasis is frequently present in patients with brain metastases due to focal neurological deficits such as hemiparesis, another important prothrombotic factor.

Steroid-induced diabetes is observed in up to 50% of patients on long-term treatment [38]. Thus, monitoring of laboratory values of patients on steroid treatment must include blood glucose levels. Treatment decisions should follow guidelines for type 2 diabetes [39], but reevaluated closely upon tapering of steroids [38].

Peptic ulcers and gastrointestinal bleeding events are potentially severe complications in patients on steroid treatment [40]. The threshold for prophylactic treatment with proton pump inhibitors or histamine blockers is therefore low. Despite this clinical practice, the particular risk to develop peptic ulcers on steroid treatment or problematic dose ranges is unknown, and there are thus no comprehensive guidelines when to start prophylaxis. A reasonable approach could be to withhold stomach prophylaxis from asymptomatic patients without a history of previous bleeding or ulcerogenic comedication (e.g., aspirin). Controlled prospective trials will be required to clarify the benefit from primary ulcer prophylaxis and to identify individuals at high risk [41].

Patients on long-term steroid treatment show furthermore increased susceptibility towards some opportunistic infections, most importantly *Pneumocystis jirovecii* pneumonia (PJP) [42]. Consensus guidelines, e.g., of the Australian College of Physicians, suggest PJP prophylaxis if duration of steroid treatment exceeds 4 weeks or during myelosuppressive chemotherapy [43].

Alkylating or other myelotoxic chemotherapy is an independent risk factor for the develop-

Table 10.2 Side effects: frequency, recommendations on diagnostics, prophylaxis, and treatment (Adapted from [15]; *P* prophylaxis, *T* therapy)

Side effects	Frequency upon long-term use	Symptoms/clinical manifestation	Clinical assessment and laboratory testing	Prophylaxis/treatment
Cushing's syndrome	Up to 70%	Moon face	Fasting cortisol	P: Steroid dose below Cushing threshold
		Hyperglycemia	Fasting glucose	
		Arterial hypertension	ACTH stimulation test	T: Tapering whenever clinically possible
		Striae		
Osteoporosis	Up to 50%	Pain	Vitamin D and parathyroid hormone	P: Short treatment periods
		Pathological fractures	Bone density measurement	T: Calcium and vitamin D supplement, bisphosphonates
Myopathy	10–60%	Muscle weakness		P: Steroid dose below 10 mg/day prednisone (equivalent)
				T: Switch from fluorinated to non-fluorinated steroids/ physical therapy
Steroid-induced diabetes	Up to 50%	Cardiovascular alterations	Monitoring of vital parameters	P: Limited use of steroids
		Renal insufficiency	Serum creatinine/ glomerular filtration rate	T: Taper steroids, symptomatic treatment of complications
		Visual impairment	Funduscopy, visual acuity testing	
Thromboembolic events	Two- to threefold increased thrombosis risk	Deep venous thrombosis	D-dimers (high rate of false-positive results)	P: Mobilization; anti-embolism stockings and/or low-dose heparin in high-risk patients
		Pulmonary embolism	Doppler ultrasound of extremities	T: Anticoagulation (therapeutic doses)
			Chest CT, lung scintigraphy	
Immunosuppression	30–100%	Pneumocystis jirovecii pneumonia	Differential blood count	P: Monitoring of lymphocyte count (>10^3/ µL), limit steroid dose
			Chest X-ray/CT	T: Prophylaxis or treatment with co-trimoxazole or other appropriate antibiotics in patients receiving steroids for more than 4 weeks
Steroid dermatitis		Rosacea like phenotype	Skin inspection	P: Short treatment periods, dose limitation
				T: Taper steroids
Psychiatric disorders	Up to 60%	Insomnia	Psychiatric assessment	P: Lowest possible dose of steroids
		Mood disorders		
		Psychosis		T: Neuroleptic drugs, other sedatives

ment of PJP, and prophylaxis should therefore be closely evaluated in these patients [44, 45]. Since the risk for PJP correlates with the grade of lymphopenia, monitoring of absolute lymphocyte counts (or alternatively CD4+ T cells) is sometimes used as a parameter in study protocols and in clinical practice. However, there are no definite cutoff values, but a lymphocyte count below 1×10^3 lymphocytes/μL [46] is typically accepted as a threshold to start PJP prophylaxis and implemented in numerous study protocols. However, in patients on long-term steroid treatment, e.g., for more than 4 weeks, PJP prophylaxis should be considered regardless of lymphocyte counts. Co-trimoxazole per os is the agent of first choice for prophylaxis. Alternative drugs are dapsone per os or inhalation of pentamidine [43].

Myopathy is another frequent complication during long-term steroid treatment and is reported to occur in about 10% of patients with brain tumors during steroid therapy and, in general, in up to 60% of patients on permanent steroid intake [47, 48]. The onset of steroid myopathy varies between 1 week and 4 months after treatment start, and is dose-dependent [48, 49]. Doses below 10 mg prednisone or 2 mg dexamethasone per day are considered to be of low risk, though clinical evidence is limited [50]. Most prominent clinical symptoms from steroid myopathy are weakness, predominantly of proximal muscle groups (pelvic girdle), rather than pain or muscular swelling [49, 50]. In severe cases, also respiration musculature can be affected [49]. There are no validated screening tools or common guidelines for early detection of steroid myopathy. Close clinical monitoring and neurological assessment are recommended [47–49]. From a pathophysiological perspective, fast-acting (type 2a) muscle fibers are primarily affected by steroids, whereas slow-acting (type 1) fibers are usually spared [51, 52]. Patients may recover from myopathy if complete and sustained tapering of corticosteroids is achieved. Fluorinated glucocorticoids such as dexamethasone, betamethasone, or triamcinolone may bear a higher risk for the development of steroid myopathy [53]. However, robust data in patients with brain tumors are lacking. Laboratory parameters associated with muscle functions such as serum lactate dehydrogenase, creatine kinase, or aldolase are usually in the normal range and may only be altered in patients with advanced myopathy [50, 53, 54]. The specificity of increased urine creatine kinase levels in patients treated with glucocorticoids needs to be further validated, since the secretion of creatine kinase is highly prone to other factors like meat consume [49]. The clinical usefulness of electromyographic assessments as a screening tool is also restricted since myopathic patterns are usually only observed in late-stage myopathy [49]. Predisposing factors for the acute onset of steroid myopathy include the concurrent use of non-depolarizing muscle relaxants (curare-like agents), for late-onset patients' age, and the cumulative corticosteroid dose [13].

Altogether, close clinical monitoring is crucial for early recognition of steroid myopathy. If steroid reduction might not be feasible, a switch toward non-fluorinated steroids might be considered [13].

Osteoporosis due to long-term steroid treatment is a further complication, and its association with pain and pathological fractures has a significant impact on morbidity. The pathomechanism of bone loss involves direct, steroid-mediated apoptosis of skeletal cells and secondary hyperparathyroidism as well as the suppression of growth factors such as insulin-like growth factor 1 and prostaglandin E2. Prophylaxis should be prescribed to all patients on long-term steroids and comprises calcium and vitamin D supplementation [55]. Bone density measurement has a high sensitivity for the diagnosis of osteoporosis and should be considered in patients requiring permanent steroid doses above 7.5 mg prednisone per day (or any equivalent steroid) [56]. Additional therapy with bisphosphonates such as alendronate or risedronate can be useful if osteoporosis is present [55, 57]. Patients with pathological vertebrate fractures might suffer from severe pain, and surgical approaches such as kyphoplasty might be required for stabilization and pain control [58].

It remains unclear if the administration of steroids increases the risk for seizures. There are few reports on epileptic seizures as a result of steroid

withdrawal [59]. The cytochrome P450 system is responsible for the hepatic metabolization of steroids as well as several antiepileptic drugs, and the combined administration of steroids and anticonvulsants may therefore result in provoked seizures due to subtherapeutic serum levels of either drug. However, the available clinical data do not indicate that steroid treatment per se is associated with an increased seizure risk.

Finally, psychiatric side effects and cognitive impairment are common (up to 60% of patients) with a major impact on the patients' quality of life. The onset varies between 2 weeks and several months after initiation of treatment in a dose-dependent manner [60, 61]. Whereas emotional instability, (hypo)manic symptoms, and sleep disturbances tend to occur early after initiation of steroid therapy, depression and other symptoms become rather relevant with long-term use. Here, discriminating direct tumor-mediated effects, e.g., due to tumor progression, from steroid-induced symptoms, might be difficult. Dose reduction is the most important measure and usually results in partial or complete recovery. However, neuroleptic drugs (preferably quetiapine, risperidone, or olanzapine) might be necessary to control psychiatric symptoms, particularly if tapering of steroids is not feasible [62, 63].

10.6 Therapy Initiation, Dosing, and Tapering of Steroids

If the origin of a cerebral lesion has not yet been confirmed histologically, steroids should not be used in the absence of strong clinical need if a CNS lymphoma is suspected. Treatment with corticosteroids prior to biopsy or resection may blur the pathological findings of a lymphoma [64, 65]. Therefore, if a CNS lymphoma is suspected, the initiation of steroid treatment should be carefully weighed, and diagnostics including histological confirmation should preferably be completed prior to the first steroid dose.

There is no consensus on the optimal steroid dose that should be used in symptomatic patients with brain metastases. Even for dexamethasone, the most frequently prescribed steroid in neuro-oncology, only limited data are available. A clinical trial comparing dexamethasone doses of 4 mg, 8 mg, or 16 mg/day did not demonstrate differences regarding edema control in patients with brain metastases. However, higher doses resulted in significantly more side effects [66]. Nevertheless, current guidelines recommend the use of even higher dexamethasone doses based on individual decisions as judged clinically appropriate. In any case, dose reductions should be considered as soon as possible [67].

It remains a matter of debate if preoperative initiation of steroid treatment exerts positive or detrimental effects on surgery outcome. A recent study showed no difference in the outcome of patients pretreated with steroids, but also no increase of peri- or postoperative complications [68]. In general, it must be assumed that steroids are rather overused in the context of surgery or radiotherapy.

During steroid treatment, several clinical and laboratory parameters should be assessed at baseline and monitored regularly, including body weight, blood pressure, electrolyte levels, fasting glucose, lipid status, and differential blood count. There are no comprehensive guidelines on how to schedule monitoring which needs to be planned on an individual base for each patient. In patients on long-term steroid treatment, bone mineral density assessment might be considered useful to determine the risk for developing clinically relevant osteoporosis as mentioned before. An ophthalmologic examination is furthermore recommended for patients on long-time steroids to assess for ocular hypertension or cataract [69].

10.7 Steroids and Immunotherapy

Steroid treatment impairs lymphocyte function and may therefore interfere with the clinical activity of immunotherapy. This is of particular importance with the emergence of the class of immune checkpoint inhibitors which includes blocking antibodies to *programmed cell death protein* (PD)-1 or *cytotoxic T-lymphocyte-associated protein* (CTLA) 4, both inhibitory

receptors on immune cells. These drugs have revolutionized therapy of certain cancers including melanoma and lung cancer [70], and there is increasing evidence that they also work against brain metastases [71].

In vitro data show an inhibition of checkpoint inhibitor-induced immune responses by steroids via an upregulation of PD-1 [72]. However, there are no controlled clinical trials available so far that assessed the potentially detrimental effect of steroids in the clinical setting of brain metastases. Nevertheless, as steroids may be a major limitation to the efficacy of immune checkpoint inhibitors, their use should be limited as far as possible in the context of immunotherapy [73]. On the other hand, corticosteroids are a crucial tool to effectively control immune-related side effects in patients treated with checkpoint inhibitors [74, 75].

10.8 Steroid-Sparing Alternatives

Given their significant side effects, strategies aiming at sparing steroids have been subject of intensive research. Albeit not improving overall survival, bevacizumab has strong antiedema activity and has been assessed extensively in the context of primary brain tumors such as glioblastoma [76–78]. Data on patients with brain metastases are limited to retrospective series or small prospective clinical trials and are largely restricted to the management or prevention of radiation necrosis [79–81]. These reports demonstrate a decrease of the size of contrast-enhancing lesions as well as the edema upon bevacizumab administration.

The use of corticorelin acetate, a synthetic analog of the human corticotropin-releasing factor, was assessed in a phase III clinical trial in patients with primary or metastatic brain tumors. Although the study failed to meet its primary endpoint (50% reduction of steroid dose), a significant reduction of adverse effects, in particular steroid myopathy and Cushing's syndrome, was reported [82]. It remains to be awaited if the clinical development of corticorelin acetate will be further pursued. Other therapeutic options to treat edema and replace steroids are boswellic acids which have also shown some direct antitumor effects in vitro [83]. In a randomized controlled trial, a significant reduction of the peritumoral edema was observed in patients treated with boswellia extracts, whereas no direct steroid-sparing effect could be detected [84]. Together with their overall benign toxicity profile, boswellic acids may be considered as a complementary treatment in patients with brain metastases-related edema [15, 85].

10.9 Concluding Remarks

Corticosteroids remain the therapeutic cornerstone in the management of peritumoral edema in patients with brain metastases. In contrast to their widespread use over approximately six decades, there is still limited knowledge on their exact mode of action. Potential clinical benefit is opposed by numerous side effects that make long-term treatment with steroids troublesome. Therefore, the administration of steroids should be done with caution and requires close clinical monitoring. Early recognition of possible complications is crucial to avoid or at least minimize detrimental effects. Whenever possible, tapering should be considered. A direct impact of corticosteroids on the survival of patients with brain metastases has not been proven so far. However, the fact that steroids have been identified as an independent negative prognostic factor in glioblastoma patients [86] suggests that a similar role might be possible in patients with brain metastases. Treatment alternatives are rare, and further clinical studies are needed to define the steroid-sparing potential of novel drugs.

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Anticoagulation in Patients with Brain Metastases

11

Christine Marosi and Cihan Ay

11.1 Introduction

Venous thromboembolism (VTE), manifesting as deep vein thrombosis (DVT) with and without pulmonary embolism (PE), is a frequent complication in patients with cancer, especially in those with advanced disease. They may cause a high symptom burden with pain, feeling of tension, breathlessness, fatigue, and impairment of mobility, and are the second leading cause of death after the tumor itself. An international meta-analysis of VTE in patients with cancer found an annual incidence between 0.5% and 20% depending on cancer type and other risk factors [1]. Interestingly, an increasing number of the so-called asymptomatic PE, incidentally found on CT imaging done for other purposes than diagnosis of suspected PE, have been reported over the last decades [2]. However, the true incidence might be even higher due to unreported cases because of patient's poor condition and lack of mobility.

One of the manifestations of advanced cancer is the occurrence of brain metastases (BM) in up to 25% of all cancer patients; but the exact incidence of BM in each tumor entity as well as the interval between tumor diagnosis and diagnosis of BM is highly variable and, so again, the number of undiagnosed cases is unknown, but suspected to be high and increasing with efficacy of systemic cancer treatment.

Like in primary brain tumors, the symptom burden of BM depends on their location, the amount of mass effect, and the velocity of growth, not on the organ of origin of the underlying cancer.

The frequency of the coincidence of brain metastases with VTE can only be estimated, as the incidence of both events is not mandatorily recorded; nevertheless, the coincidence of these two severe complications in advanced cancer cannot be infrequent, as both share a lot of common pathways involving cell aggregation, platelet activation, stasis in blood vessels, and activation of the coagulation system, to name only a few.

11.2 Incidence

Exact data are lacking; there are only few studies done in patients in late cancer stages. An autopsy study of 506 cancer patients deceased in 1970 in the Roswell Park Memorial hospital showed that 18% of deaths were due to VTE and in 43%

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TE was a contributing factor [3]. The barriers for prospective studies to this topic are numerous, ranging from the high estimated numbers of affected patients to the diversity of diagnostic methods with varying sensitivity and specificity, to legal concerns about the ability of BM patients to give valid informed consent to study participation and the probability of rapid loss of patients with advanced cancer. However, there are alarming data about the frequency of undiagnosed VTE in hospice patients. In 1999, Johnson et al. examined 298 hospice patients with advanced cancer using light reflection rheography and found evidence for DVT in 135, e.g., in 52%! In multivariate analysis, DVT was associated with poor mobility, reduced serum albumin level, and increased serum urea [4].

The Vienna Cancer and Thrombosis Study (CATS), an ongoing prospective, single-center, observational cohort study that started in 2003 at the Medical University of Vienna, Austria recruits patients with histologically confirmed, newly diagnosed cancer or patients recurring after a therapy-free interval. At inclusion, a blood sample is drawn and used for the evaluation of parameters associated with risk of occurrence of VTE. Patients are followed for 2 years. So far, more than 2400 patients have been included into this study [5, 6]. Furthermore, at the Medical University of Vienna, from 2003 to June 2017, 649 patients underwent surgical resection of a brain metastasis, 848 underwent radiosurgery for brain metastases, and 1791 were treated with radiotherapy for BM. The intersection set consists of 163 patients that received therapy directed against BM and participated in the CATS study. Of these, 16 patients developed a thromboembolic event during the CATS observation time, e.g., within 24 months of follow-up: 9 with lung cancer, 5 with breast cancer, 1 with colorectal cancer, and 1 with ovarian cancer (full data unpublished). This rate of ≈10% is slightly higher than the overall rate within the CATS study of 8.8%—but given that the observation time within the CATS study is only two years which misses most of the brain metastases of breast cancer which typically develop much later, this rate is relatively high. Interestingly, these patients developing BM and VTE could not be identified with the biomarkers and clinical predictor, neither by the Khorana score, nor by the Vienna score, nor by the two risk models proposed for patients with primary brain tumors [7].

11.3 Are There Guidelines?

The existing guidelines on VTE prophylaxis in cancer patients recommend consensually primary thromboprophylaxis in hospitalized patients, and in outpatients, general prophylaxis is not recommended. After abdominal and pelvic cancer surgery, prolonged thromboprophylaxis is recommended for 4–6 weeks. ASCO guidelines suggest educating "high-risk" patients according to a validated risk assessment tool [8, 9], NCCN guidelines recommend a patient conversation for those with a Khorana score of ≥3 [10–12], and only the ESMO guidelines foresee giving thromboprophylaxis to patients identified as high risk by predictive models [13]. BM are not explicitly mentioned in any of these guidelines. A further attempt to address VTE prophylaxis in patients with advanced cancer was done by the Pan Birmingham Cancer Network (PBCN) by defining patients with temporary higher thrombosis risk caused by acute medical illness, recent surgery, spinal cord compression, and reduced mobility with expectation of recovery, which led to the palliative-modified Thromboembolic Risk Factors (THRIFT) Consensus Group Criteria [14]. Noteworthy, brain metastases are not mentioned among the high-risk factors in THRIFT, but stroke is listed among them. There is some rationale to consider that in patients with BM, although in a minor scale than in stroke, similar thrombogenic events leading to increase of microvesicle-associated tissue factor in the blood stream occur. However, the presence or absence of BM is not discussed by THRIFT guidelines and the associated definition of temporarily elevated risk (TER).

11.4 Detection of Brain Metastases in Patients with Advanced Cancer

Recommending thromboprophylaxis in BM patients would imply that some sort of screening for BM would be mandatory in patients with advanced cancer, which is to date also not common practice in the absence of related symptoms. Currently, staging examinations are done as long as active anti-tumor treatment is given and those staging examinations do not necessarily include brain imaging in all tumor entities as long as patients do not present with evocative symptoms. In the period after active tumor treatment, most investigations are triggered by symptoms or laboratory findings and so not necessarily include brain imaging. On the other hand, brain imaging has become much more available in the last decade and most patients with any evocative symptom usually undergo a CT scan and/or brain MRI within short term. Treatment options and survival durations in BM patients have markedly improved over the last years. Most patients are treated by tumor resection, radiation therapy or radiosurgery or combinations thereof. Per se, BM do not consist an indication for thromboprophylaxis to prevent VTE so far, but the occurrence of patients with VTE events has likely to further increase—as those patients survive for longer periods in better condition.

11.5 Is Anticoagulation Feasible and Safe in the Case of a VTE Event in Patients with BM?

It is well known that patients with cancer are also at increased risk of bleeding which further increased during anticoagulation [15]. Bleeding risk is most feared in patients with BM and in fact BM present with a variable risk of spontaneous bleeding—and this risk is high in malignant melanoma and renal cell carcinoma and has to be weighed against the bleeding risk induced by prophylactic or by therapeutic anticoagulation.

There is, happily, a retrospective study and meta-analysis to this topic which provides some evidence. Donato et al. reviewed retrospectively a matched cohort study on the safety of therapeutic anticoagulation with low molecular weight heparin (LMWH) in 293 patients with cancer with brain metastases (104 with therapeutic enoxaparin and 189 controls) [16]. They performed a blinded review of radiographic imaging and categorized the severity of observed intracranial bleedings (ICH) as trace, measurable, and significant. After 1 year, the cumulative incidence of intracranial hemorrhage was not significantly different in both groups, with 19% in the LMWH group and 21% in the control group ($P = 0.97$). Of note, the risk of intracerebral hemorrhage in patients with renal cell carcinoma and melanoma was higher than in patients with lung cancer, but also in the high-risk tumors, it was not increased by LMWH. Overall survival was also similar in both groups with 8.4 months for the LMWH group and 9.7 months for the control group ($P = 0.65$). Zwicker et al. published a meta-analysis of nine retrospective cohort studies to the risk of intracranial hemorrhage in patients with brain tumors with anticoagulation [17]. Three of them dealt with patients with BM from solid tumors; the others included patients with primary brain tumors. The odds ratio (OR) for ICH in patients receiving therapeutic anticoagulation versus those who did not receive anticoagulation was 2.13 (95% confidence interval [CI], 1.00–4.56; I(2) = 46%). This apparent difference can be elucidated when a subgroup analysis pooling the data of three studies reporting of patients with BM showed no increase in the rate of ICH (OR, 1.07; 95% CI, 0.61–1.88; $P = 0.81$), whereas patients with primary brain tumors showed a significant increase of ICH when receiving LMWH (pooled OR, 3.75; 95% CI, 1.42–9.95; $P = 0.01$). Interestingly, a further subgroup analysis showed that patients with BM from melanoma and renal cell carcinoma also showed an increased rate of ICH with an OR of 2.30 (95% CI, 0.80–6.59; $P = 0.12$) without reaching statistical significance. So far available

data support anticoagulation with LMWH in patients with brain metastases suffering a thromboembolic event. In patients with tumors at high risk for ICH, like renal cell carcinoma and malignant melanoma, an individualized management and documentation of eventual spontaneous ICH before the onset of treatment appears advisable.

There are no studies on direct oral anticoagulants (DOACS) for patients with brain metastases, neither for DVT prophylaxis, nor for therapeutic anticoagulation. However, some experience with this unmet clinical need will become available from recent clinical trials on the use of DOACs in patients with cancer. The Hokusai trial showed no inferiority of edoxaban as compared to dalteparin in 1050 cancer patients with symptomatic VTE. Major bleeding occurred in 36 patients (6.9%) in the edoxaban group and in 21 patients (4.0%) in the dalteparin group. Recurrent venous thromboembolism occurred in 41 patients (7.9%) in the edoxaban group and in 59 patients (11.3%) in the dalteparin group (difference in risk, −3.4 percentage points; 95% CI, −7.0 to 0.2) [18]. No subgroup analysis regarding brain metastases has been published so far. Even as BM are listed among the exclusion criteria of the ongoing Caravaggio study observing the efficacy of preventing recurrent venous thromboembolism in nearly 1200 cancer patients, as compared to dalteparin, some data on the safety of apixaban in BM patients will be recorded in this trial [19].

To sum up, preventing and treating thromboembolic events in patients with brain metastases is a moving field that is becoming increasingly important and frequent as the survival duration of cancer patients increases. As the processes of the development of metastases and of clot formation are closely linked, research in both fields may open new therapeutic opportunities regarding prevention of metastases and of thromboembolism. Meanwhile, careful interdisciplinary analysis of the potential benefits and risks of individualized patients may help to find appropriate management available for clinical problems.

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Imaging of Brain Metastases: Diagnosis and Monitoring

12

Gabriel C. T. E. Garcia, Sophie Bockel, Michaël Majer, Samy Ammari, and Marion Smits

12.1 Introduction

Brain metastases are the most frequent brain tumors in adults [1] and represent about 25% of brain masses. Among patients with metastatic cancer, 40% will present with brain metastases [2]. These lesions are less frequently symptomatic than expected: only 19% of patients with newly diagnosed brain metastases have neurologic symptoms [3] whereas these lesions dramatically change patients' prognosis. We will see in this chapter that imaging is central for patients' care.

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12.2 Intracranial Metastases: Radiological Presentations

12.2.1 Parenchymal Metastases

12.2.1.1 General Presentation: Metastases Detection

Brain metastases detection is a major challenge in the management of patients with cancer. Computed tomography (CT) and magnetic resonance imaging (MRI) are the two radiological modalities widely used in this context; their sensitivities for metastases detection are increased by the injection of a contrast agent [4, 5], which is iodine-based for CT and gadolinium-based for MRI. The underlying physiological explanation of such an increased sensitivity in brain metastases detection with contrast-enhanced imaging is based on blood-brain barrier (BBB) features. In the brain, CT and MRI contrast media do not cross the normal BBB [6], unlike in the other organs where they can leak into the interstitial space through the endothelial fenestrations. Consequently, the disruption of the BBB created by metastases allows contrast media to leak into the brain parenchyma leading to a visible enhancement on imaging [6]. It is important to note here that brain lesion enhancement after contrast media injection is mostly due to BBB disruption, but is also partially generated by the intravascular fraction of the medium [6].

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MRI has better performance in metastases detection compared to CT [7]. MRI is therefore preferred, at least for initial patient evaluation and focused treatment planning, but also during the follow-up. The usual presentation of intracerebral metastases on MRI is a round-shaped lesion, iso- to hypointense to normal brain on T1-weighted images and variable in intensity on T2-weighted images [8]. Metastases of melanoma are commonly hyperintense on T1-weighted images, due to the presence of melanin and/or recent hemorrhage, with sometimes poor or no enhancement [9, 10]. Vasogenic edema is very often found around the metastatic lesions and is highlighted by T2-weighted images without or with fluid-attenuated inversion recovery (FLAIR) in the form of a more or less extended hyperintensity involving the white matter but sparing the cortical ribbon and the basal ganglia. Metastases, even the small ones, are often surrounded by a relatively large region of edema. Brain metastases are preferentially located in particular areas of the brain, namely the grey/white matter junction, distal vascular fields, and specifically "watershed areas" [11–13]. This can be explained by the fact that tumor emboli tend to end up and proliferate in the regions where vascular caliber is at its maximum reduction (and inferior to the size of the neoplastic emboli) [13]. Posterior fossa involvement is variable depending on the primary tumor, for example, metastases from gastrointestinal tumors tend to be present in this area more frequently than metastases from lung cancer [11].

Diffusion-weighted imaging (DWI) is an MRI technique sensitive to motion of extracellular water molecules [14]. Apparent diffusion coefficient (ADC) is the parameter quantifying this motion. It decreases when the diffusion of extracellular water molecules is restricted, for example by an excess of the number of cells in the voxel, corresponding to hypercellularity. The correlation between hypercellularity and low ADC values has been well established in brain metastases [15], especially in small-cell carcinomas. However, DWI signal can be very variable according to primary cancer and various treatments.

As mentioned in the introduction of this section, T1-weighted imaging after gadolinium-based contrast agent (GBCA) injection increases MRI sensitivity to detect brain metastases. Their size can vary from millimetric punctiform lesions to much bigger tumors with mass effect and herniation. Intracerebral metastases tend to have a peripheral enhancement with central necrosis (ring-enhancing lesion) as soon as their size is over a few millimeters, but their enhancement can be uniform or patchy. A major question to decide on the patient's treatment is the number of metastases, regardless of their size. Several therapeutic options are available, by themselves or combined, namely surgical resection, whole brain or focused radiation therapy, and systemic treatment. Their feasibility depends on how many lesions need to be treated and the size of the lesions. Optimal sensitivity of MRI is thus of great clinical relevance, and this is dependent on numerous technical parameters.

Increased strength of the magnetic field of the MRI scanner is an important parameter to improve the conspicuity of small lesions. In every day clinical practice, there is evidence that brain metastases are more visible at 3.0 T compared to 1.5 T thanks to an increased signal to noise ratio (SNR) [16, 17]. Studies have also compared 7 T to 3 T MRI scanners, demonstrating the better sensitivity of 7 T devices even with lower doses of GBCA [18]. 7 T imagers are, to date, used for research and are not yet rolled out.

The choice of optimized MRI sequences after GBCA injection is another way to improve the accuracy of brain metastases detection. It has been shown that 3D isotropic sequences are usually acquired with a slice sickness between 1 and 2 mm and no interslice gap outperforms 2D spin echo (SE) acquisitions [19] typically presenting a greater slice thickness and interslice gap inflating the risk of partial volume effect and the risk of missing a small metastasis (<5 mm) because of the gap and/or partial volume effects. Among 3D T1-weighted sequences, three-dimensional magnetization-prepared rapid gradient-echo (MP-RAGE) is widely used and offers a good spatial resolution, with well-defined signal dif-

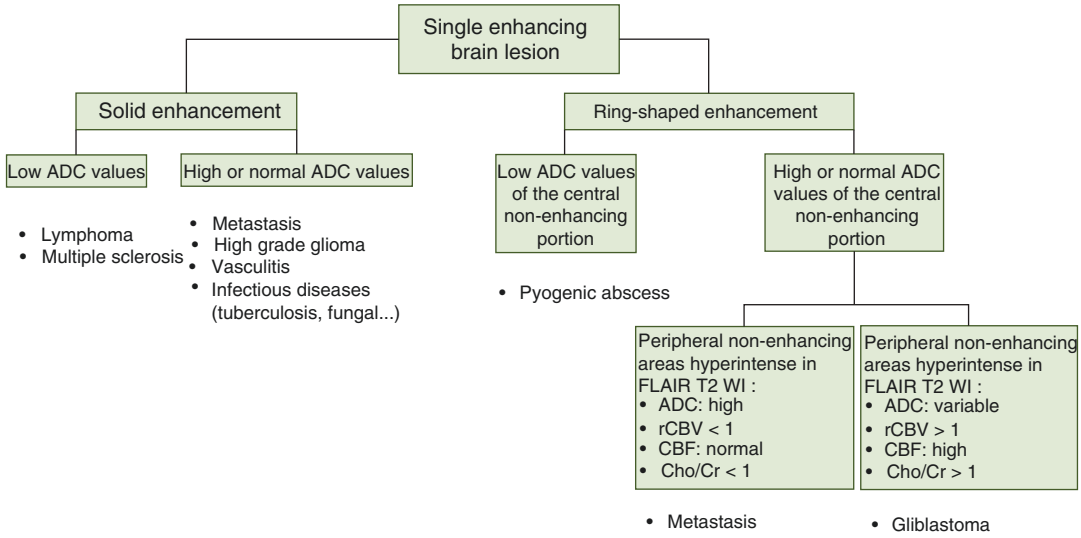

Fig. 12.1 Schematic overview of the reasoning when faced with a single enhancing brain lesion in MRI

ference between grey and white matter, making this sequence very useful for anatomical studies [20]. However, this sequence is less sensitive for detecting small metastases compared to three-dimensional turbo spin-echo imaging with variable flip angle echo train (SPACE) [21] (Fig. 12.1a, b). This latter sequence outperforms gradient-echo (GE) 3D acquisitions, because GE sequences have short repetition time, resulting in a saturation effect [22] and the relative white matter hyperintensity decreasing the contrast between normal tissues and enhanced lesions [20]. This is a good example, especially for non-radiologist physicians, to be warned that "beautiful" images are not always the most useful.

Delayed acquisitions (15 min after GBCA injection) are deemed to improve metastases detection [23] in particular for lesions smaller than 5 millimeters in diameter [24], as are increasing GBCA doses both at 1.5 T [25] and 3 T [26]. Various studies have compared the different GBCAs. They present significant differences in terms of metastases detection sensitivity because of different T1 relaxivity, as summarized by Anzalone et al. [27]. Other parameters such as chemical structure must also be taken in account, especially to maximize patient safety. Indeed, the risks of nephrogenic systemic fibrosis and gadolinium deposition in the brain are lower with macrocyclic GBCA compared to those with linear structure [28].

To sum up, metastases' conspicuity on MRI may be sensitized using higher field strength MRI scanners, 3D T1-weighted sequences (preferably turbo spin-echo) and, if needed, delayed acquisitions, particularly in cases in which the exact number of lesions, regardless of their size, must be known (for example, when SRS is considered).

Another interesting sequence is susceptibility-weighted imaging (SWI) which can help to detect hemorrhagic lesions [29].

Even if CT is less sensitive than MRI for detection of brain lesions, this imaging modality remains very useful in several cases, such as emergencies requiring a quick intervention: acute or subacute brain herniation in case of hematoma or rapid progression and hydrocephalus. CT is also essential for patients with MRI contraindications. Finally, it can be very useful to analyze bony involvement or changes secondary to intracranial lesions (e.g., meningioma, dysembryoplastic neuroepithelial tumor (DNET), dural metastases). However, renal failure and proven allergy to iodinated contrast medium are possible limitations to iodine injection in such indications.

12.2.1.2 Characterization of Brain Masses: Metastases' Specific Features

Due to the brain's highly specific functions and the risk of impairing them during intracranial invasive procedures, cerebral lesion characterization must be attempted as well as possible by noninvasive techniques such as imaging and specifically MRI.

As mentioned in the previous section, enhancement of a lesion in the brain is simply due to BBB disruption. This finding is highly nonspecific. Various cerebral lesions may be enhanced after GBCA injection and they are classically divided into two types of enhancement: solid or ring-shaped enhancement with an unenhanced central portion [8], and brain metastases can belong to both categories. They are often multiple but single lesions occur in 15–50 % of cases according to different studies [11, 30]. The most frequent differential diagnoses for solidly enhancing lesions are lymphoma, sarcoidosis, vasculitis, demyelinating lesions, cerebral toxoplasmosis, and other less frequent diagnoses like fungal abscesses, while with a ring-shaped enhancement pattern the differential diagnoses are high-grade primary brain tumor (typically glioblastoma), pyogenic abscesses and demyelinating lesions.

One of the most challenging situations is the characterization of a single ring-enhanced cerebral lesion. By order of frequency, such lesions are high-grade gliomas (40%), metastases (30%), abscesses (8%), and multiple sclerosis (6%) [30]. Figure 12.2 provides a brief

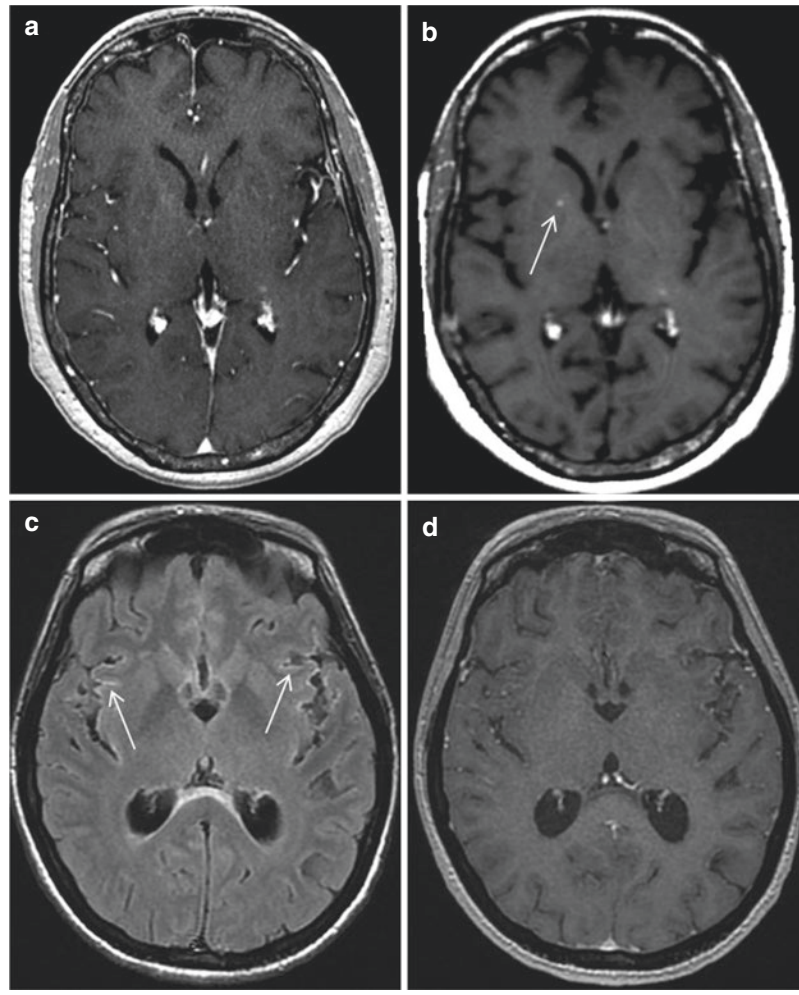

Fig. 12.2 Importance of the selection of MRI sequences. Comparison of the sensitivity of 3D T1 gradient-echo weighted images (3DT1-GE) (**a**) and 3D T1 turbo spin-echo weighted images (3DT1-TSE) (**b**) both after gadolinium-based contrast agent (GBCA) injection for detecting brain metastases. A punctiforme metastatic lesion is visualized on image **b** (white arrow) but is not on image **a**. Interest of T2-weighted FLAIR images after GBCA injection (**c**) compared to 3DT1-GE (**d**) to detect leptomeningeal metastases. A leptomeningeal enhancement is visualized on image **c** (white arrows) but is not on image **d**

schematic overview of the reasoning when facing a single enhancing brain lesion. The first step should be ruling out an abscess, which is a severe, rapidly progressive lesion requiring urgent neurosurgical intervention and specific treatment. DWI is a very helpful sequence to differentiate pyogenic abscesses from other lesions. The ADC map shows restricted diffusion in the non-enhancing central portion of the lesion corresponding to pus [31], which is generally not seen in metastases or high-grade gliomas. Among other features, abscesses have increased fractional anisotropy (FA) of the enhancing ring and lower FA and higher ADC of the surrounding edema compared to glioblastoma and metastases [32]. FA is a parameter derived from a particular DWI technique called diffusion tensor imaging (DTI) sensitive to the highly anisotropic diffusion of water molecules in the brain's white matter tract orientation. On T2-weighted imaging, 90% of abscesses present with a hypointense ring around the ring-enhanced portion [30, 31]. This enhanced wall is usually thicker on the outer part of the lesion (close to the cortex), probably because this side is more oxygenated, and thinner on the deepest part (close to the ventricles) which can lead to the pyocephalus secondary to the rupture of the abscess into the ventricular system [31]. Another very interesting tool to explore brain lesions is perfusion imaging. There are three techniques to explore brain perfusion: dynamic susceptibility contrast (DSC), dynamic contrast-enhanced (DCE), and arterial spin labeling (ASL). DSC is based on T2∗-weighted acquisitions repeated for approximately 2 min while the patient is receiving an intravenously administered bolus of GBCA. When in-vessels gadolinium passes through the brain, there is a decrease of the signal in T2∗-weighted images proportional to the quantity of GBCA (called T2∗effect). The analysis of this signal drop gives the opportunity to estimate several metrics including relative cerebral blood volume (rCBV) which approximates the proportion of a defined volume of brain tissue occupied by blood thus by vessels. rCBV is expressed in mL/100g. This technique comes with the limitations of T2∗-weighted imaging mainly artifacts secondary to hemosiderin, air, bone proximity and metallic devices, making the exploration of the posterior fossa, hemorrhagic lesions or post-surgical assessment challenging. DCE is based on T1-weighted imaging and on the increased signal when gadolinium passes through the tissues. Signal changes are due to intravascular and extravascular GBCA, allowing to evaluate the leakage of the contrast medium. Ktrans is a commonly used parameter reflecting a combination of CBF and the leakiness of blood vessels. Finally, ASL is a technique based on the labeling of the inflowing blood as an endogenous contrast agent. There is no need of GBCA injection. DCE and ASL (if used with a spin echo based read-out) present the great advantage of being less sensitive to susceptibility artifacts but don't provide CBV. Generally, an rCBV ratio is used, which is the rCBV relative to an internal control (often a zone of normal white matter). To differentiate abscess from a neoplastic lesion, perfusion imaging is found to be useful. Floriano et al. found that rCBV of the solid portion of the lesion (enhancing portion) is higher in tumors (metastases or high-grade primary brain lesion) compare to infectious lesions. A cutoff value of 1.3 was found to provide a sensitivity of 97.8% and a specificity of 92.6% to differentiate infectious lesions from neoplastic lesions (primary and metastatic combined) [33].

Magnetic resonance spectroscopy (MRS) is an MRI technique providing information about the metabolite profile of a predefined volume of the brain. Resonance peaks of each metabolites are usually constant in the brain and are expressed in parts per million (ppm). Pyogenic abscesses usually present a peak of amino acids (valine, leucine, and isoleucine which resonance peak is at 0.9 ppm) [34].

After ruling out brain abscess, we should consider multiple sclerosis (MS) as a potential differential diagnosis and especially tumefactive demyelinating disease and Balo's concentric sclerosis. Demyelinating active lesions classically present as an open ring shaped enhancement [35] and no surrounding edema [31]. The enhancement of Balo's concentric sclerosis is

often concentric, ADC of enhanced portions of the lesion tends to be low [36, 37] and there is little mass effect compared to a neoplastic lesion with the same size (except lymphoma). MRS shows a reduced concentration of N-acetyl-aspartate (NAA) and an increased peak of Choline (Cho) [37].

The main challenge is now to differentiate brain metastasis from high-grade glioma (typically glioblastoma). Neither morphological aspect nor DWI [38] helps to distinguish these entities. A recent meta-analysis [39] has shown that DWI, MRS, and perfusion imaging (alone or combined) applied to the enhancing portions of the lesions fail to differentiate brain metastasis from glioblastoma. However, these MRI techniques succeed in doing so when applied to the non-enhancing peripheral portion of the lesion, hyperintense in T2-weighted images, corresponding to edema in brain metastases and to malignant glial cell infiltrate in glioblastoma. Perfusion imaging shows a higher rCBV in the periphery of the lesion in glioblastoma compared to brain metastases [40] (Fig. 12.2). There are various cutoffs across studies but it appears that peritumoral edema around brain metastases shows no significant change in its perfusion compared to normal brain tissue, in contrast to peripheral glioma tumor cell infiltrate which present an increased rCBV. Cutoffs for rCBV value to distinguish the two lesions are thus logically around 1–1.1 [41, 42] with an area under the ROC curve of 0.98 in the study of Bulakbasi et al. [41]. The meta-analysis of Liang et al. [40] found a sensitivity of perilesional rCBV of 82%, a specificity of 96%, and a diagnostic odds ratio of 90. Another way to differentiate the two types of tumor is MRS. Spectroscopic analysis of both the central tissue portion of the lesion and the unenhanced peripheral hyperintense signal on T2-weighted images of the tumor are useful, with a better contribution of the latter. The analysis of the central necrosis spectrum shows, in both lesions, an unspecific profile of necrosis, with a decreased peak of NAA (corresponding to neuronal destruction) and increased peaks of lipid and lactate [43], with a trend of a greater peak of lipids in metastases [43]. MRS of the peripheral non-enhancing portion of glioblastoma presents a profile of proliferative intracerebral cells with neuronal destruction, while the peripheral areas of brain metastases have a profile similar to normal brain parenchyma. In the study of Tsougos et al., the peritumoral regions of glioblastoma present metabolic ratio values for NAA/Cr, Cho/Cr, Cho/NAA, and Lip+Lac/Cr of 1.46, 1.66, 1.28, and 0.68, respectively, versus 1.91, 1.29, 0.69, and 0.62, respectively, for metastases [42].

Integration of several MRI parameters or machine-learning paradigms (also based on multiple metrics) improves the ability of the technique to differentiate glioblastoma and brain metastases. For example, Bauer et al. [44] reached an AUC of 0.98 integrating DTI parameters and rCBV in a small study, and Tsougos et al. an AUC of 0.85 using rCBV and Cho/Cr ratio in the peripheral areas of the tumors [42].

12.2.1.3 Determining Underlying Primary Carcinoma

Between 10% and 15% of patients presenting with brain metastases have no identified primary lesion even after initial exhaustive examination [45, 46]. In the absence of other ways to identify the primary disease, biopsies of the brain lesions are usually performed. However, several MRI parameters can help to identify the primary cancer.

Brain repartition patterns of metastatic lesions is a first parameter to help in the diagnostic process, as briefly mentioned in the first section of this chapter. For example, metastases of non-small cell lung carcinoma are more often located in the parietal and occipital regions, compared to breast carcinoma, which tends to favor cerebellar areas [47]. There are also differences in brain location between oncological lesions originating from the same organ but with different histology, as reported by Kyeong et al. Metastases from triple-negative type breast cancer occur more often in the frontal lobe, limbic

region, and parietal lobe, whereas lesions from HER2-positive cancers occur less frequently in the frontal lobe and subcortical region, and luminal types are less frequently found in the occipital lobe, subcortical region, and cerebellum [48]. Metastases from triple-negative type breast cancer also tend to be more cystic compared to other subtypes of breast cancer [49]. Those data, even if statistically significant, have no real clinical impact, as tissue analysis is still required as the gold standard to base treatment decisions on. MRS, SWI, and DWI have also been tested alone but with, to date, a very limited clinical added value.

A potential solution in the future could be the use of machine-learning algorithms. One of these has recently shown significant classification abilities with areas under the receiver operating characteristic curve ranging between 0.64 for non-small cell lung cancer and 0.82 for melanoma [50], far from being perfect, but still being a potentially promising technique.

12.2.2 Meningeal Metastases and Unusual Locations (Pituitary Gland, Choroid Plexus, Skull)

Metastases can also affect the meninges. Dural metastases are an invasion by tumor cells of the dura mater. This is an uncommon metastatic extension, more frequent in breast and prostatic cancer [51]. MRI is a useful technique to detect these metastases but radiologic features of a focal lesion are unspecific and pose the problem of the differential diagnosis with meningioma. Neither morphologic aspects (included dural tail sign) nor advanced MRI techniques have proven clinically reliable to differentiate dural metastases from meningioma [51]. 3D T1-weighted sequences after GBCA injection are the most sensitive acquisitions to detect dural lesions. Lumbar puncture (LP) with CSF analysis is recommended to detect malignant cells. However, if no previous cerebral imaging is available, and if biopsy is hazardous, 3 months' imaging follow-up may be considered, with no growth of the lesion favoring the diagnosis of meningioma.

Dural involvement can also be diffuse, with most of the time thickening and enhancement of the entire dura mater and nodular aspect. Patient's history is often sufficient to rule out classical differential diagnosis as sarcoidosis, subdural hematoma, or empyema. CSF hypotension must also be eliminated as a differential diagnosis but this does not present as the usual nodular aspect of meningeal metastases.

5–8% of patients with solid tumors and 5–15% of patients with hematologic malignancies will present with leptomeningeal metastases [52]. This condition corresponds to a metastatic involvement of the two deepest meningeal layers: the pia mater and arachnoid. It confers a very poor prognosis with an average survival of 2–4 months [52]. Leptomeningeal metastases spread via CSF, thus LP with cytological analysis of the CSF remains the gold standard for their diagnosis. CSF cytology is positive in up to 90% of patients with suspected leptomeningeal metastases after three high-volume LP with a specificity superior to 95% [53]. MRI is recommended to make the diagnosis of a leptomeningeal involvement, presenting as an enhancement of subarachnoid space, usually visualized around the pituitary stalk, cranial nerves, and in the inner auditory canals, cerebral sulci or basal cisterns. Conspicuity of leptomeningeal metastases is optimal with 3D T1-weighted turbo spin echo sequences, but post-contrast T2-weighted FLAIR images have also a good sensitivity to detect these [54–56] (Fig. 12.3c, d). Both acquisitions should be performed when leptomeningeal metastases are suspected.

Brain and meningeal metastases are by far the most frequent locations of encephalic metastases, but other unusual sites can be involved and must be systematically checked, such as the pituitary gland, choroid plexus, skull, and skull base. Note that metastases can even occur in a pre-existent brain lesion, most commonly meningioma. This

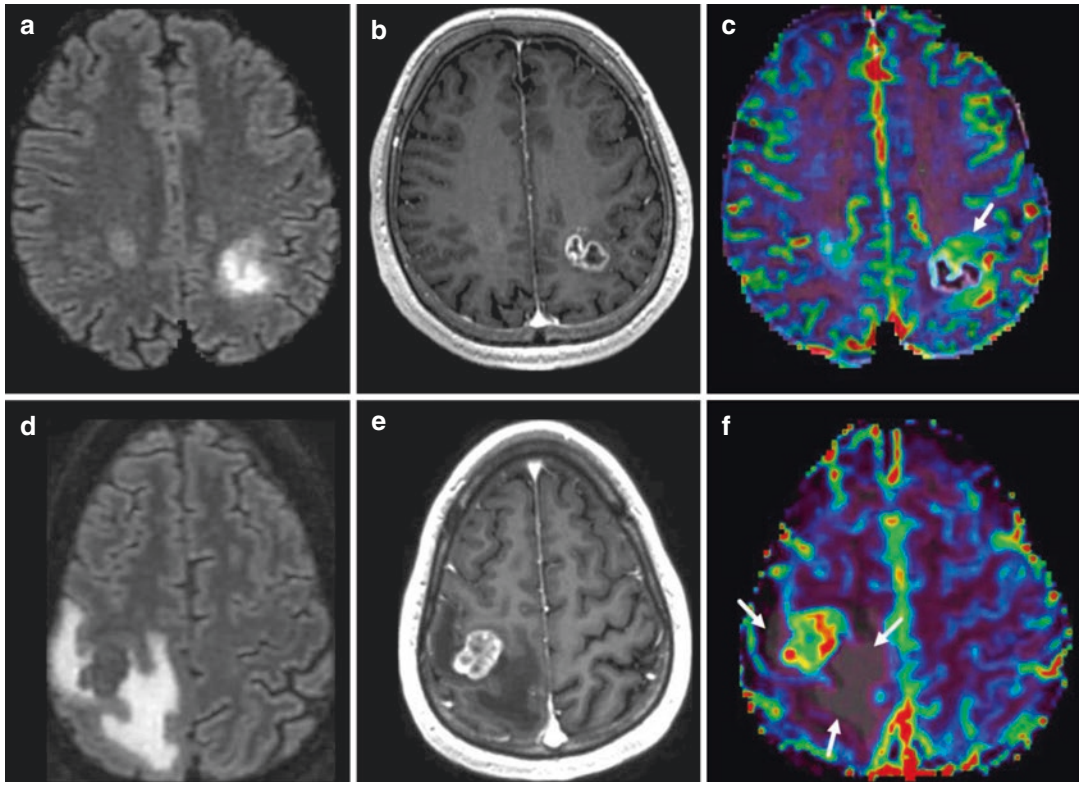

Fig. 12.3 Distinguishing metastasis from high-grade glioma with DSC perfusion MRI. Perfusion imaging for distinguishing glioblastoma (top row: **a**–**c**) from metastasis (bottom row: **d**–**f**). Post-contrast T1w (**b**, **e**) imaging shows a ring-enhancing lesion in both patients, with perifocal hyperintensity on T2w-FLAIR (**a**, **d**). There is increased rCBV (arrow) in the peritumour region (combination of tumor infiltration and vasogenic edema) of glioblastoma (**c**); rCBV is very low (arrows) in the peritumor region (vasogenic edema) of metastasis (**f**). Figure from: "CNS involvement in non-CNS tumours" in: Clinical Neuroradiology. ESNR textbook. Published by Springer. Editors: F. Barkhof, R. Jäger, M. Thurnher, A. Rovira

is known as a "tumor-within-tumor" or a "collision tumor."

12.3 Treatment Planning

12.3.1 Stereotactic Radiosurgery Planning and Prognosis Markers for Oncologic Response

As mentioned earlier in this chapter, imaging—and specifically MRI—has become mandatory for brain metastases treatment planning. First and foremost, it is the best way to get the most exact number of brain metastases and evaluate the total tumor volume. These elements are essential to decide whether patients with metastatic brain tumors should undergo SRS versus WBRT.

More than the overall number of metastases, the total tumor volume needing treatment is a better predictor of outcome and radiation necrosis: SRS alone could be considered when total tumor volume is "low" (generally <7 mL, but up to 13 mL). However, other patient-specific factors should be considered, such as disease-specific GPA, tumor histology, molecular status and radiosensitivity, status of systemic disease, and systemic therapeutic options [57]. SRS treatment is driven by the

visible enhancing part of the lesions defined as the gross tumor volume (GTV) receiving high doses of radiation with limited exposition of the healthy surrounding tissues. 3D MRI images of the patient's brain are merged with the radiation therapy planning CT scan, allowing a precise delineation of the lesions by radiation oncologists. Classically 3D T1-weighted images after GBCA injection are used. A recent study suggests that using DWI, and more specifically ADC map, could offer a better accuracy in brain metastases delineation, with a GTV including peripheral non-enhancing portions of the lesion [58]. Two pre-treatment parameters are predictive of a better response to SRS: extensive brain edema surrounding the lesions and high ADC value within the lesion [59]. Spanberger et al. showed in 2012 that extensive perifocal edema of a single brain metastasis is associated with a better response and correlate with higher overall survival [60]. Conversely, rCBV and MRS profile do not seem to correlate with tumor response [61, 62].

12.3.2 Surgical Planning

Similarly to SRS planning, surgery planning needs a precise description of the lesion to allow a complete removal, improving patient survival with minimal damage to healthy tissue, thus avoiding post-surgical neurological impairment. Special attention should be paid to lesions located in eloquent regions. They rather are treated by SRS, but when this technique cannot be used, surgical procedures sometimes need preoperative functional imaging to provide cortical function mapping and visualization of the subcortical white matter tracts. These data are very useful for surgeons during the procedure and they have been well described for glioma [63] but are also used for the surgery of metastases [64]. Briefly, cortical functions' locations are mapped using blood oxygen level-dependent (BOLD) functional MRI (fMRI) evaluating local cortical hemodynamic response to particular tasks performed by the patient during the image acquisition. The sequence is based on echo-planar gradient echo imaging, with a high susceptibility to the oxy-hemoglobin over deoxy-hemoglobin concentration ratio varying according to cortical specific activations. White matter tracts are commonly visualized using DTI. Both techniques are sensitive to magnetic susceptibility artifacts limiting their utilization around hemorrhagic lesions. Sensorimotor, language, and visual networks are the most explored functions before surgery because their impairment is highly disabling.

12.4 Post-Treatment Monitoring

12.4.1 Response to Treatment

After surgery for brain metastases, complete removal of the lesions should be assessed by MRI because partial resection is associated with recurrence. The visualization of remaining pathologic tissue is required to adapt further treatments. MRI should be performed early (within the first 48 h after surgery) before the appearance of reactive enhancement, which can lead to potential misinterpretations [65, 66]. Note that such reactive enhancement can also be seen within 24 h of surgery, but the incidence increases with the time post-surgery and doubles after 48 h.

After SRS, the expected evolution of radiosensitive lesions is an initial increase of edema with blurred enhancement of the treated lesion, followed by a progressive shrinking of the lesion and decreased surrounding edema [8]. Focal abnormalities and enhancement may never completely disappear even if there is no sign of recurrence. However, about 30% of treated lesions present a transient increase in the volume of the enhancement that typically begins at approximately 6 weeks after the treatment, and which could last beyond 15 months, with no evidence of progressive tumor [67]. This phenomenon is called pseudo-progres-

sion when it occurs during the 6 months after SRS. In the study of Patel et al. in 2011, including 120 patients and 516 metastases treated by SRS, although about 50% of patients had at least one lesion presenting with an increased size at some point during follow-up, only 8% underwent a salvage surgery [67].

Early changes of perfusion metrics can help to predict lesion response to SRS, but results are controversial. Jakubovic et al. in 2014 reported lower Ktrans and lower relative cerebral blood flow (rCBF) one week after treatment, and higher rCBF and rCBV at 1 month in association with tumor response [68]. Conversely, Almeida-Freitas also in 2014 and Essig et al. in 2003 found that increase in Ktrans between 4 and 12 weeks after SRS was associated with tumor progression at a later stage [61, 69]. Several studies present also controversial results on early ADC value changes after SRS, with no clear clinical relevance. Future multi-parametric studies should bring more data.

Recently, one study showed that early changes in the intra-extracellular water exchange rate constant, measured by MRI 1 week after SRS, highly correlated with long-term tumor response and could predict the extent of tumor shrinkage at 1 month after SRS [70].

After whole brain radiotherapy (WBRT) for brain metastases, the response is expected to be a decrease in the size of the lesions with usually an initial increase of surrounding edema.

As we can see, response assessment after treatment of brain metastases is a real challenge for neuro-radiologists. The Response Assessment in Neuro-Oncology (RANO) Group has proposed criteria to evaluate brain metastases after treatment for cerebral metastases [71] and very recently, in January 2019, revised criteria for leptomeningeal metastases [72]. We simply want to remind here that MRI is as good to detect new lesions during follow up, as it is to assess the tumor extension initially. For adequate response assessment, it is important that the same imaging protocol is used for each surveillance time point.

12.4.2 Radiation Necrosis and Radiation-Induced Changes

As described in the precedent section of this chapter, increase in size of a brain metastasis after SRS does not always indicate a recurrence. Within the 6 months following the treatment, pseudo-progression can occur. After 6 months and usually within the 2 years after SRS, lesions of radiation necrosis can also appear. These are very difficult to distinguish from tumor recurrence based on morphological parameters alone. The most useful MRI metric to differentiate radiation necrosis from recurrence is rCBV. Indeed, radiation necrosis, like all necrosis, tends to present a rarefaction of blood vessels; meanwhile, metastasis recurrence is highly perfused. The accuracy of the technique varies according to studies, as does the cutoff value. Sensitivity of rCBV to differentiate recurrence from radiation necrosis is between 70% and 100% and specificity between 90% and 95% [73, 74]. rCBV cutoffs vary in the studies between 1.52 and 2.1. In 2009, Barajas et al. used the signal recovery as a metric, yielding a sensitivity of 95% and a specificity of 100% [75]. The time course of contrast enhancement is also an interesting parameter. Radiation necrosis presents a progressive enhancement with late wash out, contrary to metastasis' recurrence, having an early wash out. A 3D T1-weighted delayed acquisition 75 min after GBCA injection shows that recurrences present a wash out with decreased signal, contrary to radiation necrosis, in which GBCA accumulates, leading to an increased signal [76] (Fig. 12.4).

Finally, a recent preliminary study on 16 patients by Mehrabian et al. suggests that two metrics of chemical exchange saturation transfer technique could help to differentiate radiation necrosis from tumor recurrence [77].

Late changes can also be observed after WBRT as leukoencephalopathy, atrophy, and cavernous hemangioma.

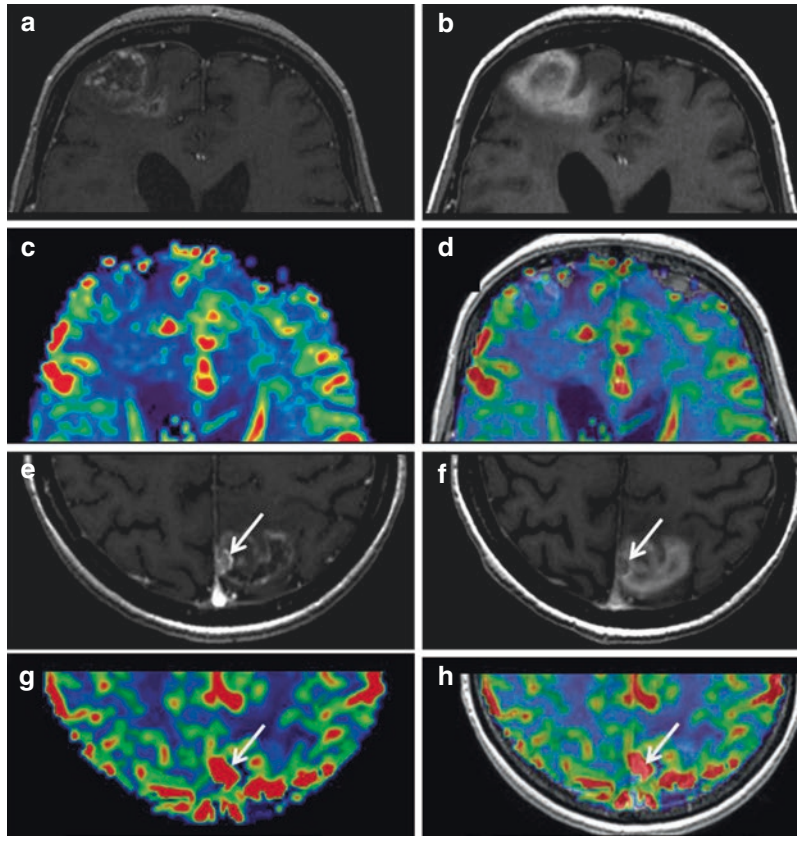

Fig. 12.4 Differences in MRI between radiation necrosis and recurrence. Radiation necrosis is characterized by a ring-shaped enhancement on 3D T1 gradient-echo weighted images (3DT1-GE) (**a**) increased on delayed images acquired 75 min after gadolinium based contrast agent (GBCA) injection (**b**) with low relative cerebral blood volume (rCBV) (**c**). Image **d** represents the merging of images **a** and **c** to check the co-location of the enhancement and the low rCBV. Recurrence has variable presentation. Here shown is a ring-shaped enhancement on 3DT1-GE (**e**). This enhanced lesion presents a vast majority of low rCBV (**g**) and delayed increased enhancement (**f**) corresponding to radiation necrosis but there is a parietal nodule (white arrows) presenting high rCBV and a wash-out on the delayed 3DT1-GE corresponding to a metastasis' recurrence. Image (**h**) represents the merging of images (**e**) and (**g**)

12.5 Conclusion

Brain metastases management is a central question for neuro-oncologists and neuro-radiologists. Imaging is essential to detect, treat, and follow patients with this condition. Radiological techniques improve rapidly and other non-invasive techniques such as metabolic imaging become available for patient care, providing useful information. These techniques are discussed in the following chapter.

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Metabolic Imaging of Brain Metastasis

13

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13.1 Introduction

Contrast-enhanced magnetic resonance imaging (MRI) is the method of choice for evaluating patients with metastatic brain tumors. This technique has widespread availability and excellent spatial resolution. However, the specificity of conventional MRI is low, resulting in important diagnostic challenges [1–3]. These challenges include discriminating brain metastases (BM) from other primary brain tumors (e.g., gliomas and primary CNS lymphomas) as well as abscesses. Furthermore, MRI signal changes (e.g., newly diagnosed contrast-enhancing lesions and increase of the contrast enhancement extent or signal changes on T2 or FLAIR sequences) may be related to inflammation, acute infection, demyelination, ischemia, or treatment-related effects (e.g., reactive changes after surgery, radiotherapy, and systemic drug treatment) and are difficult to distinguish from true BM relapse. Additionally, these reactive treatment-related effects are of considerable clinical importance because they may result in an erroneous premature treatment termination with potentially negative influence on survival [4, 5]. Furthermore, the efficacy of a subsequent therapy can be overestimated.

In patients with previously irradiated BM, the diagnosis of local recurrence by standard MRI may be particularly challenging due to radiation-induced treatment effects that range from reversible inflammation to radionecrosis. Furthermore, diagnostic challenges associated with the assessment of MRI changes in response to immunotherapy may also occur, e.g., delayed response to therapy or therapy-induced inflammation that mimic progressive disease [6, 7]. Due to the fact that treatment management decisions and prognosis may vary based on the underlying process, it is crucial to distinguish true BM recurrence from treatment-related changes [3].

Another important aspect in the management of patients with BM is the assessment of treat-

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ment response. The ability to predict response to treatment may enable the treatment termination in non-responsive patients, prevention of additional toxicity, and earlier initiation of an alternative therapy. Despite promising efforts in defining response assessment criteria for BM [5, 8], these criteria may not fully consider the limitations of anatomical MRI. In the light of newer systemic treatment options such as targeted therapy and immunotherapy, tools which provide additional information on tumor proliferation and tumor metabolism (e.g., amino acid transport via amino acid transporters of the L-type (LAT)) become increasingly important.

Positron emission tomography (PET) uses a variety of radioactive agents that target different metabolic and molecular processes, and can provide relevant additional information that enables improved diagnostics, especially in clinically equivocal situations. Besides other tracers, particularly the use of PET with radiolabeled amino acids has shown to be an important diagnostic tool [1, 9–11]. Moreover, a recent study suggests that BM strongly overexpress LAT transporters and are therefore an interesting target for amino acid PET imaging [12].

In this chapter, we discuss metabolic imaging techniques such as PET which image glucose metabolism, amino acid transport, and various other targets for the management of patients with BM.

13.2 Tracers for Pet Imaging in Patients with Brain Metastasis

Several tracers addressing different molecular targets or pathophysiological pathways in BM are available for PET imaging and are summarized in the following paragraphs.

13.2.1 ^{18}F-2-Fluoro-2-Deoxy-D-Glucose

^{18}F-2-fluoro-2-deoxy-D-glucose (FDG) PET has evolved over the last several decades into a key clinical PET modality in detecting both intra- and particularly extracranial tumors and represents the most widely used tracer in oncological PET imaging [13]. With a half-life of the ^{18}F isotope of 110 min, the tracer does not need in-house production, which facilitates supply. Therefore, FDG is available at all PET centers independently of the presence of an on-site cyclotron. Increased FDG uptake is common in highly proliferating cells because tumor cells have increased the expression of glucose transporters and hexokinase, the enzyme that converts glucose (and FDG) to a phosphorylated product. Due to an increased glycolysis in neoplastic tissue, uptake of FDG is generally higher than in non-neoplastic tissue. However, the high and regionally variable FDG uptake in normal brain parenchyma often makes the delineation of tumors in the brain difficult [9]. Another problem of FDG is the high tracer uptake in inflammatory tissue [1].

13.2.2 Amino Acid PET Tracers

Radiolabeled amino acids have been used in neurooncological practice since 1983 [14]. The most experience with this class of PET tracers for brain tumor imaging has been gained with ^{11}C-methyl-L-methionine (MET). This tracer is comprised of the essential amino acid methionine labeled with the positron-emitting isotope carbon-11, which has a half-life of 20 min [13, 15]. The relatively short half-life limits the use of MET to PET centers with an on-site cyclotron unit. More recently, amino acid tracers labeled with positron emitters that have longer half-lives have been synthesized. This has resulted in improved distribution, efficiency, and cost-effectiveness [16]. For example, *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) was developed in the late 1990s and is a ^{18}F-labeled amino acid tracer (half-life, 110 min) with logistic advantages for clinical practice compared to MET [17, 18]. The use of FET has grown rapidly in recent years, especially in Western Europe [19]. Clinical results in brain tumors with PET using MET and FET appear to be comparable [20–22]. Switzerland was the first country to approve FET PET as a medical drug in

2014 [23]. Another ^{18}F-labeled amino acid analog is 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (FDOPA), which was initially developed to measure dopamine synthesis in the basal ganglia and has also increasingly been used as a tracer for brain tumor imaging [24]. FDOPA is currently approved for the characterization of presynaptic dopaminergic activity in patients with Parkinsonian syndromes in the United States and Western Europe.

The increased uptake of MET, FET, and FDOPA in gliomas and BM reflects increased transport via the amino acid transport system L for large neutral amino acids, namely, the subtypes LAT1 and LAT2 [12, 25–27]. A feature that distinguishes FET from MET and FDOPA is the high metabolic stability of FET. After transport by L-type amino acid transporters into tumor tissue, both MET and FDOPA show metabolic degradation, incorporation into protein, or participation in other metabolic pathways [28], whereas FET is not metabolized [20]. Furthermore, overexpression of LAT1 closely correlates with malignant phenotype and the proliferation of gliomas [29].

In addition to static images, dynamic FET PET data can be acquired, allowing for the ability to characterize the temporal pattern of FET uptake by deriving a time-activity curve (TAC). It has been demonstrated that parameters derived from TACs (e.g., TAC configuration, time-to-peak, slope) contain additional biological information, which may be helpful especially for the differentiation of BM recurrence from radiation-induced changes [30–32]. This has also been described for glioma patients [33, 34] and, moreover, for glioma grading [35, 36] as well as for the prognostication of untreated gliomas [37, 38]. Up to now, this phenomenon has not been observed by dynamic MET or FDOPA PET [39, 40] and it remains to be determined whether these amino acid tracers can characterize tumors in a similar manner to that of dynamic FET PET imaging.

In some centers, the amino acid PET tracer α-^{11}C-methyl-L-tryptophan (AMT) is increasingly being used for brain tumor imaging [41]. However, despite promising results in terms of differential diagnosis in patients with newly diagnosed brain tumors including BM, the number of studies is currently low [42].

13.2.3 Other PET Tracers

In a very limited number of patients with BM, non-FDG and non-amino acid PET tracers have been used. In particular, tracers such as ^{18}F-sodium fluoride (^{18}F-NaF), 3′-deoxy-3′-^{18}F-fluorothymidine (^{18}F-FLT), ^{82}Rubidium, as well as PET tracers targeting the endothelial prostate-specific membrane antigen (PSMA) have predominantly been used for BM visualization and the assessment of treatment response [43–49]. Choline derivates (e.g., ^{18}F-choline), which are in use for the diagnosis of recurrent prostate cancer, have also been reported to detect BM [50, 51]. Animal studies have indicated that PET imaging using agents targeting the mitochondrial translocator protein (TSPO) which is upregulated on activated microglia as well as malignant tumor cells may be helpful to detect BM at an early stage of development [52]. However, despite promising results, experiences with these tracers are mainly based on single cases in patients with BM and their usefulness has to be confirmed in larger studies.

13.3 Clinical Applications for Pet Imaging in Patients with Brain Metastasis

13.3.1 Identification of Newly Diagnosed and Untreated Brain Metastasis Using FDG and Amino Acid PET

Although conventional MRI is the method of choice for the detection of BM, some centers include the skull for whole-body FDG PET/CT staging examination of cancer patients, e.g., in patients with lung cancer. However, the value of this procedure is highly questionable considering the low positive yield because of the low incidence of new BM in asymptomatic patients

together with the limited sensitivity of FDG PET in brain tumors due to physiologically high levels of glucose metabolism in healthy brain parenchyma resulting in a poor tumor-to-background contrast [53, 54]. Furthermore, a prospective study has shown that in comparison to contrast-enhanced standard MRI for cerebral staging in newly diagnosed lung cancer, a considerable number of patients are falsely diagnosed as being free from BM using FDG PET [55]. In that study, MRI detected an overall of 100 BM, whereas FDG PET detected only 17 BM resulting in a poor sensitivity for this indication (27%). Accordingly, a recent meta-analysis including more than 900 patients has suggested that contrast-enhanced MRI had higher cumulative sensitivity (77%) than FDG PET (21%) for the diagnosis of BM in lung cancer [56].

The increased expression of amino acid transporters observed in BM compared to healthy brain tissue renders radiolabeled amino acids suitable for PET imaging with high tumor-to-background contrast [12]. In contrast to FDG PET, the sensitivity of amino acid PET using FET to depict larger (>1 cm diameter) BM seems to be clearly higher (approximately 90% were FET positive with a maximum tumor/brain ratio ≥1.6) [57] but may be limited in lesions with a small diameter below 1 cm. This has been observed in a pilot study in patients with newly diagnosed and untreated BM which correlated FET uptake characteristics with MRI parameters. In that study, the sensitivity of standard MRI for the detection of BM was 100% [57]. Currently, the most sensitive and commonly used imaging modality for the detection of brain metastases remains thin-slice contrast-enhanced MRI.

13.3.2 Differential Diagnosis of Newly Diagnosed and Untreated Brain Metastasis Using FDG and Amino Acid PET

Regarding the differentiation between newly diagnosed BM and glioblastoma, it has been demonstrated that there are no significantly different FDG standardized uptake values (SUV) between these entities [58, 59], whereas the SUVs of the radiolabeled amino acid AMT were significantly lower in BM than in glioblastomas [42]. Nevertheless, some studies suggest that the metabolic activity as assessed by FDG PET is higher in primary CNS lymphomas than in BM [58, 59].

The level of expression of LAT in cancer cells was reported to correlate with aggressive tumor features and worse prognosis [60, 61] and to be higher in recurrent compared to newly diagnosed BM [12]. However, there are no studies as yet investigating the prognostic value of amino acid PET in patients with BM. Furthermore, the uptake intensity as well as LAT expression levels are also highly variable, even in metastases of the same primary tumor type [60, 61]. The origin of the primary tumor can therefore not be based on amino acid PET findings [57].

In contrast to glioma, the size and volume of a BM is usually well delineated on contrast-enhanced MRI. Thus, amino acid PET does not add valuable information for biopsy or treatment planning as that reported for newly diagnosed gliomas [62, 63].

13.3.3 Differentiation of Radiation-Induced Changes from Brain Metastasis Recurrence Using FDG and Amino Acid PET

Oncologists of all subspecialities are often confronted with the clinical problem of differentiating tumor recurrence from treatment-related changes following radiation therapy, and in particular after high-dose focal radiation (i.e., radiosurgery or fractionated stereotactic radiation therapy). Currently, conventional MRI does not reliably differentiate local brain tumor recurrence or progression from radiation-induced changes including radiation necrosis. In gliomas, radiation necrosis usually manifests within 6–12 months after standard fractionated radiotherapy and occurs in approximately 5–25% of all treated patients [64, 65]. For patients with BM treated by radiosurgery, a similar rate of radiation

necrosis (approximately 25%) has been reported [66], although depending on the irradiated brain volume receiving a specific radiation dose, the risk of radiation necrosis may be as high as 50% [66]. It should be noted that this wide variation in reported incidence is likely a consequence of varying definitions of treatment-related changes in retrospective studies, including whether the patient is symptomatic or not, and that treatment-related changes represent a spectrum of pathophysiologic changes that may be purely radiographic without associated symptoms, to symptomatic, refractory to corticosteroids, and requiring neurosurgical or other intervention.

In recent years, FDG PET has been studied as an additional neuroimaging tool to solve this relevant clinical problem (Table 13.1). However, in these studies the number of included patients was low, there were significant inconsistencies in terms of the FDG PET method applied as well as the thresholds used for the differentiation of radiation-induced changes from BM recurrence, and the diagnostic performance varied considerably (range of sensitivity, 40–95%; range of specificity, 50–100%) (Table 13.1). Dual phase FDG PET seems to be superior compared to a standard (single phase) scan [67]. However, a major limitation of that approach is the long time interval

Table 13.1 Overview of studies regarding the differentiation of radiation-induced changes from brain metastasis recurrence using FDG PET

	Chao et al. (2001) [92]	Belohlavek et al. (2003) [93]	Chernov et al. (2005) [76]	Horky et al. (2011) [67]	Lai et al. (2015) [69]	Hatzoglou et al. (2016) [70]	Tomura et al. (2017) [68]
n Recurrent metastases	18	8	4	16	6	11	10
n Radiation-induced changes	18	49	5	11	8	15	8
Neuropathological confirmation of diagnosis	36%	5%	56%	n.a.	100%	23%	56%
FDG PET method	Static scan	Static scan	n.a.	Dual phase PET; median time between early and late scan, 3.8 h	Static scan	Static scan	Static scan
Additional imaging method	None	None	MRS	None	ASL	DCE PWI	DWI, MET PET
Sensitivity	65%	75%	50%	95%	83%	82%	40%
Specificity	80%	94%	80%	100%	75%	80%	50%
Accuracy	n.a.	91%	67%	96%	79%	n.a.	n.a.
Threshold	Visually	Visually	Visually	Change of L/GM ratios >0.19 over time	3.0 (SUV_{max})	1.4 (TBR_{max})	0.97 (TBR_{max})
Performance of FDG PET compared to another imaging method(s)	n.a.	n.a.	Inferior	n.a.	Inferior	Inferior	Inferior

ASL Arterial spin labeling, *DCE PWI* Dynamic contrast-enhanced perfusion-weighted imaging, *DWI* Diffusion-weighted imaging, *FDG* ^{18}F-2-fluoro-2-deoxy-D-glucose, *L/GM* Lesion to gray matter ratio, *MET* ^{11}C-methyl-L-methionine, *n.a.* Not available, *MRS* Single- and multi-voxel proton MR spectroscopy, TBR_{max} Maximum standardized uptake value of the lesion divided by the mean standardized uptake value of the reference region, SUV_{max} Maximum standardized uptake value.

between PET scans (median time between FDG PET scans, 3.8 h; range, 2–5.7 h) [67] hampering applicability in clinical routine. Furthermore, compared to various other imaging methods such as MET PET [68] and MRI-based arterial spin labeling (ASL) [69] as well as perfusion- and diffusion-weighted imaging [68, 70], the diagnostic performance of FDG PET seems to be inferior (Table 13.1).

Amino acid PET has also been investigated as an imaging modality to address this relevant problem in clinical practice (Table 13.2). For instance, MET PET may differentiate recurrent BM from radiation-induced changes using a simple semiquantitative region-of-interest (ROI) analysis for the calculation of tumor/brain ratios. MET PET has demonstrated a sensitivity and specificity of 70–80% in differentiating treatment effect from recurrent tumor [71–73]. FDOPA PET has also been shown to differentiate recurrent or progressive BM from radiation-induced changes with high sensitivity (81%) and specificity (84%) [74]. Another study has reported an accuracy of FDOPA PET of 91% for differentiating radiation-induced changes from progressive disease in patients with BM after stereotactic radiosurgery, out-performing MRI-derived perfusion metrics 91–76% [75]. Similar diagnostic accuracy has also been reported for FET PET; using the tumor/brain ratios and dynamic parameters, FET PET differentiated locally recurrent BM from radiation-induced changes with a sensitivity of 95% and specificity of 91% [30] (Fig. 13.1). Correspondingly, dynamic FET PET studies in a larger number of patients demonstrated a sensitivity and specificity of 80–90% [31, 32]. Furthermore, compared to FDG PET, MR spectroscopy and MRI-based perfusion- and diffusion-weighted imaging, the diagnostic performance of amino acid PET seems to be superior [68, 75, 76] (Table 13.2). Across all available amino acid PET studies for this indication, the histological confirmation of diagnosis (i.e., BM recurrence or radiation injury) ranges from 11% to 56% (Table 13.2). Moreover, in Europe the cost efficiency of amino acid PET has been demonstrated for the differentiation between recurrent BM and radiation-induced changes [77].

From the methodological point of view, recent literature highlights the value of PET radiomics in assessing the tumor phenotype using non-invasive imaging [78]. Radiomics enables the high-throughput extraction of a large number of quantitative features usually from already obtained MR and PET imaging, potentially providing a comprehensive quantification of the tumor phenotype at comparatively low cost [79, 80]. One concept of radiomics is the use of textural feature analysis as a tool that objectively and quantitatively describes intrinsic properties of cancer, particularly heterogeneity. Using FET PET, it was demonstrated that radiomic textural feature analysis provided non-invasive quantitative information useful for the distinction between treatment-related changes and disease progression [81]. Furthermore, for that distinction it could be recently demonstrated that a combined FET PET and MRI radiomics analysis using textural features was able to increase the diagnostic specificity of more than 90% [82].

13.3.4 Differentiation of Treatment-Related Changes Following Immunotherapy from Brain Metastasis Recurrence Using FDG and Amino Acid PET

Immuno-oncology is a rapidly developing therapeutic field with potential applications regarding the therapy of CNS malignancies, especially in patients with BM [83]. However, early phase studies have indicated diagnostic challenges associated with the assessment of radiological changes in response to immunotherapy, wherein a subset of patients exhibit a delayed response to therapy or therapy-induced inflammation that mimic progressive disease. In particular, following immunotherapy, long-term survival and tumor regression may occur after what was believed to represent initial disease progression or even after the appearance of new lesions [6]. Literature exists characterizing pseudoprogression occurring in patients with BM treated with immunotherapy and in particular with immune checkpoint inhibitors such as cytotoxic

Table 13.2 Overview of studies regarding the differentiation of radiation-induced changes from brain metastasis recurrence using amino acid PET

	Tsuyuguchi et al. (2003) [72]	Terakawa et al. (2008) [71]	Galldiks et al. (2012) [30]	Lizarragaet al. (2014) [74]	Ciconeet al. (2015) [75]	Minamimoto et al. (2015) [73]	Romagnaet al. (2016) [32]	Cecconet al. (2017) [31]	Tomura et al. (2017) [68]	Yomo et al. (2017) [94]
n recurrent metastases	9	24	19	32	20	n.a.	21	36	10	19
n radiation-induced changes	12	32	21	51	26	n.a.	29	40	8	18
Neuropathological confirmation of diagnosis	52%	n.a.	28%	11%	24%	n.a.	40%	34%	56%	46%
Tracer	MET	MET	FET	FDOPA	FDOPA	MET	FET	FET	MET	MET
Amino acid PET method	Static scan	Static scan	Dynamic scan	Static scan	Static scan	Static scan	Dynamic scan	Dynamic scan	Static scan	Static scan
Additional imaging method	n.a.	n.a.	n.a.	n.a.	DSC PWI	n.a.	n.a.	n.a.	DWI, FDG PET	n.a.
Sensitivity	78%	79%	74%	81%	90%	82%	86%	86%	90%	82%
Specificity	100%	75%	90%	73%	92%	86%	79%	88%	75%	75%
Accuracy	n.a.	n.a.	83%	76%	91%	83%	82%	87%	n.a.	n.a.
Threshold (TBR_{mean})	1.4	1.4	2.0	1.7	1.6 (TBR_{max})	1.3 (TBR_{max})	2.0	2.0	1.4 (TBR_{max})	1.4 (TBR_{max})
Performance of amino acid PET compared to another imaging method(s)	n.a.	n.a.	n.a.	n.a.	Superior	n.a.	n.a.	n.a.	Superior	n.a.

DSC PWI Dynamic susceptibility contrast-enhanced perfusion-weighted imaging, *DWI* Diffusion-weighted imaging, *FDG* ^{18}F-2-fluoro-2-deoxy-D-glucose, *FDOPA* 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine, *FET* *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine, *MET* ^{11}C-methyl-L-methionine, *n.a.* Not available, $TBR_{mean/max}$ Mean or maximum standardized uptake value of the lesion divided by the mean standardized uptake value of the reference region.

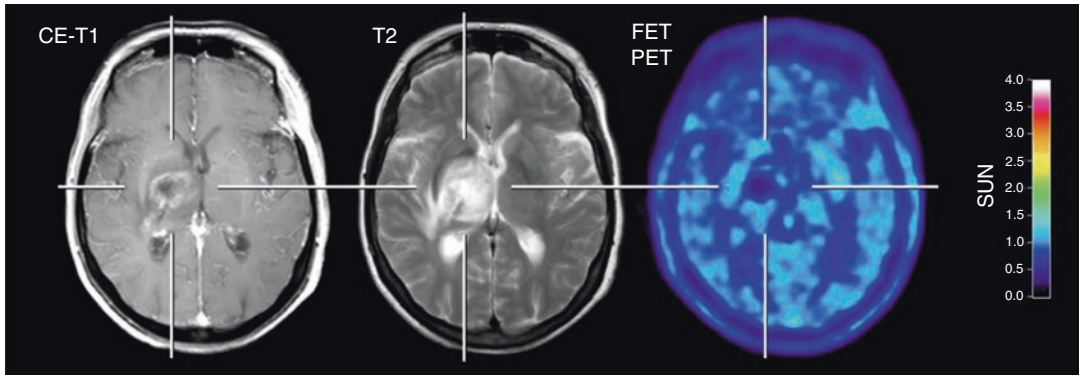

Fig. 13.1 A 66-year-old female patient with a brain metastasis secondary to ovarian cancer underwent FET PET and MR imaging. Nine months after stereotactic radiosurgery, MRI suggests tumor recurrence. In contrast, FET PET shows no increased metabolic activity, indicating a radiation injury. The diagnosis was confirmed by a stable clinical course of 6 months without a therapeutic intervention

T lymphocyte-associated antigen 4 (CTLA-4) inhibitors using ipilimumab and programmed cell death 1 receptor (PD-1) inhibitors using pembrolizumab or nivolumab [6, 7, 84, 85]. A small pilot study showed the potential of FET PET to identify pseudoprogression in patients with BM originating from melanoma treated with immune checkpoint inhibitors [86]. For this indication, data on FDG PET are currently not available.

13.3.5 Assessment of Treatment Response

As stated above, standard MRI has its limitations to differentiate BM relapse from treatment-related effects such as radionecrosis or pseudoprogression due to unspecific contrast enhancement and alterations in T2/FLAIR sequences. The use of FDG as tracer for the assessment of treatment response in PET imaging is hampered due to its high physiologic brain uptake which limits the discrimination of tumor and healthy brain metabolic activity [9]. Furthermore, in light of newer systemic treatment options such as targeted therapy and immunotherapy, tools which provide additional information on molecular aspects (e.g., metabolism, proliferation) become increasingly important.

The PET tracer FLT is an analog to the nucleoside thymidine and was developed as a PET agent to assess cellular proliferation by tracing the thymidine salvage pathway [87]. More recently, in patients with BM originating from breast cancer, FLT has been applied to assess therapy response to taxane chemotherapy (i.e., paclitaxel covalently linked to Angiopep-2, designed to cross the blood-brain barrier) and was found to supplement the information derived from contrast-enhanced MRI in terms of clarifying equivocal MRI findings [45]. In BM from malignant melanoma being treated with targeted therapy and immunotherapy, Nguyen and co-workers found in a subset of patients that metabolic responders may show a proliferative reduction on FLT PET despite apparent morphologic progression on standard MRI (i.e., pseudoprogression) [49].

Regarding amino acid PET, studies evaluating its value for the assessment of treatment response are currently not available.

13.4 Current Limitations

Despite promising initial results regarding the use of PET in patients with BM for various indications (e.g., differentiation of radiation injury from BM recurrence using amino acid PET), it has to be noted that these results were derived mainly from retrospective studies performed in single centers. Furthermore, in approximately only one-third of patients

the confirmation of imaging findings could be performed histologically. Thus, multicenter studies in a higher number of patients are necessary, optimally with histological confirmation of imaging findings.

A major clinical challenge is the detection of multiple, especially very small, BM (usually below a diameter of 1 cm). Due to the limited spatial resolution of PET, miliary disseminated metastatic disease or leptomeningeal metastasis might be missed. This is of great clinical importance because it may change the prognosis and justify the use of more aggressive treatment options (e.g., whole-brain irradiation, systemic and intrathecal chemotherapy).

To further improve patient management, well-validated prognostic markers as well as predictive imaging markers for the assessment of treatment response derived from PET are currently lacking. Newer treatment options (e.g., immunotherapy) have other requirements on neuroimaging which cannot be covered by anatomical MRI. Therefore, PET studies should be aimed on the identification of early response markers to identify successful treatment prior to changes in tumor size.

13.5 Future Perspectives

From the methodical point of view, the use of hybrid PET/MR scanners, allowing the simultaneous acquisition of both imaging modalities, might support research work in patients with BM. For example, the acquisition of static and dynamic FET PET, anatomical MRI, perfusion- and diffusion-weighted MRI, and other advanced MRI sequences such as MR spectroscopy and fMRI in a single session within can easily be performed. Besides optimizing the co-registration of various imaging modalities, this technology appears particularly attractive in patients with BM with poor clinical condition because there is no exposition to the additional radiation dose associated with a PET/CT scan, considerably reduces scanning time, and avoids multiple transports to imaging facilities. Thus, this technology provides optimal requirements for comparative imaging studies using amino acid PET and advanced MR imaging, ideally combined with neuropathological confirmation of imaging findings by stereotactic biopsy.

In order to increase the number of treatment options, PET ligands initially used for diagnostic imaging might also be instrumental for therapy by changing the radioisotope, according to the concept of "theranostics" as it has already been introduced into the management of prostatic cancer [88–90].

Further possible indications for PET in patients with BM are the prediction of BM origin, especially in patients with cancer of unknown primary (CUP syndrome), and the diagnosis of especially very small and newly diagnosed BM. Newer PET tracers targeting TSPO might help to overcome the latter mentioned problem [91] and eventually could also help targeting local treatment options such as radiotherapy.

13.6 Summary

At present, the differentiation of radiation injury from BM recurrence using amino acid PET is currently evaluated has the best evidence. Amino acid PET can add valuable information in cases of unclear differential diagnosis between post-therapeutic reactive changes after radiotherapy and recurrent BM. For this indication, present studies show consistently a high diagnostic accuracy. FDG PET can also be useful for this indication; however, present studies show a large variety of diagnostic accuracy. Thus, when using PET for this indication, amino acid PET should be given preference. Furthermore, there is only limited evidence regarding the direct comparison of advanced MRI with PET techniques. Amino acid PET seems to have a potential benefit compared to advanced MRI techniques, whereas FDG PET appears to be inferior.

A few studies show also a potential benefit of PET for the diagnosis of pseudoprogression derived from immunotherapy (i.e., checkpoint inhibitors) and for treatment response assessment of systemic treatment options (e.g., targeted therapy), but the current body of literature is comparatively small.

Regarding patients with newly diagnosed BM, the most sensitive and commonly used imaging modality for the detection of BM remains contrast-enhanced MRI. Amino acid PET using the tracer FET has a clearly higher diagnostic accuracy for the detection of BM than FDG PET. However, FDG or amino acid PET are limited in detecting smaller lesions below a diameter of 1 cm. Additionally, there is only limited evidence for a potential benefit of amino acid PET for the differential diagnosis of newly diagnosed and untreated BM versus glioma.

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14 Clinical, Imaging, and CSF Cytological Presentation of Leptomeningeal Metastases from Solid Non-CNS Primary Tumors

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14.1 Introduction

Leptomeningeal metastasis (LM) is defined as the spread of malignant cells in the subarachnoid space and in the leptomeninges. It is sometimes denoted as carcinomatous meningitis, in case of carcinoma, or neoplastic meningitis, but this term is misleading since it suggests a disorder that is primarily of inflammatory origin. LM may be observed in approximately 10% of patients with metastatic cancer [1].

The risk of experiencing LM in the course of systemic cancer today is probably higher than that figure, given that patients survive much longer, that diagnostic approaches have changed dramatically with the introduction of magnetic resonance imaging (MRI) and advanced cytology and even liquid biopsy techniques to detect cancer cells in the cerebrospinal fluid (CSF), and that the cerebrospinal compartment may be more difficult to control using systemic therapies than other body compartments. In up to 70%, the diagnosis of LM is made in the context of systemic disease progression. Breast cancer, lung cancer and melanoma are the three main causes of LM.

The median survival is limited to a few months and once neurological signs are present, they are fixed and rarely improved by therapeutic interventions. Thus, the diagnosis should be made as soon as possible in case of suspicion of LM in order to prevent neurological deterioration. The diagnosis is based on clinical evaluation, cerebrospinal MRI and CSF analysis [2].

14.2 Risk Factors

Risk factors for LM include an opening of the ventricular system during brain metastasis surgery, resection of cerebellar metastases especially when using a piece-meal resection [3–8] and primary tumor-related factors. In breast cancer patients, lobular subtype and triple negative status (absence of estrogen receptors, absence of progesterone receptors, absence of HER2 expres-

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sion) have been reported as risk factors of LM [9]. HER2 overexpression alone has been shown to be a risk factor of brain metastases; however, its role as a risk factor of LM is less clear. In lung cancer patients, EGFR mutation has been reported as being a risk factor of LM in a large retrospective cohort of 5387 non-small-cell lung (NSCLC) patients, where 184 cases of LM were identified [10]. The role of other driver mutations for LM risk has not been defined.

Only limited data are available on melanoma LM patients, and no risk factor has been identified.

14.3 Clinical Presentation

Symptoms and signs depend on the neuroanatomical regions involved by LM and are often multifocal. Headache, nausea and vomiting, mental changes, gait difficulties, cranial nerve palsies, sensori-motor deficits, cauda equina syndrome, and radicular and back pain, depending on the distribution of tumor cells in the CNS, are considered typical signs of LM [2]. The clinical presentation can be subtle with discrete and isolated symptoms and signs. Thus, a detailed clinical evaluation is required at diagnosis and during follow-up. Symptoms and signs of LM should be differentiated from those related to concomitant brain metastases and neurological complications of the cancer and its treatment. A standardized scorecard has been proposed by the RANO group [11], but it has not been validated yet.

14.4 Radiological Presentation

LM may be a diffuse disease of the entire central nervous system and cerebrospinal imaging is thus required for the staging of LM [2, 12]. Cranial computed tomography (CT) should be performed only in patients with contraindications to MRI and has its limitations in particular for the assessment of the spinal cord. The radiologic assessment of LM can be challenging. Some technical aspects should be considered when evaluating LM patients, such as slice positioning and slice thickness, and time interval between injection of contrast agent and acquisition of images. Contrast agent should be injected 10 min before image acquisition and the slice thickness should be 1 mm or less in the brain and 3 mm or less for the spinal cord [2]. Lumbar punctures should be performed after MRI since they may induce a meningeal enhancement. The most sensitive sequence for the detection of LM is the contrast-enhanced T1-weighted sequence [13, 14]. The follow-up should be performed on the same device or on an MRI scanner with identical field strength.

Typical MRI findings include linear or nodular leptomeningeal enhancement on the leptomeninges. These findings can be observed at sulcal, ependymal, cranial nerve or cauda equina levels. Communicating hydrocephalus can also be observed in LM because of poor CSF resorption. Differential diagnosis includes focal dural enhancement after surgery, pachymeningitis, meningioma en plaque, brain metastases, CNS vasculitis, Moyamoya disease, neuro-sarcoidosis, and various inflammatory and infectious diseases.

A scorecard to rate neuroimaging findings in LM has been proposed by the RANO group, but this has not been validated and is therefore currently under revision.

The radiological presentation of LM help to guide clinical decision making. Four subtypes have been delineated in the EANO ESMO guidelines [2]: A, diffuse linear leptomeningeal disease, B nodular leptomeningeal disease, C a combination of A and B, and D no focal lesions, but potentially hydrocephalus (see Table 14.1).

Parenchymal brain metastases are associated with LM in 31–66% of patients with breast cancer [15–23], 56–82% of patients with lung cancer [24–30] and 57–87% of patients with melanoma [31–33].

^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET-CT) is not helpful for the diagnosis or follow-up of LM. CSF flow studies using ^{111}indium-DTPA or ^{99}technetium macroaggregated albumin have been recommended in candidates for intra-CSF pharmacotherapy if CSF flow blocks are suspected.

Table 14.1 EANO ESMO classification of LM (based on Le Rhun et al., 2017) [2]

		Cytology/ biopsy	MRI	Confirmed	Probable[a]	Possible[a]	Lack of evidence
Type I: positive CSF cytology or biopsy	IA	+	Linear	+	n.a.	n.a.	n.a.
	IB	+	Nodular	+	n.a.	n.a.	n.a.
	IC	+	Linear + nodular	+	n.a.	n.a.	n.a.
	ID	+	Normal	+	n.a.	n.a.	n.a.
Type II: clinical findings and neuroimaging only	IIA	− or equivocal	Linear	n.a.[b]	With typical clinical signs	Without typical clinical signs	n.a.
	IIB	− or equivocal	Nodular	n.a.	With typical clinical signs	Without typical clinical signs	n.a.
	IIC	− or equivocal	Linear + nodular	n.a.	With typical clinical signs	Without typical clinical signs	n.a.
	IID	− or equivocal	Normal	n.a.	n.a.	With typical clinical signs	Without typical clinical signs

[a]Requires a history of cancer
[b]Not applicable

14.5 CSF Cytology

Indirect, but non-diagnostic pathological findings are frequently observed in the CSF of LM patients. An increased opening pressure (>200 mm H_2O) is noted in 21–42% [28, 34], high protein levels (>50 mg/dL) in 56–91% [16, 21, 28, 34, 35], decreased glucose levels (<60 mg/dL) in 22–63% [21, 28, 34, 35] and increased leukocyte counts (>4/mm^3) in 48–77.5% of the patients [21, 28, 34, 35].

CSF standard cytology is the gold standard to confirm the diagnosis of LM. The identification of malignant cells in the CSF during standard CSF cytology confirms the diagnosis of LM. The CSF should be considered as negative only in the unequivocal absence of tumor cells. In the presence of suspicious or atypical cells, the CSF should be reported as equivocal.

The sensitivity of standard cytology is moderate to low. Simple measures should be taken to facilitate the detection of malignant cells in the CSF, such as obtaining at least 5 mL of CSF, ideally more than 10 mL, processing the CSF within 30 minutes after sampling and avoiding blood contamination of the CSF [2, 11, 36–38]. If the first CSF cytology is negative or equivocal, a second sample should be obtained which reportedly increases the sensitivity to 80%. The usefulness of further CSF samples remains unclear. CSF fixation in dedicated tubes has been shown to increase the diagnostic yield in hematological diseases, but the usefulness of this approach remains to be established for solid tumors [39].

Novel technologies using epithelial cell adhesion molecule (Ep-CAM) antibodies or other tumor-specific antibody-covered magnetic nanoparticles such as high-molecular weight-melanoma-associated antigen/melanoma-associated chondroitin sulfate proteoglycan (HMW-MAA/MCSP) can identify circulating tumor cells and should contribute in the future to a higher sensitivity of detecting malignant cells in the CSF.

The Veridex Cellsearch® assay has been approved by FDA for the detection of tumor cells in peripheral blood [40]. Different adaptations of the technique have been developed for

the detection and quantification of tumor cells in the CSF [41–46], but no standard has been established until now. Tumor cells can be identified using flow cytometry with fluorescently labelled antibodies against membrane-bound proteins of tumor cells coupled with fluorescence-activated cell sorting (FACS) for the quantification of tumor cells [47, 48].

Cell-free circulating tumor DNA (ctDNA) represents a fraction of total cell-free DNA originating from necrotic and apoptotic cells. Genomic alterations can be detected by micro-arrays [49], digital/real-time polymerase chain reaction (RT-PCR), targeted amplicon sequencing and whole exome sequencing [50–53]. Analysis of ctDNA in the CSF may help the diagnosis when the standard CSF cytology is negative, detect actionable genomic targets and monitor the response to treatment [54]. CSF ctDNA is probably more sensitive than CSF standard cytology for the detection of LM [55]. However, the detection of ctDNA in the CSF may be caused by concomitant brain parenchymal metastases or by blood contamination during CSF sampling and should be interpreted cautiously for the diagnosis and follow-up of LM [2]. In NSCLC, the determination of EGFR and T790M status at LM diagnosis and during the follow-up can help to guide the therapeutic strategy. Promising results were observed after treatment with osimertinib, an oral third-generation EGFR tyrosine kinase inhibitor that is active in tumors expressing the EGFR T790M resistance mutation [56]. DNA methylation profiling in the CSF represents another promising tool for the diagnosis and the management of LM [57] .

14.6 Diagnosis of LM

According to EANO ESMO guidelines, the diagnosis of LM can be either confirmed, in the presence of tumor cells in the CSF, or probable, or possible, or there may be lack of evidence [2] (see Table 14.1). Two major criteria define the LM classification: (1) the confirmation of the diagnosis by CSF cytology (confirmed LM, type I) versus not confirmed (type II), and (2) the MRI presentation: linear disease for type A, nodular disease for type B, a combination of both linear and nodular disease for type C and no neuroimaging evidence of LM except hydrocephalus for type D. This classification aims at guiding the therapeutic strategy and requires confirmation in prospective studies.

14.7 Conclusion

The diagnosis of LM is based on clinical manifestation, cerebrospinal MRI findings and standard CSF cytology and is often challenging. Standardized scorecards should be used for the clinical and imaging follow-up of patients; however, no such scorecard has been validated yet. Characterization of genomic alterations and methylation profiles may improve the sensitivity of CSF analysis in the future.

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Part III

Surgery, Radiation Therapy and Systemic Treatments

15 Surgery in Brain Metastasis Management: Therapeutic, Diagnostic, and Strategic Considerations

Philippe Metellus, Johan Pallud, Zvi Ram, Colin Watts, and Manfred Westphal

15.1 Introduction

Brain metastases (BM) represent a major health problem in patients with cancer. It is estimated that approximately 20–40% of patients with malignant neoplasia will develop brain metastasis during their disease [1, 2]. These lesions, whose incidence is increasing due to the improvement of primary cancer management, represent the most frequent intra-axial brain tumors.

Whole-brain radiation therapy (WBRT) [3–5] has been for a while the standard treatment of BM. However, the advent of modern imaging techniques (CT and MRI), the improvement of surgical techniques, neuroanesthesia [6–9], and the positive impact of stereotactic radiotherapy [10] led to a reappraisal of local treatment modalities in BM management. Therapeutic decision depends on several factors related to tumor characteristics (number, radiological aspect, size, location), patient clinical status (neurological deficit, general condition, comorbidities, performance status), and primary disease status (controlled or uncontrolled, extracranial active metastatic disease) [11]. In this chapter, we will provide a review of available data on the impact of surgery in BM management and surgical indications in these patients.

15.2 Survival Impact of Surgery in BM

Actual impact, in terms of overall survival (OS), of surgery associated with WBRT in patients with single brain metastasis of solid cancers, in comparison with WBRT alone, has been demonstrated in several studies (Table 15.1). In 1990, Patchell

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Table 15.1 Results of phase III randomized trials assessing the impact of local treatment on brain metastases

	Study design/level of evidence	Treatment	Population	Median survival	Patient with recurrence/ progression Control Rate	Median time to recurrence/ progression
Patchell et al. (1990) [8]	Randomized trial Class 1	G1: WBRT ($n = 23$) G2: surgery + WBRT ($n = 25$)	Single metastasis	G1: 15 weeks G2: 40 weeks *Overall survival curves* *Log rank $p < 0.01$*	*Surgical site* G1: 12/23 (52%) G2: 5/25 (20%) *$p < 0.02$* *Remote site* G1: 3/23 (13%) G2: 5/25 (20%) *$p = NS$*	*Surgical site* G1: 21 weeks G2: >59 weeks *Local recurrence curves* *Log rank $p < 0.0001$*
Patchell et al. (1998) [13]	Randomized trial Class 1	G1: surgery ($n = 46$) G2: surgery + WBRT ($n = 49$)	Single metastasis	G1: 43 weeks G2: 48 weeks *Overall survival curves* *Log rank $p = NS$*	*Surgical site* G1: 21/46 (46%) G2: 5/49 (10%) *$p < 0.01$* *Remote site* G1: 17/46 (37%) G2: 7/49 (14%) *$p < 0.01$*	*Surgical site* G1: 27 weeks G2: >52 weeks *Local recurrence curves* *Log rank $p < 0.001$*
Kocher et al. (2011) [14]	Randomized trial Class 1	G1: surgery or SRS ($n = 179$) G2: surgery or SRS + WBRT ($n = 180$)	1–3 metastases	G1: 10.9 months G2: 10.7 months *Overall survival curves* *Log rank $p = 0.89$*	*Intra-cranial* G1: 139/179 (78%) G2: 57/180 (48%) *$p < 0.001$*	*Intra-cranial* G1: 3.4 months G2: 4.6 months *Local recurrence curves* *Log rank $p < 0.020$*

Mahajan et al. (2017) [18]	Randomized trial Class 1	G1: surgery + SRS ($n = 63$) G2: surgery ($n = 65$)	1–3 metastases	G1: 17 months G2: 18 months *Overall survival curves* *Log rank p = 0.24*	*Local control rate*[a] G1: 72% G2: 43% *p = 0.015* *Distant control rate*[a] G1: 42% G2: 33% *p = 0.35*	*Surgical site* G1: not reached G2: 7.6 months *Fine–Gray regression* *p = 0.0097*
Brown et al. (2017) [19]	Randomized trial Class 1	G1: surgery + SRS ($n = 98$) G2: surgery + WBRT ($n = 96$)	1–3 metastases	G1: 12.2 months G2: 11.6 months *Overall survival curves* *Log rank p = 0.70*	*Local control rate*[a] G1: 61.8% G2: 87.1% *p = 0.00016* *Distant control rate*[a] G1: 64.7% G2: 89.2% *p = 0.00045*	NR

WBRT Whole-brain radiation therapy, *SRS* Stereotactic radiosurgery, *NR* Not reported, *NS* Non-significant
[a]Control rate at 12 months

et al. [8] firstly showed that surgery associated with WBRT led to a significant increase of OS in patients with a unique brain metastasis compared to WBRT alone. In 1993, Vecht et al. [9] confirmed the positive impact on OS of the association of surgery and WBRT, in single brain metastasis. In 1996, Mintz et al. [12] did not find such a positive impact of surgery on OS. However, in this study only 21.4% of patients had a controlled extra-cerebral disease, and none of the patients had brain MRI assessment conversely to the two other studies, which suggests that these results should be interpreted with caution.

Eventually, the survival impact of surgery associated with WBRT in comparison with surgery alone has then been evaluated [13, 14] (Table 15.1). While adjuvant WBRT led to a significant improvement of global intra-cranial control, it fails to improve the duration of functional independence and OS [13, 14]. The conclusion was that in well-performing patients with otherwise stable systemic disease and a limited number of BM (1–3) treated initially with surgery alone, WBRT can be withheld if neuroimaging monitoring is adequately performed. However, even if surgical techniques have substantially improved since the study reported by Patchell and colleagues [8], local recurrence after surgery alone reported in the available literature is still of 50% at 6 months. Also, although adjuvant WBRT allows an improved local control, results from recent studies have shown an association with cognitive decline [14–16]. In order to avoid such a toxicity, tumor bed stereotactic radiosurgery (SRS) has been extensively assessed in this population and has progressively replaced adjuvant WBRT although high-level evidence is still lacking [17]. Recently, two phase 3 studies have been conducted to address the adjuvant strategy question in patients with an oligo-metastatic disease treated by surgery. The first study by Mahajan and colleagues addressed, in a series of 132 patients, the value of postoperative SRS compared to observation in a surgical resection cavity. They showed that adjuvant tumor bed SRS was associated with a reduced local relapse but failed to improve OS [18]. Twelve-month freedom from local recurrence was 43% in the observation group (68 patients) and 72% in the SRS group (64 patients) (Table 15.1). Also, they found the metastasis size to be inversely associated with better local control. Indeed, in patients harboring tumors up to 2.5 cm in maximal diameter, 12-month freedom from local recurrence was 91% versus 40% in patients with tumors of 2.5–3.5 cm in maximal diameter (HR 8.3 (95% CI 2.5–27.6) $p = 0.0005$) [18]. Another phase 3 study reported by Brown and colleagues addressed the value of WBRT compared to SRS in 194 patients with one resected brain metastasis and a resection cavity less than 5.0 cm in maximal extent. They failed to show any difference in terms of OS but in the WBRT group time to cognitive decline was significantly shorter. Actually, median time to cognitive deterioration was 3.7 months in the SRS group (98 patients) compared to 3.1 months in the WBRT group (96 patients) [19].

15.3 Surgical Indications

BM surgery goal is to improve brain tumor control, allow patient's neurological symptoms relief, and provide an accurate tumor molecular characterization. Large tumors responsible for intra-cranial hypertension and symptomatic tumors located in eloquent area represent a surgical indication. Posterior fossa location with associated obstructive hydrocephalus should also be removed surgically. For cystic or necrotic tumors with cortico-subcortical topography, surgery should also be discussed considering the low efficacy and the potential adverse effects of radiotherapy in these situations. Surgery may also have a diagnostic role. In case of unknown primary, surgery is warranted to have a histological diagnosis. Also, when a differential tumor diagnosis or pseudo-progression (radionecrosis) is suspected, a histological authentication may be necessary [6]. Finally, in some cases, it may be interesting to document biologically the cerebral metastatic disease. Indeed, molecular or gene expression changes may occur between primary tumor and BM. This could actually impact surgical decision making in patients with BM. Furthermore,

for some patients whose initial tumor material is not available, biological metastatic disease documentation could identify patients eligible for a specific targeted therapy. Therefore, surgical resection of BM, in these cases, represents a pivotal step in the treatment strategy decision making process that can lead to an actual change in the therapeutic management.

In summary, surgical excision, when possible, should be performed in the following situations:

Therapeutic:

- Voluminous lesion >3 cm, symptomatic or not
- Cystic or necrotic lesion with edema
- Symptomatic lesion located in eloquent area
- Lesion located in the posterior fossa with mass effect or associated hydrocephalus

Diagnostic:

- No known primary cancer
- Potential differential diagnosis
- Suspected radionecrosis in previously irradiated patients

Strategic:

- Biological documentation of brain metastatic disease in patients potentially eligible for new targeted therapy

Finally, surgical resection of brain metastatic lesions also contributes to the constitution of a BM tissue database that could allow for a better understanding of the molecular determinants underlying the brain metastatic disease and for identifying new potential molecular targets and its associated treatments.

15.3.1 Selection of Patients for Surgical Resection

The selection of patients who will have surgical resection should take into account three factors: the clinical and functional status of the patient, the systemic disease status and the characteristics of intra-cranial metastases.

15.3.1.1 Clinical and Functional Status of the Patient

To have a surgical resection of BM, the patient should be in relatively good general condition and not present of major cardiovascular or lung defects, which making incur a significant anesthetic risk. The patient's functional status must be taken into account. The Karnofsky index is a major element in making local therapeutic decision. Indeed, in the recursive partitioning analysis (RPA) classification of RTOG [age < or >65 years, Karnofsky Performance Status (KPS) score < or >70, control of systemic disease yes/no], a KPS score <70 is a poor prognostic and should raise the question of the legitimacy of surgical resection [11]. However, if the score of KPS is low because of the neurological deficit due to brain metastasis then it is an argument in favor of the surgical resection. The patient's functional status must challenge a surgical indication only if it is secondary to impaired general condition related to systemic disease or the existence of numerous BM with no criteria for surgical resection.

15.3.1.2 Systemic Disease Status

The control of systemic disease defined by the activity of the primary site and the existence of extra-cerebral metastases represents an essential factor in choosing the therapeutic strategy. Indeed, in patients with BM, systemic disease status is a major prognostic factor included in RPA classification. Several studies have shown that the control of systemic disease was a confounding factor in detecting a benefit in OS in patients who underwent surgical resection of BM [6]. In the phase III randomized trial of Mintz et al., comparing surgery + WBRT versus WBRT alone, no survival benefit has been found [12]. However, in this study 78.6% of patients had extra-cerebral disease controlled versus 37.5% and 31.7% in the studies of Patchell et al. and Vecht et al., respectively [8, 9]. Analysis of the results of Mintz et al. showed that the majority of deaths were related to the evolution of systemic disease [12]. Thus, it does not seem legitimate to propose a surgical resection in patients whose life expectancy is less than 3 months.

15.4 Characteristics of Intracranial Metastases

Surgical resection of BM was initially validated for single lesions. The presence of multiple metastases has been longtime an against-indication to the surgical approach. However, the introduction of new technologies and the improvement of surgical techniques have favored the inclusion of surgical resection combined with adjuvant WBRT in therapeutic strategy of multiple metastases. Indeed, several studies have shown the interest of surgical resection in multiples metastases. Bindal et al. have reported a benefit in terms of survival in a series of 56 patients with multiple metastases (2–3), when all lesions were resected [20]. Another study on a breast cancer did not shown survival difference between patients operated on for single or multiple lesions [6]. More recently, two retrospective studies have shown that in patients with multiple metastases, patients with 2 to 3 lesions should benefit from the resection of dominant lesions associated with an adjuvant WBTR [6]. Indeed, these two studies show that the benefit in terms of survival and functional independence was the same as for single metastases. A similar observation was performed in recurrent metastases. Two retrospective studies have shown that repeated surgical resection of recurrent BM was a benefit in terms of survival and quality of life [21].

15.5 New Surgical Indications in the Era of Targeted Therapies

The interest of having a biological documentation of the metastatic disease is to identify a potential molecular phenotype switch in the metastatic tumor that could help the clinician in defining the therapeutic strategy. A recent study has shown that genetic and phenotypic heterogeneity in metastases of breast cancer explained the resistance to targeted therapies [22]. Indeed, it is well established that there can be a molecular phenotypic conversion between primitive and metastatic disease, which is influenced by the time to onset of metastasis and by the metastatic site [23–30]. Thus, the possibility to obtain a molecular characterization of the cerebral metastatic disease may be warranted when the molecular status of primary tumor is insufficiently documented or when modern profiling tests used where not available at time of diagnosis. Indeed, molecular profiling of the metastatic disease can lead not only to a change of the local treatment but also could impact the systemic treatment strategy [23, 31–33]. This emphasizes the critical role of the surgeon who is not only as an actor of the local treatment (large, symptomatic and life-threatening lesions) but mostly plays a pivotal role in the decision making global therapeutic strategy [24, 25]. In 2012, a pioneer randomized phase II study have compared the use of targeted therapies based on the molecular profile of the tumors versus conventional chemotherapy in all types of cancers in treatment failure. This study showed that this approach was well tolerated, feasible, and consistent with routine clinical practice [22]. However, if this study has shown that this approach is feasible, it remains to demonstrate that the choice of a target based on the molecular profile of the tumor improves prognosis of patients. Thus, in this perspective, a French multicenter study led by the same group reported the interest of molecular screening by Array-CGH and high- throughput sequencing of metastatic breast cancer. This innovative approach consisted of identifying genomic alterations in metastatic tumors that could be targeted by new agents. However, the results of this study, while promising, were disappointing because to date there is no effective molecular therapies available to target the identified genomic alterations. Also, this approach does not integrate other components of personalized medicine as immunotherapy, modulation of DNA repair and heterogeneity intra-tumoral [34]. More recently, several studies dedicated to brain metastases have reported genomic, post-genomic and epigenomic profiling in primary and matched brain metastases [31–33, 35–38]. Brastianos and colleagues first reported the genomic characterization of brain metastases and their matched primary tumors. They showed that brain metastatic tumors shared genetic alterations that were frequently not detected in the primary tumor. These data suggested that sequencing of the primary tumor may miss a substantial number of opportunities for targeted therapies [33]. Since this pioneering report, several studies have reported the comparison of genetic alterations between brain metastases and primary tumor. Most of these studies were performed in breast cancer patients [23,

32, 37]. Since this pioneering report, several studies have reported the comparison of genetic alterations between brain metastases and primary tumor. Most of these studies were performed in breast cancer patients [23]. Another study reported by Tyran et al. on DNA mutation and copy number profiles of primary breast cancer and paired brain metastases also provided strong evidences that BM tumor samples harbored more genetic alterations than their primary counterparts underlining its potential interest in precision medicine [37]. In line with these published data, several recent works have provided strong evidence of the genetic heterogeneity between primary tumors and their brain metastases pointing out the actual necessity to further characterize the biology of the metastasis. Gene expression profiling recently reported data also uncovered recurrent gene expression acquisitions in brain metastases distinct from their matched primary tumors [31]. All these studies provided a growing body of evidence that there is a specific acquired molecular phenotype in brain metastases that is not present in the primary tumors and which warrants immediate clinical attention. The identification of these metastases-acquired aberrations in key oncogenic pathways could provide suitable therapeutic targets. Hence, paired specimen genomic and post-genomic profiling represents a compelling and underutilized strategy to identify targetable dependencies in advanced cancer patients. All in all these data underline the actual need to obtain tissue from brain metastases patients because it provides immediate opportunity for more informed decision-making based on genetic analysis. From this perspective the neurosurgeon does not only act as an actor of the local treatment but rather as a key player involved in all diagnostic, therapeutic and strategic stages in brain metastases patients management.

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16 Surgical Resection for Brain Metastases

Ali S. Haider, Raymond Sawaya, and Sherise D. Ferguson

16.1 Introduction

Brain metastases are the most common intracranial neoplasms in adults, affecting 150,000–200,000 cancer patients per year in the United States [1, 2]. The most common primary sources of brain metastases are lung cancer, breast cancer, and melanoma, with melanoma most predisposed to metastasize to the brain [3]. Brain metastases traditionally result in poor outcomes and, unfortunately, often indicate the terminal stage of systemic cancer. Brain metastases pose a significant public health issue, as over one million people are diagnosed with cancer each year in the USA (www.cancer.gov/about-cancer/understanding/statistics). In addition to the obvious potential functional burden of brain metastasis to patients, the socioeconomic burden is also profound. A number of studies have demonstrated increased health care utilization and costs for patients after a diagnosis of brain metastasis. In a retrospective review of 132 patients with non-small cell lung cancer, prior to brain metastasis diagnosis, patients had a 6-month healthcare cost of $5983, which increased to over $22,000 after the diagnosis of brain metastasis. This same study found that patient resource utility also substantially increased, with a three-fold increase in outpatient visits and a six-fold increase in inpatient admission [4]. Furthermore, patients with brain metastases missed significantly more workdays, resulting in a salary loss of $2853 per patient over a 6-month period. Similarly, in breast cancer, relative to a matched control cohort, patients with brain metastasis had a mean overall healthcare cost of $99,899 over 12 months compared with $47,719 in patients without metastases [5]. Strategies for the management of brain metastases have developed tremendously over the past decade, including the use of immunotherapy [6, 7] and advancements in radiation techniques [8]. Surgical resection remains a cornerstone in the treatment of brain metastasis. This chapter will focus on the role of surgery in the treatment of patients with metastatic brain disease and discuss current perspectives in the surgical management of this complicated issue.

16.2 Solitary/Single Brain Metastasis

16.2.1 Clinical Impact of Surgical Resection

The positive impact of surgery for brain metastasis is established based on two historical randomized

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clinical trials. Patchell and colleagues randomized patients with a single brain metastasis to receive whole-brain radiation therapy (WBRT) alone (n = 23) or surgical resection followed by WBRT (n = 25) and reported the respective outcome of each treatment paradigm. Surgery had a considerable impact on survival. Patients undergoing upfront resection survived significantly longer than patients treated with WBRT alone (median survival of 40 weeks versus 15 weeks, respectively). Additionally, surgical patients also maintained functional independence (defined by a Karnofsky Performance Scale [KPS] score of >70) significantly longer (median 38 weeks) compared with those treated with WBRT alone (median 8 weeks). Lastly, patients in the surgical group were also afforded a lower risk of local recurrence (20%) relative to those receiving WBRT alone (52%) [9]. A second prospective randomized trial, which included 63 patients, also confirmed the indispensable benefit of surgery [10]. Specifically, patients undergoing surgery improved in functional status more quickly, benefited from significantly longer survival, and had prolonged functional independence compared with patients undergoing WBRT alone.

16.2.2 Surgical Indications

Careful patient selection and strong surgical indications are essential to attain the maximal benefit of surgery. The most well-accepted surgical indication is for patients with a solitary/single brain lesion; this is particularly true in the face of a large mass (> than 3 cm in maximal diameter). In this situation, surgical resection is often indicated to relieve mass effect, offer seizure control, decrease intracranial pressure, and address neurological symptoms. Large masses can also result in significant cerebral edema, often requiring the use of corticosteroids; surgical resection of the offending lesion is the most effective way to reduce this edema and allow for the prompt cessation of steroid administration. Additionally, if the lesion is in proximity to or involving the ventricular system, surgery can help prevent or address hydrocephalus from obstructed cerebrospinal fluid (CSF) flow. Furthermore, for larger lesions, surgery may offer superior local tumor control compared with radiation treatment modalities such as single fraction stereotactic radiosurgery (SRS) [11–13]. Ebner et al. reported that lesions >3 cm in maximal diameter undergoing SRS had a lower one-year local control rate (68%) than lesions less than 3 cm in size (86%) [14]. Specifically, in the treatment of large lesions, single fraction SRS in particular becomes more limited, as larger volume masses require a reduced radiation dose to avoid toxicity, and treatment is thus more prone to failure [15]. A recent multi-institutional study evaluated the outcome of single fraction SRS alone relative to surgical resection followed by postoperative SRS for brain metastases over 4 cm^3 (diameter of ~2 cm) in volume and reported a significantly lower local recurrence rate for patients treated with upfront surgery (36.7% and 20.5%, respectively; P = 0.007) [16]. As such, SRS is accepted as an ideal treatment for smaller lesions, particularly those less than 2 cm in maximal diameter.

Apart from tumor size, there are clinical scenarios where surgical resection is warranted, even for smaller lesions. Surgery can aid in the confirmation of diagnosis in patients with a brain metastasis from an unknown primary tumor. Clinically, the identification of a brain metastasis has been demonstrated to be the first sign of a neoplasm in approximately 10% of cancer patients; thus, surgery can be helpful in establishing diagnosis if the primary cancer cannot be found [9]. Additionally, a patient with a known primary cancer may present with a lesion that is radiographically suggestive of an alternate pathological diagnosis, making tissue diagnosis critical.

In addition to radiographic and tumor factors, multiple clinical issues should be taken into account when evaluating surgical candidacy. A patient's systemic cancer status is a serious consideration, and generally patients with controlled or absent systemic disease are ideal surgical candidates. However, these decisions must be individualized and discussed in conjunction with the patient's medical oncology team to assess the patient's overall prognosis and the availability of additional therapy for systemic disease. For

example, if a patient presents with concurrent brain and systemic metastases and is treatment naïve, then surgical resection may a reasonable first step in the treatment plan. In addition to oncological status, the patient's functional status is important, specifically a Karnofsky performance scale (KPS) score of at least 70 is desirable. Moreover, patients with multiple serious comorbidities, coagulopathy, or who are undergoing systemic chemotherapy may be better served with less invasive treatment modalities.

In order to assist with clinical decision-making, the Radiation Therapy Oncology Group (RTOG) developed the recursive partitioning analysis (RPA) classification system, which captures the salient factors that go into treatment planning. RPA is graded based on the KPS score, patient age, and status of extracranial disease; RPA class I is associated with the most favorable prognosis, whereas patients with RPA class III have the worst anticipated outcome. Tendulkar et al. analyzed the outcome of 271 patients undergoing resection of a single brain metastasis [17] and reported that patient survival significantly correlated with RPA class, with the mean survival times of RPA classes I, II, and III patients post tumor resection being 21.4, 9, and 8.9 months, respectively, validating the prognostic significance of this scale. The predictive impact of RPA class has since been validated in multiple surgical series [18, 19]. Another prognostic score, the Graded Prognostic Assessment (GPA) is an updated prognostic index for patients with brain metastases. This prognostic index is based on age, KPS score, number of intracranial lesions, and status of systemic disease and was originally developed from a database of 1960 patients accrued to four RTOG protocols for patients with brain metastases [20]. The median overall survival times based on GPA score were: 2.6 months for 0–1 points, 3.8 months for 1.5–2.5 points, 6.9 months for 3 points, and 11 months for 3.5–4 points. The GPA has been refined to include histology-specific prognostic indices based on multi-institutional analyses of 4259 patients with brain metastases from breast carcinoma, small cell and non–small cell lung carcinoma, GI cancers, melanoma, and renal cell carcinoma [21].

16.2.3 Impact of Extent of Resection (EOR) and Surgical Technique

When it's anatomically safe to perform it, gross-total resection (GTR) is the goal of surgery for metastatic disease, as it improves outcome, particularly in patients with single or solitary metastasis [17, 18]. A single institution study evaluated the predictors of outcome in 271 patients with single brain metastases. In this study, patients who received a GTR had a median survival time of 10.6 months compared with 8.7 months in patients who had a subtotal resection (STR) [17]. In another retrospective study analyzing the surgical outcome of 157 patients with brain metastases, 96 of whom (60%) had a single brain metastasis, the authors reported that the extent of resection (EOR) significantly impacted patient survival. Patients who had a STR had a median survival time of 15.1 months compared with 20.4 months in patients where a GTR was achieved [18]. Furthermore, GTR strongly affected patients' functional status; KPS scores of the GTR group improved from 82 to 87 and those of the STR group changed from 79 to 77, and this difference was found to be statistically significant. It is important to note that even though patients with metastatic disease represent a higher risk population, with diligent patient selection, maximal safe resection is often well tolerated and with an acceptable risk. A retrospective study examining the outcomes of 206 surgical patients with brain metastases reported mortality and morbidity rates of 0% and 10.3%, respectively [22]. This low perioperative morbidity was similar to that described in another retrospective study that included 208 surgical patients and reported an operative mortality of only 1.9% [19].

In addition to attaining maximal resection, there is ample literature indicating that the method of surgical resection also influences outcome, specifically the value of en bloc resection. En bloc resection entails circumferential dissection of the metastatic lesion along the brain-tumor interface and avoiding breech of the tumor capsule. This technique has multiple practical benefits relative to piecemeal resection (i.e., internal tumor debulking and

removal), including avoidance of tumor cell spillage into the surrounding brain, reduction of intraoperative bleeding, and clearer visualization of tumor borders. In addition to its intraoperative benefits, en bloc resection also imparts clinical advantages. A notable study analyzed the predictors of local recurrence in 570 patients with single brain metastasis who underwent surgery where GTR was achieved. The authors demonstrated that patients who had a piecemeal tumor resection were 1.7 times more likely to develop local recurrence than those whose tumors were removed en bloc [23]. In addition to its impact on local recurrence, resection technique also influences the risk of metastatic CSF dissemination, i.e., leptomeningeal disease (LMD), which carries a universally poor prognosis. In a surgical series of 242 patients with brain metastases (68% with a single lesion), 16% of the patients subsequently developed LMD. Analysis of the potential clinical predictors of LMD demonstrated that piecemeal resection carried a fourfold increased risk of developing LMD compared with piecemeal resection [24]. In addition, another study focusing on surgically treated posterior fossa metastases (260 patients) also showed the benefit of en bloc resection [25]. Note, posterior fossa lesions are of particular interest regarding LMD development due to their proximity to CSF spaces. In this study, GTR was achieved in 96% of the patients, and 10% of the patients developed LMD. Piecemeal resection was significantly associated with an increased risk of LMD, specifically 13.9% of piecemeal resection patients eventually developed LMD compared with only 5.7% of en bloc resection patients [25]. In addition to being effective, en bloc resection is safe, even for metastases found near functional (eloquent) cortex. Recent data indicate that en bloc resection technique is both feasible and safe in this setting. In an analysis of 1033 surgical patients, 62% of whom underwent en bloc resection, the authors reported that an en bloc resection was not associated with increased complication rates compared with piecemeal resection, even for tumors located in eloquent cortex [26].

16.2.4 Surgical Intraoperative Adjuncts

Intraoperative imaging and brain mapping technologies have emerged as powerful adjuncts for maximizing the extent of resection of brain metastases while minimizing morbidity. However, the clinical benefit of aggressive surgical resection is negated if it results in severe neurological deficits postoperatively. New functional deficits can increase the risk of thromboembolic complications, remove eligibility for selected systemic treatment regimens or clinical trials, and seriously impact patient quality of life. With this in mind, the use of surgical adjuncts has proven to be vital in making surgical resection effective and safe. Both preoperative and intraoperative imaging modalities can contribute to surgical success. Standard three-dimensional preoperative magnetic resonance (MR) imaging is routinely performed to facilitate accurate targeting of a specific lesion for surgical approach planning and tailoring of the craniotomy. In the situation where the lesion abuts or involves eloquent cortex (e.g., speech or motor centers), additional functional imaging modalities are often required. Predicting the exact location of eloquent cortex with standard anatomical imaging can be difficult at times due to distortion of the normal anatomy by the tumor or surrounding edema. Preoperative localization of eloquent brain regions using functional MR imaging, diffusion tensor (DT) imaging tractography, and/or transcranial magnetic stimulation (TMS) allows for more detailed surgical planning through visualization of the spatial relationship between the lesion and surrounding eloquent cortex [27–29]. These preoperative imaging data also assist the surgeon and treatment team when counseling the patient regarding preoperative risk and potential postoperative recovery time. Intraoperatively, ultrasound is a useful and cost-effective technological imaging

adjunct that provides real-time data to confirm the extent of resection [30]. Additionally, intraoperative MR imaging is widely used as an adjunct to resection for infiltrative glial tumors but can also be used to aid the resection of brain metastases, particularly deep-seated lesions [31, 32].

Intraoperative neuro-monitoring is another key adjunct for the resection of brain metastases in eloquent regions. Even with notable advancements in pre- and postoperative imaging techniques, the gold standard for identifying eloquent cortex during surgery remains the use of intraoperative mapping. Brain mapping provides real-time information regarding the relationship between the lesion and surrounding critical structures. For metastases abutting or involving the precentral gyrus (posterior frontal lobe; motor cortex) or the deep subcortical motor tracts, intraoperative localization of these motor fibers is critical to conducting safe resection. With the assistance of a neurophysiology team, the location of the motor cortex can be confirmed intraoperatively by the placement of a grid electrode on the cortical surface prior to initiation of tumor resection. The location of subcortical motor fibers (corticospinal tract) can be localized and continuously monitored during surgical resection using direct stimulation with a current-generating monopolar or bipolar electrode. The benefit of motor mapping in the management of brain metastases has been confirmed in the literature [33, 34]. For example, a retrospective study of 33 surgical patients with lesions in proximity to the motor cortex reported favorable outcomes using intraoperative mapping techniques. Specifically, GTR was achieved in 94% of patients. Six patients (18%) experienced worsening neurological symptoms, but all patients were neurologically recovered at their 3-month follow-up visit [34]. For lesions located in language areas (e.g., posterior temporal lobe, inferior frontal lobe, and interior parietal lobule), intraoperative speech mapping is often needed, and this requires awake surgery. After the initial craniotomy and cortical exposure, a bipolar electrode is used to stimulate the cortical region of interest while language tasks are performed by the patient. Areas on the cortex that produce frank speech arrest or language disturbances (semantic errors, paraphasias, perseverations) are marked and subsequently avoided during the remainder of the surgical resection. Overall, the benefit of intraoperative mapping is clear and has shown improved neurological outcomes in patients with brain metastases in difficult locations [35].

16.3 Multiple Brain Metastases

Though a number of clinical studies have clearly defined the role of surgical resection for single brain metastases, the role of resection for multiple brain metastases is less well established. More than 50% of patients with brain metastases present with multiple brain metastases [36], but there have been no prospective randomized clinical trials dedicated to this patient population. However, there are retrospective reports that indicate that surgery may be beneficial in a subset of oligometastatic patients [19, 37, 38]. Overall, if it is anatomically feasible and safe to do so, removal of all lesions produces the best outcome, particularly in the setting of limited intracranial disease. Bindal et al. demonstrated the clinical benefit for patients with multiple brain metastases when all lesions are resected [37]. This study included 56 patients, all of whom underwent resection for multiple brain metastases. Thirty patients had one or more lesions left unresected (Group A) and 26 had all lesions resected (Group B). Regarding neurological outcome, symptoms improved in 65% of patients in Group A compared with 83% in Group B. Furthermore, the survival of patients who had all lesions resected (14 months) was significantly longer than in patients who had residual lesions (six months). A recent study retrospectively analyzed the outcome of patients with multiple brain metastases (maximum of 3 lesions) who underwent surgical resection of all lesions (n = 32). Furthermore, the outcome of this cohort was compared with that of a group of patients with single metasta-

ses who underwent resection during the same time period (n = 30). The authors reported no significant difference in median postoperative survival time between the two patient cohorts [38]. Though the literature is still unclear on the use of surgical resection for patients with multiple brain metastases, as discussed, there is evidence showing that resection can improve the survival and enhance quality of life in select patients.

16.4 Recurrent Brain Metastases

Surgical resection has also been demonstrated to be a useful treatment modality for recurrent brain metastases. A retrospective study of 25 patients with recurrent solitary brain metastases from lung cancer demonstrated significant functional improvement after surgical resection. Specifically, the median KPS score improved significantly after surgery for patients with recurrent disease, with 66% of them having improvement in preoperative neurological deficits [39]. In a retrospective series of 48 patients with recurrent brain metastases, Bindal et al. reported that surgical resection can increase overall survival. The median survival time after initial reoperation was 11.5 months. Furthermore, patients who underwent a second reoperation for recurrent disease had a median survival time of 8.6 months relative to 2.8 months for patients who did not undergo an additional resection [40]. Though no prospective clinical trials have been performed to evaluate the role of resection for recurrent brain metastases, the current literature suggests a clinical benefit regarding the use of surgical resection for select patients.

In addition, for open resection, laser interstitial thermal therapy (LITT) is emerging as another surgical approach to treat recurrent brain metastasis. Laser electromagnetic radiation is focused energy that is transformed into thermal energy to induce coagulation thermal damage to tumor cells while concurrently avoiding damage to adjacent normal tissue [41]. For this procedure, a small hole is drilled in the skull, and laser apparatus is secured to the skull. Under image guidance, the laser probe is advanced to the target lesion. The laser is heated and MR thermography is used to monitor temperature and heat spread [42, 43]. Once the lesion has been sufficiently thermally exposed, the laser is manually shut off.

Even though large studies employing LITT are limited, a number of investigators have suggested the safety and efficacy of LITT for recurrent brain metastases [44–47]. Rao et al. monitored 15 patients after LITT for lesions that had shown progression (based on MR imaging) after SRS. The overall survival rate was 57%, local control was achieved in 75% of patients at a median of 6 months follow-up, and the progression-free survival time was 37.8 weeks [46]. Note that this study did not distinguish between true tumor progression and pseudoprogression/treatment changes, but the study is significant in that it showed a decrease in lesion size regardless of pathology. Torres-Reveron et al. used LITT to treat six patients with confirmed metastatic lesions that had recurred after SRS [47]. LITT proved to be safe, with all treated patients being discharged within 48 hours of surgery. All patients in this analysis demonstrated a decrease in size of the lesion at two weeks. Overall, the current literature suggests that LITT is feasible and safe for the treatment of recurrent brain metastases.

16.5 Conclusion

Surgical resection has been firmly established as a cornerstone of treatment for patients with brain metastases. Novel operative techniques, technological innovations, and improved understanding of patient selection have assisted neurosurgeons in tailoring more aggressive yet safer operations. Prospective randomized clinical trials for surgical resection of patients with multiple brain metastases and recurrent brain metastases are needed in order to further maximize the treatment plan for these patients.

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Stereotactic Radiosurgery for Brain Metastases

17

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Abbreviations

3DCRT	Three-dimensional conformal radiotherapy
ASTRO	American Society for Radiation Oncology
BM	Brain metastasis/metastases
CBCT	Cone-beam computed tomography
CI	Conformity (or conformality) index
CKRS	CyberKnife radiosurgery
CT	Computed tomography
CTV	Clinical target volume
EBRT	External beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
FACT-BR	Functional Assessment of Cancer Therapy-Brain
FSRS	Fractionated SRS
GI	Gradient index
GKRS	Gamma knife radiosurgery
GTV	Gross tumor volume
HBO	Hyperbaric oxygen
HR	Hazard ratio
HVLT-R	Hopkins Verbal Learning Test-Revised
IDL	Isodose line
IV	Intravenous
KPS	Karnofsky performance status
kV	Kilovolt
LINAC	Linear accelerator
MLC	Multileaf collimator
MMSE	Mini–Mental State Examination
MRI	Magnetic resonance imaging
MU	Monitor unit
MV	Megavolt
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	Non-small cell lung cancer
PIV	Prescription isodose volume
PS	Performance status
PTV	Planning target volume
PTX	Pentoxifylline
QOL	Quality of life
RCC	Renal cell carcinoma
RION	Radiation-induced optic neuropathy
RN	Radionecrosis or radiation necrosis
RPA	Recursive partitioning analysis
RT	Radiotherapy
RCT	Randomized controlled trial
RTOG	Radiation Therapy Oncology Group

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SCLC	Small cell lung cancer
SGRT	Surface guided radiation therapy
SI	Selectivity index
SRS	Stereotactic radiosurgery
TV	Target volume
VitE	Vitamin E
VMAT	Volumetric modulated arc therapy
WBRT	Whole brain radiation therapy

17.1 Introduction and Historical Background

Stereotactic radiosurgery (SRS) refers to the use of a three-dimensional coordinate system ("stereotactic") to deliver high doses of image-guided focal radiation to intracranial targets with submillimeter localization in a noninvasive manner ("radiosurgery") as a substitute for surgery while avoiding irradiation of the surrounding healthy tissue. Dr. Lars Leksell, a prominent neurosurgeon in Sweden, pioneered SRS in the 1950s using orthovoltage X-ray tube radiation to treat trigeminal neuralgia-related facial pain [1]. Gamma knife radiosurgery (GKRS), which uses cobalt-60 as the source of ionizing radiation, was developed by Dr. Leksell and physicists Dr. Kurt Lidén and Dr. Börje Larsson in 1967 as a surgical tool to produce discoid-shaped radiation lesions for functional neurosurgery patients with movement disorders and intractable pain refractory to conventional treatment (Fig. 17.1). Since the 1970s, SRS was used for vascular malformations unsuitable for resection or embolization as well as for benign tumors.

In 1989, professor Christer Lindquist [2] published the first report of a patient with a recurrent solitary brain metastasis (BM) treated successfully using SRS. In the following years, studies analyzed the effectiveness of this treatment either alone or in combination with whole brain radiation therapy (WBRT). During that time, evidence emerged that SRS can provide local tumor control without compromising neurocognitive function as opposed to the WBRT counterpart.

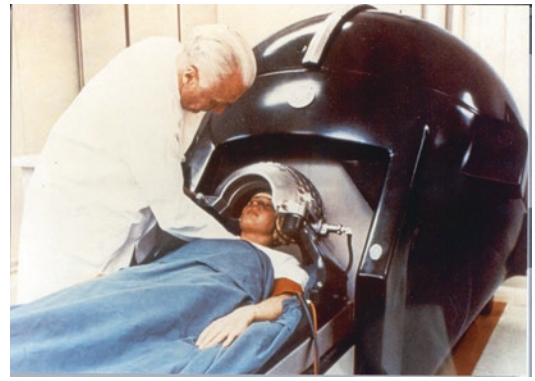

Fig. 17.1 Dr. Lars Leksell using the Gamma Knife® prototype with a patient in 1968 [Image courtesy of Elekta].

Metastatic brain tumors have become the most common indication of SRS. The technique is most commonly delivered by devices such as Gamma Knife® (cobalt-60 radioactive source units), CyberKnife® (robotic arm-mounted lightweight linear accelerator), and linear accelerators (LINACs) equipped with modern onboard imaging systems and radiation delivery methods. The SRS procedure is carried out by a multidisciplinary team which typically consists of a neurosurgeon, radiation oncologist, medical physicist, and a nurse to assure a safe delivery of the plan.

Due to the abundance of commercially available devices able to deliver radiation to the brain and radiotherapeutic techniques, a meeting of the American Association of Neurological Surgeons (AANS), the Congress of Neurological Surgeons (CNS), and the American Society for Radiation Oncology (ASTRO) agreed on a unified contemporary definition of SRS which AANS/CNS published in 2007 [3]. An important part of the definition is as follows: "Stereotactic radiosurgery typically is performed in a single session, using a rigidly attached stereotactic guiding device, other immobilization technology and/or a stereotactic image-guidance system, but can be performed in a limited number of sessions, up to a maximum of five." Although this definition was established, several studies in the literature refer to multifractional SRS between 2 and 5 fractions as fractionated SRS (FSRS) or hypofractionated SRS.

This chapter will address the technique of SRS, review evidence-based medicine of the procedure, and look at future directions.

17.2 Radiobiology

17.2.1 Fractionation

Conventionally fractionated radiation therapy originates from radiobiologic experiments carried out in France in the 1920s and 1930s. French investigators Regaud and Ferroux [4] published their work on sterilization of a ram. They discovered that the animal could not be sterilized by exposing its testes (equivalent model of tumor cells) to a single dose of radiation without causing severe skin toxicity to the scrotum (equivalent model of healthy surrounding tissue). By providing radiation in small daily doses (fraction) divided over several weeks, sterilization was successfully carried out with acceptable skin damage.

Later in the 1960s and 1970s, relevant radiobiologic experiments revealed dose effects and the "Four Rs of Radiotherapy: repair, reoxygenation, redistribution, and repopulation" [5] which were found to be key aspects of multifractionated radiotherapy (RT). Research shows dividing a dose of radiation into smaller doses given over days allows repair of sublethal damage of normal tissues caused by ionizing radiation and repopulation of those cells that survive radiation. In the meantime, damage to tumor cells is increased by fractionation by allowing reoxygenation (oxygen makes permanent the damage produced by free radicals in DNA) and reassortment of tumor cells into radiosensitive phases of the cycle between dose fractions. Excessive prolongation during treatment, however, can cause tumor cells to proliferate.

In the setting of SRS, single-fraction treatment is the antithesis of conventionally fractionated radiation therapy, and fractionation with 2–5 fractions (FSRS) is not validated by standards such as the linear-quadratic model commonly used by radiobiologists.

Whether the primary effect from ionizing radiation on tumor cell killing is direct or indirect could be via compromised blood supply.

One possible explanation for the positive tumor responses to high-dose radiation therapy is that the tumor blood supply is more sensitive to radiation than has been predicted by conventional radiobiology. Park et al. [6] reviewed studies on radiation-induced vascular changes in human and experimental models, and showed that in human tumors treated with conventionally fractionated radiation therapy, the integrity of the vasculature is preserved. However, although a single dose of radiation in the range of 5–10 Gy to human tumor xenografts or rodent tumors causes relatively mild vascular changes, increasing the dose to higher than 10 Gy per fraction induces severe vascular changes resulting in reduced blood perfusion. The authors suggest that higher than 10 Gy likely causes significant vascular damage, likely damages the intratumor microenvironment, and indirectly causes tumor cell death. The departure from conventional radiobiology is that the latter states that the oxygenation status of the tumor cells influences radiosensitivity and depends on *intact microvasculature*.

In a previous study, Szeifert et al. [7] reported an experience with five patients (two with multiple BM, one with a vestibular schwannoma , one with a malignant glioma, and one with a meningioma), who underwent a craniotomy for tumor removal 3–12 months after GKRS with efforts to collect normal brain tissue outside the prescription dose volume. Immunohistochemical results showed that vascular endothelial cells are the principal targets of single high-dose irradiation.

17.2.2 Targeted Agents

Based on a review of several retrospective series by Chowdhury et al. [8], there was evidence of synergistic effect of targeted agents in local control when combined with SRS: lapatinib for HER2-positive BM; sunitinib, sorafenib, and temsirolimus for renal cell carcinoma (RCC) BM; and dabrafenib and ipilimumab for BRAF-mutated and wild-type melanoma BM. The authors, however, recommended engaging in prospective studies to provide higher level of evidence.

17.2.3 Radiosensitizers

Radiosensitizers are agents that enhance the effect of radiation therapy on tumor cells.

17.2.4 Hyperbaric Oxygen

Oxygen is known to enhance the killing effect of radiation on tumor cells (by making permanent the damage produced by free radicals in DNA), and oxygen levels can be increased in all body tissues after immersion into hyperbaric oxygen (HBO). The NCT01850563 clinical trial, which included providing HBO prior to SRS for BM, had its preliminary results published by Hartford et al. [9]. In the trial, patients received 100% O_2 at 2.4 atm for 30 min followed by SRS within 15 min of completing HBO. The completed study with 18 patients, 26 lesions, BM ≤5 cm diameter, and Karnofsky performance status (KPS) >60 achieved an average time between HBO and SRS of 8.3 min. The median follow-up was 13.3 months. The study proved feasibility but is still pending longer follow-up to report local recurrence-free survival, WBRT-free survival, and adverse events.

17.3 Techniques and Apparatus

The following treatment platforms evolved over time to treat BM with SRS.

17.3.1 Leksell Gamma Knife® (Elekta AB, Stockholm, Sweden) Prototype, Models U, B, C, 4C, Perfexion®, and ICON®

All Leksell Gamma Knife® models use cobalt-60 as the radiation source, which produces gamma rays with half-life of 5.27 years (Fig. 17.2). The Leksell Gamma Knife® Perfexion™, launched in 2006, is the fifth-generation device from Elekta. The Perfexion™ contains 192 cobalt-60 sources, all converging towards a radiologic isocenter, via a conical-shaped tungsten collimator system (Fig. 17.2a). The sources are divided into 8 sectors each containing 24 sources, and each sector can be independently positioned in front of any of three collimator sizes, 4 mm, 8 mm, and 16 mm, or be blocked (beam-off). During treatment, these sources are moved in front of the desired collimator channel with predetermined dwell times while the patient positioning system (PPS) is moved in relation to the isocenter. The cumulative radiation dose distribution is created by each "shot" representing a cross firing of up to 192 tightly collimated beams, to deliver the optimal radiation treatment plan.

The day of treatment, the Leksell® Coordinate Frame G stereotactic frame is secured to the patient's skull after local anesthesia is injected at the 4-pin fixation sites. The frame contains three to four side plates, each with an N-localizer [10] which contains fiducial marker material ($CuSO_4$ solution for magnetic resonance imaging or MRI) visualized on the subsequent MRI acquisition step. Many methods have been outlined to determine the z-axis, but the most popular method uses small channels with an "N" shape configuration where the position of the oblique fiducial relative to the vertical fiducials defines the *z*-plane of the slice.

MRI with intravenous (IV) contrast is the preferred imaging modality, although computed tomography (CT) with IV contrast is used when the patient is either unable to tolerate an MRI or carries an MRI-incompatible implanted device.

The frame will remain attached throughout the entire treatment procedure to maintain stereotactic accuracy (Fig. 17.2b). Since imaging is acquired immediately before the treatment, the precise location and size of the targets are known and transferred to Leksell GammaPlan® which is the integrated treatment planning software for Leksell Gamma Knife®.

GKRS is usually given on a single day as a single frame-based treatment on an outpatient basis.

Conversely, Icon™, the 6th-generation Leksell Gamma Knife®, is equipped with an integrated stereotactic cone-beam computed tomography (CBCT) which determines three-dimensional stereotactic coordinates and permits frameless and fractionated radiation treatment (Fig. 17.2c). It is also equipped with real-time motion management (High Definition Motion Management,

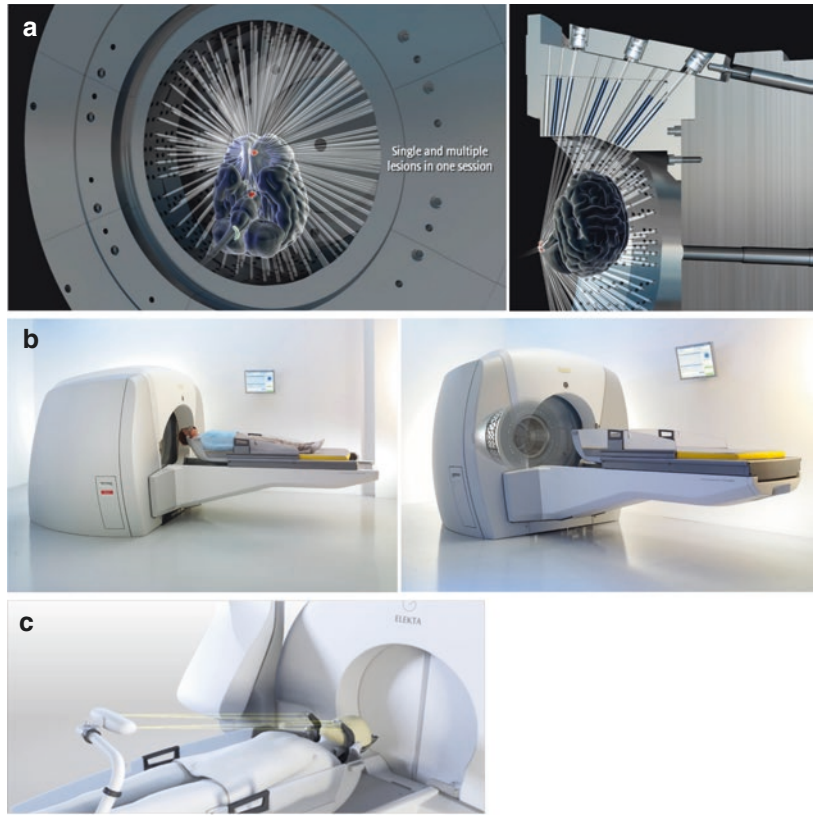

Fig. 17.2 Leksell Gamma Knife® [Images courtesy of Elekta] (**a**) Leksell Gamma Knife® collimator system (present in both Perfexion™ and Icon™ models) showing radiation targets and beams on. (**b**) Leksell Gamma Knife® Perfexion™ showing (left) a patient with head mounted Leksell® Coordinate Frame G and (right) look-through view of the device revealing the tungsten collimator. (**c**) Leksell Gamma Knife® Icon™ showing the High Definition Motion Management (HDMM) system

HDMM) which automatically turns off beam delivery if the patient shifts outside a preset limit. HDMM is composed of an infrared stereoscopic camera, a set of reference markers, and a patient marker (attached to the nose with adhesive).

17.3.2 CyberKnife® Accuray®

CyberKnife® is a frameless radiation system delivered by a lightweight compact X-band 6 Megavolt (MV) X-ray photon LINAC mounted on a robotic arm and equipped with an integrated image guidance system (Fig. 17.3). It was invented by Dr. John Adler, neurosurgeon at Stanford University, California, USA, and was cleared by the Food and Drug Administration (FDA) to treat intracranial tumors in 1999. Soon after, in 2001, it was cleared to treat tumors anywhere in the body. A non-contrast CT scan of the head is acquired after the patient is immobilized in supine position using a customized thermoplastic mask. A contrast-enhanced MRI of the brain is also completed prior to treatment and fused with the CT scan for treatment planning.

Two orthogonal X-ray systems (two ceiling-mounted X-ray sources and two corresponding in-floor image detectors) generate real-time stereoscopic kilovolt (kV) images during treatment to help track and detect skull anatomy motion (using the proprietary 6D Skull Tracking System) and correct for patient movement. The six degrees of freedom of the robotic arm allow hundreds of

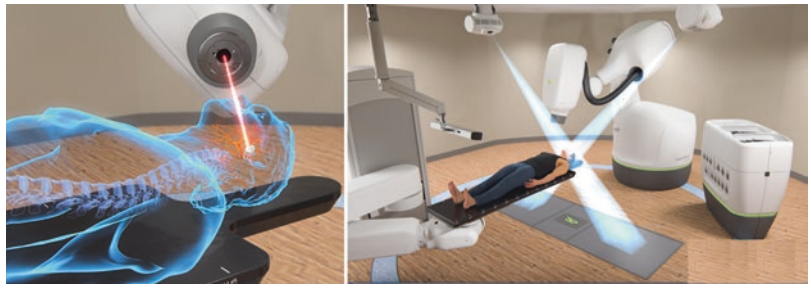

Fig. 17.3 CyberKnife® M6™ System; (left) head of the robotic arm with the beam on; (right) overall layout with robotic arm, Xchange® Robotic Collimator Changer, patient couch, X-ray sources (ceiling mounted), and image detectors (in-floor mounted) [Image courtesy of Accuray Incorporated—©2018 Accuray Incorporated. All Rights Reserved]

non-coplanar, non-isocentric, and isocentric radiation beams from multiple directions to crossfire the tumor. Multiple targets can be treated with a single pass of the robot around the patient.

Six models have been produced as of mid-2018, including the most recent CyberKnife® M6™ System released in 2012. The Xchange® Robotic Collimator Changer gives the user the ability to automatically mount a secondary collimator amongst three available housing choices:

- Fixed circular collimators, with 12 choices of circular field sizes ranging from 5 to 60 mm in diameter at the isocenter
- Iris™ Variable Aperture Collimator, which can replicate the fixed 12 collimator sizes and improves the ability to use multiple field sizes in a treatment
- InCise™ 2 Multileaf Collimator (MLC), for larger field sizes than the Iris™ or fixed circular collimators, chosen for large-size tumors, allows to significantly reduce treatment time

17.3.3 LINAC-Based SRS

Stereotactic alterations to LINACs have made alternatives to GKRS and CKRS possible. The process started in the 1980s with a LINAC modified for stereotactic purposes. LINACs which produce megavoltage ionizing radiation (hence, no use of radioactive source), typically at 6MV, have been used to deliver SRS. X-rays result from the impact of accelerated electrons over a high atomic mass element. The X-ray emitting head of the machine or "gantry" is mounted on an axis which can rotate around the patient in a full circle; meanwhile, the patient lies on a table or "couch" which typically permits three-dimensional translational motion and one-dimensional angular motion. Both the gantry and the couch can move according to the treatment plan.

Because of the large geographical availability of LINACs, normally used to treat all body sites, significant effort has been put into developing LINAC-based SRS. Technological advancements now allow precise and time-efficient radiation delivery. Although GKRS is still the most commonly used single-fraction SRS modality, based on a National Cancer Database Study from 2003 to 2011 [11], LINAC-based SRS has been rapidly disseminating from 3.2% of cases in 2003 to 30.8% in 2011, in particular in the community vs. academic facilities.

17.3.3.1 LINAC-Based SRS Delivery Techniques

- Cone-based SRS: Special collimators (with typical nominal bore hole diameters from 5 to 50 mm) are mounted to the LINAC's accessory device holder and used to sharpen the edge of the radiation beam by reducing the penumbra.
- Micro-multileaf collimator-based SRS (mMLC-based SRS): High-definition MLCs with projected leaf widths below 5 mm are

either an integral part of the LINAC or mounted to the LINAC's accessory device holder.

Cone-based SRS utilizes a regular-shaped collimator and is ideal for lesions of simple shape. This type of collimator can also be used for larger tumors where overlapping spherical fields with multiple isocenters must be used for proper coverage of the target. However, a treatment plan using multiple isocenters increases treatment time and dose inhomogeneity, the latter potentially causing toxicity to the patient [12]. Field-shaping devices such as mMLCs can circumvent these inconveniences, reducing treatment time caused by dose inhomogeneity [13].

In conventional LINACs, flattening filters (typically made of materials such as stainless steel, brass, tungsten, or aluminum) are placed in the path of the bell-shaped radiation beam before reaching the patient to create uniform intensity radiation across the treatment field. For small fields such as used in SRS, the treatment field is already nearly flat over the central few centimeters and the benefit of a flattening filter is not as relevant. Based on a recent study from the American Association of Physicists in Medicine (AAPM) Therapy Emerging Technology Assessment Work Group [14], there are comparable dosimetric results between flattened and flattening filter-free (FFF) beams with reduction in beam on-time of 50–75%.

17.3.3.2 Large LINAC Manufacturers Provide Both Capabilities

Varian TrueBeam® and the Edge® Radiosurgery System (Varian Medical Systems, Inc., Palo Alto, CA, USA)

The most commonly used platforms in the USA are Varian TrueBeam®, a megavoltage LINAC, and the specialized Varian Edge® (Fig. 17.4). Varian started developing SRS in 1992 and later entered into a partnership with BrainLAB. In 2007, the Novalis Tx™ became the first product of their collaboration and offered a comprehensive SRS treatment unit. The unit uses the BrainLAB ExacTrac® X-Ray 6D room-mounted imaging system and Varian's onboard imaging system for image guidance, as well as Varian's Eclipse™ combined with BrainLAB iPLAN as treatment planning software. TrueBeam® was released in 2010 followed by the Edge® Radiosurgery System released in 2012.

The Edge® is equipped with a high-definition 120 Multileaf Collimator (HD 120™ MLC) made of 2.5 mm width leaves over the central 8 cm area with 5 mm leaves over the periphery and a PerfectPitch™ 6 degrees of freedom (6DoF) couch. Intracranial real-time tracking can be done with various options. Most commonly, it utilizes real-time surface tracking (a type of surface guided radiation therapy or SGRT) to monitor target motion after patient setup has been completed using the Optical Surface Monitoring System (OSMS) made by Varian.

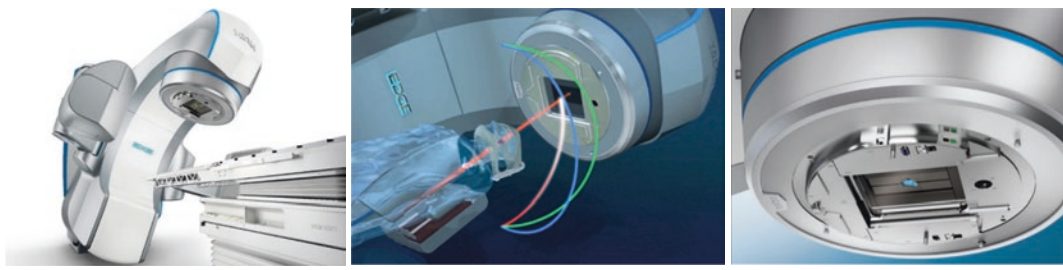

Fig. 17.4 Varian Edge® Radiosurgery System; left to right: perspective view showing LINAC and PerfectPitch™ 6 degrees of freedom (6DoF) couch, rendition of patient undergoing frameless SRS with thermoplastic mask-based immobilization, high-definition 120 Multileaf Collimator [Images courtesy of Varian Medical Systems, Inc. All rights reserved]

Movements outside user-defined tolerances are detected automatically, and the beam can be turned off until the patient returns within tolerance. Varian is also compatible with other real-time tracking systems such as IDENTIFY by HumediQ (another SGRT system) or ExacTrac® by BrainLAB.

The LINAC can also be equipped with conical collimators (from 4 to 17.5 mm) which are mounted on the gantry, although they are typically used to treat trigeminal neuralgia or other functional neurological disorders.

SRS can be carried out using the Varian head frame or in a frameless manner. If a frame is used, the process is similar to GKRS where the frame attachment is followed by a scan to precisely locate the tumor location.

In 2016, Varian released HyperArc™ high-definition RT, an optimization package for automated planning and radiation delivery for TrueBeam® or the Edge®. It incorporates volumetric modulated arc therapy (VMAT) and uses all degrees of freedom provided by a combination of gantry head rotation, collimator rotation, and couch movements (sometimes referred to as "couch kicks") with PerfectPitch™ using Eclipse™ as treatment planning platform. Radiation delivery based just on one isocenter can treat single or multiple lesions and takes advantage of non-coplanar beam arrangements. HyperArc™ currently uses MV imaging for real-time tracking of patient movement.

Elekta Versa HD™ (Elekta AB, Stockholm, Sweden)

A high-end LINAC platform is Versa HD™ (Fig. 17.5). It is equipped by default with Agility™ MLCs, made of 160 interdigitating fast-speed moving leaves with 5 mm widths at isocenter. For cone-based SRS, the platform is compatible with third party Aktina Medical's Small Field Circular Collimators, which are mounted to the LINAC head via an adapter. Interchangeable cones are available over a range of 5–40 mm nominal diameter and each size is automatically recognized by the Elekta LINAC to reduce potential errors during treatment delivery. Onboard imaging is done with MV and kV X-rays and provides kV CBCT. Treatment can be delivered with a frame using a third-party device, which is rare, or framelessly, in which case real-time image verification feedback is done in partnership with BrainLAB ExacTrac® or with SGRT using AlignRT® (from Vision RT Ltd, London, England). The Versa HD™ model also comes with a 6-degree couch which attaches to the top of the exiting couch and provides 6 degrees of positioning (three translational with x, y, and z, plus three rotational with roll, pitch, and yaw).

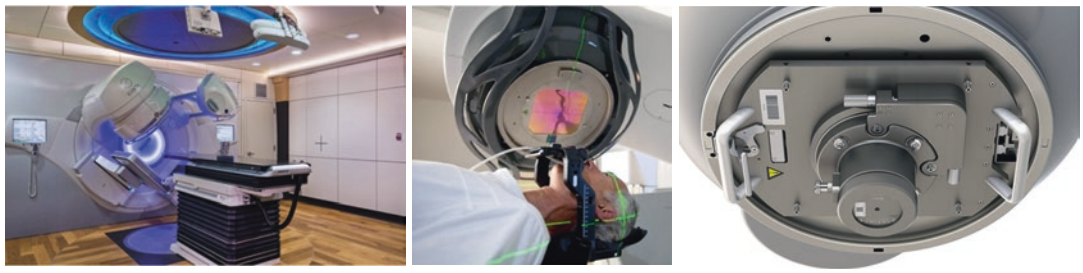

Fig. 17.5 Elekta Versa HD™ system; left to right: LINAC with onboard imaging system deployed, built-in Agility™ MLCs [Images courtesy of Elekta], Aktina's Small Field Circular Collimator add-on mounted on the gantry head [printed with permission of Aktina Medical]

17.3.4 Proton Radiosurgery

Proton beam therapy is also used to treat BM and has unique dose characteristics. It deposits most of the radiation dose at a certain depth with no exit dose (called the Bragg peak) within tissue. These properties translate into a decrease in normal tissue integral dose. These advantages are particularly beneficial when treating patients with multiple lesions or requiring repeated SRS sessions over time. Proton therapy, however, is both costly as well as time- and resource-intensive, thus limiting its access.

A recent report by Atkins et al. provided a single-institution experience from Massachusetts General Hospital of 370 patients treated with proton SRS for single or multiple BM and is the first series to report failure patterns, survival outcomes, and toxicity analysis [15]. Although the study is retrospective and lacks patient-reported outcome or quality of life (QOL) data, it provides evidence that proton SRS is well-tolerated with failure patterns and survival outcomes comparable to those of photon-based SRS series.

17.4 Radiation Dose Considerations

SRS techniques take advantage of the fact that the maximal dose tolerated by normal tissue is volume dependent. At the same time, innovations in SRS technology (from imaging, to treatment planning hardware and software) have allowed a reduction in radiation treatment volumes by reducing the margins.

17.4.1 Target Dose Prescription

Currently, prescribed SRS radiation doses are usually based on the results from the phase I Radiation Therapy Oncology Group (RTOG) brain tumor committee dose-escalation study published by Shaw et al. in 2000 as part of RTOG 9005 [16]. The study determined the maximal single fraction-tolerated dose given with frame-based GKRS or LINAC in patients with recurrent brain tumors, not involving the brainstem, who had received prior radiation treatment. In the study, 64% had recurrent BM (largely from breast origin and with previous median dose of 30 Gy), and the remaining 36% had a recurrent glioma (with previous median dose of 60 Gy). The dose received was tumor size dependent according to the study design and started at 12, 15, and 18 Gy for tumor diameters of 31–40 mm, 21–30 mm, and $\leq$ 20 mm, respectively. Dose was prescribed to the 50–90% isodose line (IDL) which was to encompass the entire margin of the tumor. For each tumor size group, dose was escalated in 3 Gy increments until irreversible CNS toxicity (defined as RTOG CNS toxicity grade 3–5) developed in more than 20% of the patients within 3 months of SRS. The study concluded that the tolerated doses were 15 Gy, 18 Gy, and 24 Gy for tumor diameters 31–40 mm, 21–30 mm, and $\leq$20 mm, respectively. Dose escalation up to 27 Gy for tumors $\leq$20 mm was not attained, not due to toxicity, but due to reluctance from the investigators. Unacceptable CNS toxicity was found to be more likely in patients with large tumors, with an odds ratio of 16 in tumors 31–40 mm compared to $\leq$20 mm, and the two-year overall incidence of radionecrosis (or RN, discussed in detail later in this chapter) was 11%.

RTOG 9005 excluded patients with brainstem metastases; however, a recent retrospective chart review by Trifiletti et al. [17] from multiple international institutions on their cumulative experience with brainstem SRS, collected through the International Gamma Knife Research Foundation, showed that of 596 brainstem metastases treated with SRS in 547 patients, 7.4% developed severe SRS-induced toxicity with increased odds associated with larger tumor volume and WBRT. The

rate of local control was 81.8% at 12 months after SRS. The study concluded favorable local control and relatively rare toxicity for brainstem metastases treated with SRS.

17.4.2 Normal Tissue Tolerance: Cranial Nerves

Challenges encountered during planning are caused by the prescription dose of radiation desired, and the proximity and sensitivity of normal brain tissue. The most sensitive structures are cranial nerves, in particular the optic nerve, including the chiasm and the vestibulocochlear nerve (cranial nerve VIII).

Stafford et al. [18] published a retrospective Mayo Clinic study of 215 patients who underwent GKRS procedures with median maximum radiation dose to the optic nerve of 10 Gy for tumors of the sellar and parasellar region. Eleven percent had previous external beam radiation therapy (EBRT) with a median dose of 50.2 Gy. Four patients (less than 2%) developed radiation-induced optic neuropathy (RION), three of which had received prior EBRT, one of whom had not, but had received GKRS alone with a dose of 12.8 Gy to the optic nerve or the chiasm. The study concluded the risk of developing a clinically significant RION was 1.1% for patients receiving 12 Gy or less to a short segment of the anterior optic apparatus, the risk being statistically significant higher for those with prior or concurrent EBRT. Based on this study, it was deemed safe to avoid single-fraction doses greater than 10 Gy to the optic apparatus. However, a more conservative dose limit was reported earlier by Tishler et al. [19], based on a combined series review of 62 patients treated with SRS for various types of lesions (71% meningiomas) in or adjacent to the cavernous sinus. Results showed that cranial nerves III to VI dysfunction was infrequent and without definite evidence of dose relationship. However, the optic apparatus was more sensitive to radiation and complications occurred in a dose-dependent manner. No case of RION was reported for single-fraction SRS doses <8 Gy. The incidence was significantly higher at 24% for patients who received single-fraction SRS doses >8 Gy.

Care is usually put into sparing radiation to the cochlea and cranial nerve VIII. True dose limitation is difficult to determine as many studies are based on acoustic neuromas in which patients have baseline hearing loss, caused in part by damage from the tumor. Jacob et al. [20] reported a review of 59 patients with serviceable pretreatment hearing who underwent SRS for sporadic vestibular schwannoma (VS) treated with Gamma Knife Perfexion™. Thirty-six percent developed nonserviceable hearing at a mean of 2.2 years after SRS. The study found that patients who received <5 Gy cochlear volume mean dose were more significantly likely to retain serviceable hearing at their last follow-up on univariate analysis.

Kano et al. [21] recommend a dose to the central cochlea <4.2 Gy. Results are based on their retrospective study in which 77 patients at the University of Pittsburg, with acoustic neuromas and serviceable hearing (Gardner-Robertson Class I or II), underwent SRS with a median dose of 12.5 Gy at the tumor margin using GKRS and had no prior treatment. Patients who received a radiation dose of <4.2 Gy to the central cochlea had significantly better hearing preservation of the same Gardner-Robertson class; of the patients who were less than 60 years old, serviceable hearing at 2 years post-SRS was retained.

A more recent study by Baschnagel et al. [22] reported 40 patients with VS and serviceable hearing (defined as pure tone average less than 50 dB and speech discrimination greater than 50%), treated with GKRS with a median marginal dose of 12.5 Gy, a median cochlear maximum and median cochlear mean dose of 6.9 and 2.7 Gy, respectively. Patients who received a mean cochlear dose of <3 Gy had a two-year hearing preservation rate of 91% compared with 59% in those who received a mean cochlear dose of ≥3 Gy, with a statistically significant difference. They concluded that a mean cochlear dose of <3 Gy was associated with higher serviceable hearing preservation.

17.4.3 Fractionation to Help Meet Tissue Tolerance

Based on traditional radiobiological concepts, dose fractionation is one way to reduce toxicity. The decision not to treat BM with a single SRS fraction and to increase the number of fractions up to 5 is typically due to (i) the large size of the target, generally speaking >4 cm (maximal dimension of the unresected lesions or the postoperative cavity), which allows to reduce the risk of toxicity to the normal brain tissue, or (ii) the closeness to a critical structure such as the optic pathway or the brainstem (maximal tolerance not met during treatment planning).

17.4.3.1 Effects of Tumor Histology

One of the concerns of fractionation is loss of tumor control in setting of radioresistant primaries, as illustrated by a retrospective study by Oermann et al. [23]. In this study, 214 patients, of which 30 had radioresistant tumors such as RCC, melanoma, or sarcoma and 184 had radiosensitive tumors such as lung and breast cancer, were treated with CKRS at The University of North Carolina at Chapel Hill and Georgetown University Hospital. Authors concluded that single-fraction SRS was equally effective in terms of local control for radioresistant and radiosensitive primaries; yet, for radioresistant primaries, FSRS (2 to 5 fractions) failed at a higher rate (odds ratio 5.37) with statistical significance compared to single-fraction SRS.

However, a recent and larger single-center French retrospective study by Lesueur et al. [24] of 60 patients with 193 BM <3 cm compared the impact of single-fraction vs. more fractions (three or six) using CKRS, on local control of radioresistant tumors (melanoma and RCC). Overall local progression-free survival at 12 months was 74% with no statistical difference between the two groups and with no difference in the rate of RN. Authors suggested three- or six-fraction therapy for tumors near highly functional zones such as the brainstem or the cavernous sinus.

17.4.3.2 Effects of Target Size and Dose

A retrospective Italian study by Minniti et al. [25] compared rates of local control and RN in 289 patients with various cancer primaries (29% NSCLC, 17% breast, 10% gastrointestinal, 10% melanoma, 7% RCC, and 6% other), median KPS 80 (range 60–100), and 343 new BM >2 cm treated with LINAC-based single-fraction (15–18 Gy) vs. FSRS (3 × 9 Gy fractions). Planning target volumes (PTV) were created with 1–2 mm expansion from gross tumor volumes (GTV), based on postcontrast enhancement on axial T1-weighted sequence MRI. Single-fraction doses were 18 Gy for lesions 2–3 cm and 15–16 Gy for lesions ≥3 cm. FSRS was most commonly used to treat BM ≥3 cm in size or located near critical areas. The study yielded statistically better rates of cumulative local control at 1 year (median radiologic follow-up of 10 months) in the FSRS vs. single-fraction group (91% vs. 77%) as well as improved rates of RN (9% vs. 18%).

Marcrom et al. [26] published a University of Alabama single-institution retrospective study of 72 patients with various cancer primaries (46% lung, 16% genitourinary, 15% melanoma, 9% breast, 8% gastrointestinal, and 6% other) with median KPS 80 (range 50–90) with 182 new BM treated with LINAC-based FSRS comparing 5 × 5 Gy (25 Gy) vs. 5 × 6 Gy (30 Gy). FSRS was generally considered if a tumor was ≥3 cm, near a critical or eloquent structure or if proximity of moderately sized tumors would have led to dose bridging in a single-fraction SRS treatment plan. The median tumor diameter was 1.68 cm (range 0.31–5.50 cm) and the GTV was defined based on abnormal postcontrast enhancement on T1-weighted sequence MRI and CT scan. While 78% had no margin expansion to PTV, 22% of the lesions had 1–3 mm expansion. The overall 12-month local control (median radiologic follow-up of 5 months) was 86%. On multivariate analysis, increased local failure was significant with tumor diameter ≥ 3 cm (hazard ratio or HR 8.11) and decreased local failure with a dose of 30 Gy (HR 0.26). The 12-month local control was 95% vs. 61% for tumors <3 cm vs. ≥3 cm,

with no failure in tumors <2 cm. The 12-month local control was 91% vs. 75% for tumors treated with 30 Gy vs. 25 Gy. Treatment was well tolerated overall, with CNS toxicity defined by the RTOG 9005 criteria. No increase in toxicity was observed with 30 Gy vs. 25 Gy but significant increase was found with increasing tumor diameter (HR 2.45). While no irreversible grade 3 or 5 toxicities were experienced, 6% of the patients experienced severe grade 4 toxicity which required surgery. The study concluded that FSRS was associated with high rates of local control and low rates of CNS toxicity, but recommended additional dose-escalation studies for larger BM.

Kirkpatrick et al. [27] recently published a review on the subject of FSRS (2–5 fractions). Authors concluded that although results are promising, a lot of research is still needed to understand the fractionation radiobiologic mechanisms of SRS which drive the dose-volume response relationship for tumors and normal brain tissues. The reader can consult this reference for more details.

17.4.3.3 Staged Radiosurgery

Staged radiosurgery is a novel approach to fractionated radiosurgery, originally investigated in Japan by Higuchi et al. [28] for patients with large BM (size >3 cm). In these patients, dose-dense radiation is given in pre-planned SRS sessions at a time interval ranging from several weeks to a few months.

Angelov et al. at the Cleveland Clinic recently reported a case review evaluating the efficacy and toxicity of 2-staged SRS in 54 patients (70% with KPS ≥80) with 63 BM ≥2 cm from various cancer primaries (43% NSCLC, 15% RCC, breast 13%, melanoma 11%, gastrointestinal 11%, and other 7%) treated using GKRS [29]. Patients were immobilized using a head-frame and received dexamethasone 10 mg IV at each GKRS session, and no PTV margins were applied. Median tumor volumes were 10.5 mL (range 2.4–31.3 mL) at the first and 7.0 mL (range 1.0–29.7 mL) at the second SRS session. Median tumor maximal diameters were 3.3 cm (range 2.1–5.1 cm) at the first and 2.9 cm (range 1.3–5.1 cm) at the second SRS session. The median target dose was 15 Gy (range 12–18 Gy) at the 54% IDL at the first and 15 Gy (range 12–15 Gy) at the 53% IDL at the second SRS session, with a median time interval of 34 days between sessions. New lesions discovered at the time of the second SRS session were treated per RTOG 9005 dose scheduling. Three-month follow-up MRI was available for 43 lesions (68.3%), at which time there was a significant median change in volume of 54.9% compared to baseline (time of first SRS session). The estimated 3-month and 6-month local control rates were 95% and 88%, respectively. Adverse effects occurred in seven lesions (11%) at a median of 6.7 months after the first SRS session (6.4% grade 1 or 2 and 4.8% grade 3). Shorter time to progression was significantly associated with greater tumor volume at baseline, as well as smaller absolute and relative decrease in tumor volume. Authors concluded safe and excellent tumor control at a rate comparable to prior single-fraction SRS or FSRS series, but recommended prospective studies to assess durability and late toxicities of staged radiosurgery.

17.5 Prognostic Factors

Over the years, after emergence of SRS, several tools were developed to help determine the prognosis (overall survival) of patients with BM and help decide the optimal initial management.

17.5.1 Overall Survival

In 1997, Gaspar et al.'s retrospective review of three RTOG trials (all of which were non-SRS brain irradiation trials comparing various fractionation schemes and the role of radiosensitizers) of patients with BM treated with radiation [30] used a recursive partitioning analysis (RPA) and determined that age, KPS, primary tumor status (controlled or not), and the presence of extracranial metastases were the most significant indicators on the patients involved in those trials and proposed a three-stage prognostic system (each corresponding to a median

survival time) for future classification and reporting of BM.

In 2001, Weltman et al. [31] proposed the score index for radiosurgery (SIR) in BM using retrospective single-institution analysis of 65 patients treated with SRS, 89% of whom had received WBRT at some point, and found age, KPS, extracranial disease status, number of brain lesions, and largest brain lesion volume as meaningful prognostic factors. With this scoring system, patients were placed into three possible survival groups. After comparison, RPA was found to be a reliable prognostic factor; however, SIR was more accurate in predicting prognosis.

In 2004, Lorenzoni et al. [32] suggested a prognostic tool called basic score for brain metastases (BS-BM) based on single-institution data from 100 patients treated exclusively with GKRS and determined that KPS, primary tumor control, and the presence of extracranial metastases were meaningful factors. Patients could be classified into 4 survival groups, and it was found that SIR first and BS-BM second were the most reliable indicators of survival, BS-BM having the advantage of ease of use.

In 2008, the Graded Prognostic Assessment (GPA) score, also known as Sperduto index [33], was developed because of limitations of the RPA class and the other prognostic tools (e.g., failure to incorporate the number of BM and variability in estimating systemic disease control) and due to the publication of the RTOG 9508 phase III randomized controlled trial (RCT). The GPA score was the total sum of the points assigned to each prognostic factor (points allocated either 0, 0.5, or 1), defined as age, KPS, extracranial metastases (none and present), and number of metastases (one, two to three, and more than three), and stratified patients into four distinct median survival groups (or "classes"). The GPA score was tested against five RTOG trials, including RTOG 9508. It was found to be as prognostic as the RPA class; however, it was also the least subjective, most quantitative, and easiest to use compared to RPA and preexisting indices. The relationship between GPA score and median survival was (i) GPA 0–1, 2.6 months; (ii) GPA 1.5–2.5, 3.8 months; (iii) GPA 3.0, 6.9 months; and (iv) GPA 3.5–4.0, 11 months.

In 2010, an updated version called Diagnosis-Specific GPA (DS-GPA) score was proposed to help identify diagnosis-specific (by primary tumor histology) prognostic factors [34] and stratify patients into the original GPA median survival groups. For NSCLC and small cell lung cancer (SCLC), scoring was identical as in the original GPA and involved the same four significant prognostic factors. For melanoma and RCC, scoring was also identical as in the original GPA, but now only involved KPS and number of BM. For breast and gastrointestinal cancer, KPS was the only significant prognostic factor and a new scoring system was created (points allocated either 0, 1, 2, 3, or 4 based on KPS value). In 2012, the DS-GPA for breast cancer was updated [35], and the significant prognostic factors were age, KPS, and subtype (basal, LumA, LumB, and HER2). To note, primary tumor control is not a significant prognostic factor in DS-GPA, unlike in RPA or BS-BM.

Because the RPA and DS-GPA systems were both based on data from patients treated with WBRT, Likhacheva et al. [36] used a MD Anderson Cancer Center (MDACC) single-institution database of patients who were treated initially with SRS alone (excluding prior craniotomy and/or WBRT) to test the RPA and DS-GPA indices. Both RPA and DS-GPA were successful in dividing SRS patients into prognostically meaningful groups; however, there was a higher survival in each group than in the original reports (more so using RPA than DS-GPA) in which authors attributed to selection bias and the aggressive initial management of the patients at MDACC. Neither the RPA class or DS-GPA score was prognostic of local tumor control or new-lesion-free survival. The study determined that age >60, KPS ≤80, and total lesion volume >2 mL were significant adverse prognostic factors for overall survival.

In 2014, Serizawa et al. updated the BS-BM and defined the modified BS-BM [37], which predicts not only survival but also preservation of neurological function and prevention of neurological death. As in the original BS-BM, four main survival groups are created based

on KPS, primary tumor control, and the presence of extracranial metastases. In the modified BS-BM, each survival group is split into 2 subgroups (A, with better neurological outcome, and B, with poorer outcome) based on four additional significant factors: number of BM, total tumor volume, presence of MRI findings of localized meningeal dissemination, and presence of neurological symptoms. The modified BS-BM was validated using retrospective data from 2838 patients treated with GKRS without upfront WBRT at initial treatment and found to be excellent for predicting neurological outcomes—independently of survival—in SRS-treated patients with BM.

The DS-GPA for patients with NSCLC and BM was updated in 2017 by Sperduto et al. [38] to include gene and molecular alteration data. The new Lung-molGPA prognostic index is based on 2186 patients (1521 adenocarcinoma and 665 nonadenocarcinoma) diagnosed with new BM who received combination of SRS, WBRT, and surgery. Significant prognostic factors included the original four factors used in the DS-GPA index plus two new factors: EGFR and ALK alterations in patients with adenocarcinoma (nonadenocarcinoma patients were not routinely tested). Based on this update, patients with adenocarcinoma and nonadenocarcinoma were grouped in 4 and 3 distinct median survival groups, respectively.

In 2017, Sperduto et al. [39] updated the original Melanoma-GPA to include the impact of molecular markers, creating the Melanoma-molGPA with a free online tool, based on a multi-institutional retrospective database analysis of 823 melanoma patients with newly diagnosed BM, 56% of whom got SRS alone and the rest had combinations of SRS, surgery, and WBRT. The five significant prognostic factors for survival were age, KPS, presence of extracranial metastases, number of BM, and BRAF status, which allowed patients to be placed in four distinct survival groups. Of note, only KPS and number of BM were significant in the original Melanoma-GPA.

17.5.2 Distant Failure Predictive Nomogram

As distant brain failure (DBF) is the main downside of primary SRS for the treatment of BM, Ayala-Peacock et al. [40] developed a nomogram to find factors that predict for early DBF after GKRS. Authors suggested that such predictive model would be a clinically useful tool in identifying patients who may have early DBF and, thus, would benefit from earlier WBRT. Single-institution data of 464 patients treated with GKRS without WBRT for primary management of newly diagnosed BM was used to develop the nomogram, and it was found that systemic disease status (unknown, stable, and progressive), number of BM (1–3 and 4–13), and histology (lung cancer subtype adenocarcinoma, squamous cell carcinoma or other; breast cancer subtype HER2 positive or negative; RCC; melanoma) were significant factors that predict earlier time to DBF after primary SRS management of BM.

17.5.3 Local Control Radiologic Predictors

Rodrigues et al. [41] performed a RPA of a retrospective SRS database of 380 patients with 1–3 newly diagnosed BM (total of 536 BM) treated with LINAC-based SRS as single modality and created three distinct prognostic groups of patients in terms of time to lesion progression. It was found on RPA that lesion radiological phenotype or pattern of contrast enhancement on gadolinium-enhanced T1-weighted sequence MRI (homogeneous, heterogeneous, thin-walled cystic or necrotic center) and RT schedule were independent factors associated with progression outcomes defined in the study: time to progression (time from initiation of SRS to development of progressive disease on a per-lesion level) and time to first progression (time-to-progression endpoint at a per-patient level). Tumor necrosis was associated with worst outcome in terms of progression, whereas most intense RT fraction-

ation schedule (21 Gy in single fraction) was associated with best outcome. The SRS lesion RPA groups were also found to be predictive of overall survival.

17.5.4 Impact of Histology and Systemic Disease Control

A unified prognostic tool including tumor histology and primary tumor control as meaningful factors on overall survival has yet to be developed. DS-GPA, on one hand, includes histology, while modified BS-BM, on the other hand, includes primary tumor control, but neither includes both. Sia et al. [42], in a single-institution study of 162 patients with 318 BM treated with SRS as first-line treatment, as well as SRS for residual or recurrent BM, WBRT, or both, showed that SIR, BS-BM, GPA, DS-GPA, and RPA prognostic indices all demonstrated excellent correlation with survival in univariate analysis. Authors also showed that Eastern Cooperative Oncology Group (ECOG) performance status (PS), uncontrolled systemic disease, and melanoma histology were significantly prognostic for survival both in univariate and multivariate analysis. On multivariate analysis, melanoma histology and tumor volume were both poor prognostic factors of local control. With the advent of immune checkpoint inhibitors, these results may need to be re-validated in the era of immunotherapy.

17.5.5 Physician Prognosis Estimates

As illustrated by Kondziolka et al. [43], who prospectively studied 150 patients undergoing SRS and surveyed 18 medical, radiation, or surgical oncologists to predict survival from the time of treatment, it is difficult to predict the survival of cancer patients. The actual median patient survival was 10.3 months, while the physician-predicted median survival was 9.7 months (11.8 months for neurosurgeons, 11.0 months for radiation oncologists, and 7.2 months for medical oncologists). Based on the study, all physicians had individual patient survival predictions incorrect by as much as 12–18 months, and 14 of 18 physicians had individual predictions in error by more than 18 months.

17.6 Application of SRS to Brain Metastases

Over the last 10 years, the role of SRS in the management of patients with BM has evolved significantly in its favor over traditional WBRT owing to multiple retrospective and phase III RCTs which proved adequate local control at no significant change in survival and, importantly, with better preservation of neurocognitive function. Historically, WBRT with steroids was the standard of care for patients with BM, until Patchell et al. [44] demonstrated in a randomized trial that WBRT after resection of a single BM vs. a simple biopsy in patients with KPS $\geq$70 resulted in a significant improvement in overall survival (40 vs. 15 weeks), reduction of local recurrence rates (52% vs. 20%), and increased duration of functional independence. In a second prospective randomized trial, Patchell et al. [45] demonstrated that the addition of WBRT to the MRI-verified complete total resection of a single BM, vs. observation, significantly decreased the rate of local recurrence (46% vs. 10%), distant intracranial recurrence (37% vs. 14%), overall intracranial recurrence (70% vs. 18%), and death of neurologic causes (44% vs. 14%). However, there was no effect on overall survival or the length of time that patients remained functionally independent.

Maintaining QOL by minimizing radiation treatment-related side effects on cognitive function or by reducing the risk of brain injury is essential in cancer patients with BM who are now able to live longer because of the increased efficacy of systemic therapies.

SRS use was initially reported as a boost in combination with WBRT in an attempt to increase local control and eventually was studied

alone or as adjuvant treatment to postoperative surgical cavities. In certain cases, SRS can offer similar or even better local control than surgical resection without the risks and complications of neurosurgery [46].

The last ASTRO guidelines on BM published in 2012 [47] were written before the emergence of level 1 evidence on treating more than four newly diagnosed BM and before large studies comparing neurocognitive outcomes between adjuvant SRS and WBRT. In 2014, ASTRO Choosing Wisely® recommended against adding adjuvant WBRT routinely to SRS for limited BM as long as careful surveillance is established.

However, the definition of limited BM is evolving over time, as new evidence is published.

NCCN Guidelines Version 1.2018 [48] updated their definition of "limited number" of BM compared to 2017, for which it states that "SRS is generally preferred over WBRT, with the possible exception of patients with poor performance or uncontrolled systemic tumors." The definition was changed from 1–3 BM to no absolute limit. It now defines "limited brain metastases" as "a group of patients for whom SRS is equally effective and offers significant cognitive protection compared with WBRT." The definition of *limited* BM in terms of number of metastases or total intracranial disease volume is evolving and may depend on the specific clinical situation based on the study by Yamamoto et al. [49, 50].

The seven most recent phase III RCTs and one prospective multi-center non-randomized trial addressing the efficacy of SRS are summarized in Tables 17.1 and 17.2. The patients recruited generally include age ≥ 18 (except for the MDACC study by Mahajan et al. with surgery followed by observation vs. SRS alone [57] where age was ≥3), good performance status (ECOG PS 0–2 or KPS ≥70), and a recent brain MRI scan (most within 6 weeks of radiation treatment). Patients excluded typically had prior brain surgery or radiation, or radiosensitive histologies such as SCLC (except for the case of RTOG 9508 [51] and JLGK0901 [49, 50]), leukemia, lymphoma, or germ cell tumors. Outcomes measured included median overall survival, local intracranial control (in case of SRS or surgical resection), distant intracranial control, overall intracranial control, rate of salvage therapy (with SRS, WBRT, or surgical resection), and rates of neurological death.

17.6.1 SRS as a Boost to WBRT vs. WBRT Alone, for Newly Diagnosed 1 to 3 Brain Metastases

Although previous randomized studies had established WBRT preceded by surgical resection as standard of care in the early 1990s [44], for the case of a single BM due to improvement in prognosis, the contemporary introduction of SRS for the treatment of BM [2] provided the hopes of a less invasive intervention compared to surgery with similar outcome, especially for lesions in eloquent cortex or deep-seated tumors usually thought to be unresectable.

In the RTOG 9508, Andrews et al. [51] provided the first multi-institutional prospective randomized comparison of WBRT with vs. without SRS boost where patients had one to three newly diagnosed BM and KPS ≥70 at the time of randomization and could have undergone prior BM resection. BM were deemed unresectable if they were located in deep gray matter or in eloquent cortex. Inclusion criteria permitted the largest remaining lesion maximum diameter ≤4 cm with additional tumors ≤3 cm. Patients with lesions in the brainstem or <1 cm from the optics were excluded. Patients were randomized to WBRT with vs. without SRS boost within 1 week of completing WBRT, using SRS doses by size group per RTOG 9005. In this study, 63% of the cancer primaries were from lung origin. WBRT was given with a dose of 37.5 Gy in 2.5 Gy fractions in both arms. Despite a 19% failure to receive SRS, there was a significant survival benefit by univariate analysis in patients with a single unresectable BM allocated to the SRS group, with median survival time of 6.5 vs. 4.9 months in the WBRT alone group, with a predominance in RPA class II patients. In patients with multiple BM, however, researchers detected no significant difference in survival with SRS boost treatment

Table 17.1 Comparison of seven randomized trials and one prospective multi-center non-randomized trial outcomes on tumor control, survival, salvage therapy, and neurological death

Institution/management	N	Number of lesions	Target size	12-month local intracranial control	12-month distal intracranial control	12-month overall intracranial control	Median overall survival	Rate of salvage therapy	Rate of neurological death
WBRT +/− SRS or SRS +/− WBRT									
RTOG 9508 (1996–2001) [51]	331	1–3	≤4 cm largest						
Arm 1: WBRT + SRS	164		≤3 cm others	82%	NR	72%	6.5 mo	NR	28%
Arm 2: WBRT alone	167			71%	NR	65%	5.7 mo	NR	31%
				p = 0.01		*p = 0.1278*	*p = 0.1356*		
MDACC (2001–2007) [52]	58	1–3	<4 cm						
Arm 1: SRS + WBRT	28			100%	73%	73%	5.7 mo	33%	28%
Arm 2: SRS alone	30			67%	45%	27%	15.2 mo	100%	40%
				p = 0.012	*p = 0.02*	*p = 0.0003*	*p = 0.0036*		
JROSG-99-1 (1999–2003) [53, 54]	132	1–4	≤3 cm						
Arm 1: WBRT + SRS	65			89%	59%	53%	7.5 mo	15%	23%
Arm 2: SRS alone	67			73%	36%	24%	8.0 mo	43%	19%
				p = 0.002	*p = 0.003*	*p < 0.001*	*p = 0.42*	*p < 0.001*	*p = 0.64*
NCCTG (Alliance) N0574 (2002–2013) [55]	213	1–3	<3 cm						
Arm 1: SRS alone	111			73%	70%	51%	10.4 mo	32%	NR
Arm 2: SRS + WBRT	102			90%	92%	85%	7.4 mo	8%	NR
				p = 0.003	*p < 0.001*	*p < 0.001*	*p = 0.92*	*p < 0.001*	
Postoperative radiation									
EORTC 22952–26001 (1996–2007) [46, 56]	359	1–3	Single met ≤3.5 cm						
Arm 1: SRS + OBS	100		Multi mets ≤2.5 cm	71%	57%	NR	10.7 mo	51%	44%
Arm 2: S + OBS	79		(Complete resection)	46%	62%	NR			

(continued)

Table 17.1 (continued)

Institution/management	N	Number of lesions	Target size	12-month local intracranial control	12-month distal intracranial control	12-month overall intracranial control	Median overall survival	Rate of salvage therapy	Rate of neurological death
Arm 3: SRS + WBRT	99			85%	71%	NR NR	10.9 mo	16%	28%
Arm 4: S + WBRT	81			74%	82%				
				p = 0.04 (1 vs. 3) *p < 0.001 (2 vs. 4)*	*p = 0.023 (1 vs. 3)* *p = 0.008 (2 vs. 4)*		*p = 0.89*		*p < 0.002*
MDACC (2009–2016) [57]	128	1–3	Resection cavity ≤4 cm					(Salvage with WBRT)	
Arm 1: S + SRS	63	All resected	(Complete resection)	72%	58%	NR	17 mo	38%	48%
Arm 2: S alone	65			43%	67%	NR	18 mo	46%	64%
				p = 0.015	*p = 0.35*		*p = 0.24*		*p = 0.13*
NCCTG N107C/ CEC.3 (2011–2015) [58]	194	1–4	Resection cavity <5 cm	(Resection cavity)[a]					
Arm 1: S (1 met) + SRS	98	1 resected	Unresected <3 cm	61%	65%	37%	12.2 mo	NR	NR
Arm 2: S (1 met) + WBRT	96			81%	89%	72%	11.6 mo	NR	NR
				p = 0.00068	*p = 0.00045*	*p < 0.0001*	*p = 0.70*		
SRS alone (non-randomized)									
JLGK0901 (2009–2012) [49, 50]	1194	1–10	<3 cm or 10 mL						
Arm 1: SRS alone to 1 met	455		≤15 mL total	87%	63%	NR	13.9 mo	NR	10%
Arm 2: SRS alone to 2–4 mets	531			93%	46%	NR	10.8 mo	NR	6%
Arm 3: SRS alone to 5–10 mets	208			94%	36%	NR	10.8 mo	NR	9%
				p = 0.45 (1 vs. 2) *p = 0.70 (2 vs. 3)*	*p < 0.0001 (1 vs. 2)* *p = 0.067 (2 vs. 3)*		*p = 0.0004 (1 vs. 2)* *p = 0.78 (2 vs. 3)*		*p = 0.27 (2 vs. 3)*

[a]For unresected BM, the 12-month local intracranial control was 62% vs. 87% for the SRS and WBRT groups, respectively (*p = 0.00016*)

NR not reported, *BM* brain metastases, *mo* month, *S* surgical resection, *WBRT* whole brain radiation therapy, *SRS* stereotactic radiosurgery, *NCCTG* North Central Cancer Treatment Group, *JLGK* Japan Leksell Gamma Knife (Society), *EORTC* European Organization for Research and Treatment of Cancer, *JROSG* Japanese Radiation Oncology Study Group, *MDACC* MD Anderson Cancer Center, *RTOG* Radiation Therapy Oncology Group

Table 17.2 Comparison of seven randomized trials and one prospective multi-center non-randomized trial outcomes on functional status, quality of life, neurocognitive function, and CNS toxicity

Institution/management	N	Number of lesions	Target size	Functional status change	QOL change	Neurocognitive change	CNS toxicity
WBRT +/− SRS or SRS +/− WBRT							
RTOG 9508 (1996–2001) [51]	331	1–3	≤4 cm largest	KPS improvement at 6 mo		MMSE at 6 mo	RTOG CNS grade
Arm 1: WBRT + SRS	164		≤3 cm others	13%	NR	Similar	Similar early and late
Arm 2: WBRT alone	167			4%	NR		
				p = 0.0331			
MDACC (2001–2007) [52]	58	1–3	<4 cm		FACT-BR change from baseline at 4 mo	HVLT-R total recall drop at 4 mo	
Arm 1: SRS + WBRT	28			NR	−1.8 pts	52%	NR
Arm 2: SRS alone	30			NR	+1.0 pts	24%	NR
					p = 0.76		
JROSG-99-1 (1999–2003) [53, 54]	132	1–4	≤3 cm	KPS ≥70 preservation at 12 mo		MMSE 3pt deterioration from baseline at 12 mo	NCI CTCAE
Arm 1: WBRT + SRS	65			34%	NR	24%	Similar early/late
Arm 2: SRS alone	67			27%	NR	41%	
				p = 0.53		*p = 0.79*	
NCCTG (Alliance) N0574 (2002–2013) [55]	213	1–3	<3 cm	Barthel ADL index change from baseline at 3 mo	FACT-BR change from baseline at 3 mo	Neurocognitive deterioration (any of 7 tests) >1SD from baseline at 3 mo	NCI CTCAE Grade3+
Arm 1: SRS alone	111			−1.5 pts	−0.1 pts	64%	41%
Arm 2: SRS + WBRT	102			−4.2 pts	−12 pts	92%	43%
				p = 0.26	*p = 0.001*	*p < 0.001*	*p = 0.8897*
Postoperative radiation							
EORTC 22952–26,001 (1996–2007) [46, 56]	359	1–3	Single met ≤3.5 cm	Median duration until WHO PS > 2 drop	HRQOL change from baseline at 12 mo		Late effects LENT/SOMA Scales
Arm 1: SRS + OBS	100		Multi mets ≤2.5 cm	10 mo	−1.3 pts	NR	Similar
Arm 2: S + OBS	79		(Complete resection)				
Arm 3: SRS + WBRT	99			9.5 mo	−1.5 pts	NR	
Arm 4: S + WBRT	81						
				p = 0.71	*p = 0.7*		

(continued)

Table 17.2 (continued)

Institution/management	N	Number of lesions	Target size	Functional status change	QOL change	Neurocognitive change	CNS toxicity
MDACC (2009–2016) [57]	128	1–3	Resection cavity ≤4 cm				
Arm 1: S + SRS	63	All resected	(Complete resection)	NR	NR	NR	NR
Arm 2: S alone	65			NR	NR	NR	NR
NCCTG N107C/CEC.3 (2011–2015) [58]	194	1–4	Resection cavity <5 cm	Barthel ADL index 10% drop from baseline at 3 mo	FACT-BR decline ≥10pts from baseline at 3 mo	Cognitive deterioration >1SD from baseline at 6 mo	NCI CTCAE grade
Arm 1: S (1 met) + SRS	98	1 resected	Unresected <3 cm	6%	29%	52%	Similar
Arm 2: S (1 met) + WBRT	96			12%	41%	85%	
				p = 0.036	*p = 0.3496*	*p < 0.00031*	
SRS alone (non-randomized)							
JLGK0901 (2009–2012) [49, 50]	1194	1–10	<3 cm or 10 mL	KPS ≥70 preservation at 12 mo		MMSE 3pt deterioration from baseline at 12 mo	NCI CTCAE Grade3+
Arm 1: SRS alone to 1 met	455		≤15 mL total	92%	NR	7%	3.7%
Arm 2: SRS alone to 2–4 mets	531			92%	NR	9%	4.2%
Arm 3: SRS alone to 5–10 mets	208			91%	NR	8%	3.5%
						p = 0.18 (1 vs. 2) *p = 0.43 (2 vs. 3)*	*p = 0.80 overall*

NR not reported, *BM* brain metastases, *mo* month, *S* surgical resection, *WBRT* whole brain radiation therapy, *SRS* stereotactic radiosurgery, *NCCTG* North Central Cancer Treatment Group, *JLGK* Japan Leksell Gamma Knife (Society), *EORTC* European Organization for Research and Treatment of Cancer, *JROSG* Japanese Radiation Oncology Study Group, *MDACC* MD Anderson Cancer Center, *RTOG* Radiation Therapy Oncology Group, *KPS* Karnofsky Performance Status, *WHO PS* World Health Organization Performance Status, *ADL* activities of daily living, *QOL* quality of life, *FACT-BR* Functional Assessment of Cancer Therapy-Brain, *HRQOL* health-related quality of life (based on EORTC QOL questionnaire C30 aka EORTC QLQ-C30 and the EORTC QLQ Brain Cancer Module aka EORTC QLQ-BN20), *MMSE* Mini–Mental State Examination, *HVLT-R* Hopkins Verbal Learning Test-Revised, *SD* standard deviation, *NCI CTCAE* National Cancer Institute Common Terminology Criteria for Adverse Events, *LENT/SOMA* Late Effects Normal Tissue Task Force/Subjective, Objective, Management, Analytic

vs. WBRT alone (5.7 vs. 6.5 months), unless patients belonged to RPA class I or had a favorable histologic status (squamous cell or NSCLC) by multivariate analysis. Statistically significant stability or improvement in KPS and decreased steroid use at 6 months was noted in all patients who had SRS boost treatment vs. those who did not. At 12 months, SRS boost vs. WBRT alone provided significant improvement in local intracranial control (defined as unchanged or improved on serial post-treatment MRI scans) with 82% vs. 71%, with no difference in overall intracranial control, as expected due to the local effect of SRS. No difference in rates of neurological death was noted between groups, and similar rates of early and late CNS toxicity were seen. RTOG 9508 provided a recommendation for SRS boost after WBRT as standard of care for single BM and suggested a consideration of SRS for two to three BM based on improved performance in all patients.

17.6.2 Omission of WBRT with SRS Treatment

Several phase III RCTs have provided evidence supporting the use of SRS alone without WBRT for the treatment of BM.

The Japanese Radiation Oncology Study Group Protocol 99-1 (JROSG-99-1) study published by Aoyama et al. [53, 54] was the first prospective RCT comparing SRS alone vs. WBRT upfront plus SRS. The trial included patients with a maximum of four BM, maximum diameter ≤3 cm, and KPS ≥70 at the time of randomization, while the primary outcome was overall survival. WBRT was given with a total dose of 30 Gy in 10 identical fractions. SRS dose was prescribed to the tumor margin and was a function of lesion size (22–25 Gy for lesions ≤2 cm and 18–20 Gy for lesions >2 cm). SRS dose was reduced by 30% when EBRT was given. Aoyama et al. reported no significant difference in survival with SRS alone vs. WBRT upfront plus SRS (8.0 vs. 7.5 months). The addition of WBRT statistically improved all rates of intracranial relapse, while local tumor progression was defined as a radiographic increase of 25% or more in the size of a BM. SRS alone vs. WBRT upfront plus SRS had a 12-month local control rate of 73% vs. 89% (similar to the combination therapy arm rate of 82% in RTOG 9508), a 12-month distal control rate of 36% vs. 59%, and a 12-month overall control rate of 24% vs. 53%. The overall rate of salvage therapy was significantly worse with SRS alone vs. WBRT upfront plus SRS (43.3% vs. 15.4%), although there was no significant difference in rate of neurological death, early, or late CNS toxicities.

Functional status preservation was a secondary outcome of the JROSG-99-1 study and was evaluated using the KPS score. The rate of preservation of KPS ≥70 at 12 months was not statistically different between both groups. Neurocognitive function was assessed using the Mini–Mental State Examination (MMSE) score as sole measurement, although the MMSE is a screening test originally designed for dementia and lacks sensitivity [59] to detect more subtle neuropsychological changes. For the analysis of the post-treatment changes in the MMSE, patients with no available follow-up MMSE were excluded. A statistically meaningful change was defined as a three-point change in the MMSE score, and a score of ≤26 was defined as abnormal. In the patients with a baseline MMSE score ≥27 or whose baseline MMSE score was ≤26 but had improved to ≥27 after the initial SRS treatment, the three-point deterioration in MMSE at 12 months was worse at 40.7% in the SRS group vs. 23.9% in the WBRT upfront plus SRS group, with no statistical difference. This led to the assumption that tumor control was the most important factor in determining neurologic progression. Authors concluded that WBRT upfront plus SRS did not improve survival for patients with one to four BM compared to SRS alone, although intracranial relapse occurred considerably more often in those who did not receive WBRT, causing salvage treatment to be frequently required when upfront WBRT was not used.

The MDACC study [52]—published by Chang et al., comparing upfront SRS plus WBRT vs. SRS alone in the initial management of

patients newly diagnosed with one to three BM, maximum diameter <4 cm—evaluated primary outcome of neurocognitive function objectively measured as a significant deterioration (five-point drop compared to baseline) in the Hopkins Verbal Learning Test-Revised (HVLT-R) in total recall at four months. Very importantly, this study was also the first to report formal neurocognitive testing to adequately compare side effects of treatment as illustrated in Table 17.3.

Previous studies either omitted any neurocognitive testing entirely or used MMSE, which lacks sensitivity. The MDACC trial was halted early by the data monitoring committee according to the early stopping rules based on strong evidence of excessive neurocognitive toxicity at 4 months after treatment in the WBRT arm. While patients recruited had RPA Class I or II, KPS ≥70, and had to be SRS eligible (in other words, individual lesions ≤3 cm), WBRT was given with a dose of 30 Gy in 12 identical fractions and the SRS dose was given per RTOG 9005. Although Chang et al. reported an overall survival in the combined SRS plus WBRT treatment arm of 5.7 months, similar to that reported in JROSG-99-1 and RTOG 9508, the overall survival in the SRS alone arm was 15.2 months and significantly improved, departing from JROSG-99-1 and the more recent study NCCTG (Alliance) N0574 [55] which showed no difference in survival between similar treatment groups. To help explain the improvement in survival in the SRS alone arm, Chang et al. found on post-hoc analysis of the timing of systemic therapy that patients assigned to the SRS alone arm received systemic therapy over 1 month earlier and for a median of two more cycles than patients assigned to upfront SRS plus WBRT, implying that more prompt systemic therapy might have contributed to the prolonged survival of patients in the SRS alone group. Authors also suggested a

Table 17.3 Neurocognitive domain and corresponding test, as used in large randomized controlled trials

Domain	Test	MDACC (Chang et al., 2007) [60]	MDACC (Chang et al., 2009) [52]	NCCTG (Alliance) N0574 (Brown et al., 2016) [55]	NCCTG N107C/CEC.3 (Brown et al., 2017) [58]	ICCTF (Wietske et al., 2011) [61]
Attention	WAIS-III digit span	√	√			
Information processing	WAIS-III digit-symbol-coding	√	√			
Processing speed	TMT Part A	√	√	√	√	√
Executive function	TMT Part B	√	√	√	√	√
Memory	HVLT-R total recall	√	√			√
Learning and immediate memory	HVLT-R immediate recall			√	√	√
Delayed memory	HVLT-R delayed recall	√	√	√	√	√
Recognition	HVLT-R recognition	√	√	√	√	√
Verbal fluency	COWA of the Multilingual Aphasia Examination	√	√	√	√	√
Fine motor dexterity	Lafayette Grooved Pegboard	√	√	√		

ICCTF International Cancer and Cognition Task Force, *WAIS-III* Wechsler Adult Intelligence Scale-III, *TMT* Trail Making Test, *HVLT-R* Hopkins Verbal Learning Test-Revised, *COWA* Controlled Oral Word Association

possible imbalance between the 2 treatment arms, where patients randomly assigned to upfront SRS plus WBRT had a greater systemic disease burden than their counterparts in the SRS alone arm at the time of enrollment.

The addition of WBRT statistically improved all rates of intracranial relapse. Local tumor progression was defined as any initial SRS-treated lesions increased by more than 25% in diameter on contrast-enhanced MRI or requiring resection. The addition of WBRT improved the 12-month local control rate from 67% to 100%, the 12-month distal control rate from 45% to 73%, and the 12-month overall control rate from 27% to 73%. The overall rate of salvage therapy was 100% vs. 33% for SRS alone vs. upfront SRS plus WBRT, and the overall rate of neurological death was 40% vs. 28%. The study also measured changes in QOL using the Functional Assessment of Cancer Therapy-Brain (FACT-BR), but results at 4 months were similar between arms. Neurocognitive analysis, as mentioned previously, was significantly worse in the WBRT arm and will be further discussed in another section of this chapter. Authors recommended that initial treatment with SRS alone combined with close clinical monitoring should be the preferred strategy in the early management of patients newly diagnosed with one to three BM, with tailoring surgical salvage for local failures, and SRS or WBRT for distant failures.

The NCCTG (Alliance) N0574 trial [55] published by Brown et al. compared upfront SRS plus WBRT vs. SRS alone in the initial management of patients with one to three BM with primary outcome to determine whether there was less cognitive deterioration (defined as a decline >1 standard deviation from baseline on at least 1 cognitive test at 3 months) after SRS alone vs. upfront SRS plus WBRT. Patients recruited had tumors <3 cm, ECOG PS 0-2, and those excluded notably had lesions located within 5 mm of the optic chiasm or within the brainstem. For SRS alone, the dose was 24 Gy for lesions <2.0 cm and 20 Gy for lesions 2.0–2.9 cm, prescribed to the highest IDL encompassing the target (ranging 50–80% of the maximum dose). If randomized to upfront SRS plus WBRT, SRS doses were decreased to 22 Gy for lesions <2.0 cm and 18 Gy for lesions 2.0–2.9 cm. WBRT was given within 14 days of SRS at a dose of 30 Gy in 12 identical fractions.

Brown et al. reported statistically significant less cognitive deterioration at three months and statistically significant higher QOL at 3 months (estimated using FACT-BR change from baseline at 3 months) after SRS alone than when combined with WBRT. There was no difference in functional independence (measured using Barthel ADL index change from baseline at 3 months) or Grade 3 or above CNS toxicity (measured using NCI CTCAE) between groups. There was no difference in overall survival time in SRS alone 10.4 vs. 7.4 months in the upfront SRS plus WBRT group.

Similarly, as evidenced in the previous studies, the addition of WBRT statistically improved all rates of intracranial relapse. The 12-month local control rate was improved by the addition of WBRT from 72.8% to 90.1%, the 12-month distal control rate from 69.9% to 92.3%, and the 12-month overall control rate from 50.5% to 84.6%. The overall rate of salvage therapy was significantly greater at 32.4% in the SRS alone vs. 7.8% in the other group; however rates of neurological death were not reported. Considering the significant cognitive deterioration at three months using SRS combined with WBRT in patients with one to three BM with absence of a difference in overall survival, authors suggested SRS alone as a preferred strategy for one to three BM amenable to SRS.

Kocher et al. reported the results of EORTC 22952-26001 [46, 56], in which patients with one to three newly diagnosed BM were treated with complete surgical resection or SRS then randomly assigned to adjuvant WBRT or observation with primary outcome to assess survival with functional independence (defined as time to a deterioration of more than 2 points of the WHO PS). Health-related quality of life (HRQOL) was a secondary endpoint in the trial and published at a later point by Soffietti et al. [56]. Patients recruited had WHO PS 0-2, with no size limit for BM which underwent complete surgical resection; however, size limit for patients random-

ized to SRS was ≤3.5 cm if single or ≤2.5 cm if multiple BM. Patients with brainstem metastases were excluded from the study. SRS dose was prescribed to 25 Gy at the center of each metastasis and the minimal dose at the PTV surface (defined as GTV plus a margin of 1–2 mm) was 20 Gy. WBRT was initiated at a maximum of 6 weeks after SRS or surgical resection and the dose was 30 Gy in 10 identical fractions. The study failed to show a difference in median survival with functional independence (9.5 vs. 10 months) between the groups who underwent WBRT vs. observation or a difference in overall survival (10.9 vs. 10.7 months).

The 12-month rate of local and distal intracranial control was significantly worse in the observation vs. WBRT group as shown in Table 17.1 and the difference was the greatest for patients who underwent complete surgical resection vs. those who underwent SRS. The overall rate of salvage therapy was 51% in the observation group vs. 16% in the WBRT group with significantly worse rates of neurological death in the observation group, 44% vs. 28%. QOL assessment was done at baseline, at 8 weeks, and then every 3 months for 3 years with the European Organization for Research and Treatment of Cancer (EORTC) QOL Questionnaire C30 and Brain Cancer Module. The primary scales considered were global health status, functioning (physical, cognitive, role, and emotional), and symptom of fatigue. Overall, patients who were in the observation arm reported better HRQOL scores than patients in the WBRT arm; a statistically significant and clinically meaningful difference was only detected at nine months, but no differences were found at any other points. There was no formal neurocognitive assessment.

In summary, the existing trials comparing SRS to SRS combined with WBRT all show better intracranial control (local, distal, and overall) at no benefit in survival (except as reported by Chang et al. [52] , possibly caused by unbalanced treatment arms) or CNS toxicity. SRS provides preservation of neurocognitive function and, in some trials, better QOL even at higher rates of salvage therapy.

17.6.3 Postoperative SRS to Newly Diagnosed Brain Metastases

Brain metastases which are resectable and which cause significant neurological symptoms (such as mass effect) are often surgically removed based on early data from Patchell et al. which showed improved survival [44]. Later data from Patchell et al. [45] showed postoperative radiation using WBRT, even after MRI verified complete total resection, was essential to significantly reduce recurrence in the surgical bed and the incidence of new BM. Hence, resection alone is insufficient. Studies comparing SRS to WBRT have also shown the detrimental impact of WBRT on neurocognitive and QOL, although WBRT provides superior intracranial control. Large RCTs were initiated to analyze the effectiveness of SRS treatment to the margins of the postoperative surgical beds compared to WBRT or observation alone to decrease local recurrence.

The MDACC single-institution study by Mahajan et al. [57] was the first completed phase III RCT addressing the efficacy of SRS to the surgical cavity compared to surgical resection alone (observation) in patients presenting with one to three BM. The study included patients with all BM completely resected (neuroradiologist verified) and resection cavities ≤4 cm, and primary outcome was the time to local recurrence. SRS dose was dependent on target volume (defined as surgical cavity plus a margin of 1 mm) as follows: 16 Gy if ≤10.0 mL, 14 Gy if 10.1–15.0 mL, and 12 Gy if >15.0 mL. The study showed significant improvement in local control with the addition of SRS from 43% to 72% at 12 months, which on post-hoc analysis was shown to be true for all the ranges of initial tumor sizes (0.5–2.5 cm, >2.5–3.5 cm, and > 3.5 cm). There was no difference in distal intracranial control or overall survival (17–18 months). Rates of salvage therapy with WBRT and neurological death were greater in the observation groups (46% and 64%) vs. in the SRS group (38% and 48%). Functional status change, QOL, or neurocognitive outcomes were not addressed in the study. Since no SRS treatment-related toxicities were reported, authors noted that local control might have been

improved with escalating dose by at least 2 Gy per target size category.

The NCCTG (Alliance) N107C/CEC.3 trial [58] reported by Brown et al. was the largest phase III RCT addressing the efficacy of SRS vs. WBRT to a surgical cavity in patients presenting with 1–4 BM and surgical resection of one of them. In both arms, all unresected BM were treated with SRS. The primary outcomes were overall survival and cognitive-deterioration-free survival (drop of greater than one standard deviation from baseline in at least one of the six cognitive tests). Patients recruited had a resection cavity <5 cm, including patients with a subtotal resection (8% to 14%), up to 3 unresected BM each <3 cm and excluded patients with lesions located within 5 mm of the optic chiasm or within the brainstem. SRS dose was prescribed to the highest IDL encompassing the target volume. SRS dose to the resection cavity was target volume dependent (defined as surgical cavity plus a margin of 2 mm) as follows: 20 Gy if <4.2 mL, 18 Gy if 4.2–7.9 mL, 17 Gy if 8.0–14.3 mL, 15 Gy if 14.4–19.9 mL, 14 Gy if 20.0 to 29.9 mL, and 12 Gy if ≥30 mL up to the maximal surgical cavity extent of 5 cm. For patients assigned to SRS to the surgical cavity, SRS dose to the unresected BM was maximal diameter-dependent as follows: 24 Gy if <1.0 cm, 22 Gy if 1.0–2.0 cm, and 20 Gy if 2.1–2.9 cm. For patients assigned to WBRT, SRS dose to the unresected BM was also maximal diameter-dependent but decreased by 2 Gy in each size category. WBRT was delivered with either 30 Gy in 10 fractions or 37.5 Gy in 15 fractions based on institutional preference.

Brown et al. reported significantly worse rate of cognitive deterioration from baseline at 6 months in the WBRT vs. the SRS arm (85% vs. 52%), with no difference in overall survival (11.6 vs. 12.2 months). Surprisingly, the addition of WBRT vs. SRS, statistically improved local control at the tumor bed as well as all other metrics of intracranial control: 12-month local control rate at surgical bed (61% vs. 81%), 12-month local control rate of unresected BM (62% vs. 87%), 12-month distal control rate (65% vs. 89%), and 12-month overall control rate (37% vs. 72%). No rates of salvage therapy or neurological death were reported. Authors note that the surgical bed control rate after SRS was inferior to that reported by Mahajan et al. [57], possibly due to the inclusion in NCCTG (Alliance) N107C/CEC of patients with subtotal resection and lack of central review.

Functional independence defined as a Barthel ADL index drop of 10% from the baseline at 3 months was significantly worse in the WBRT arm, although no significant change in QOL (measured as a FACT-BR decline ≥10 points from the baseline at three months) was detected. The study yielded similar rates of CNS toxicity between arms. Based on more toxicity (worse decline in cognitive function and functional independence) with WBRT at no added overall survival benefit compared to SRS, authors recommended SRS after resection of a BM.

Evidence provided so far supports the use of adjuvant (postoperative) SRS to a limited number of resected BM over WBRT's standard of care due to good surgical bed control with less toxicity.

17.6.4 Neoadjuvant SRS Before Surgical Resection

Growing interest in preoperative SRS originated as a theoretical solution to the following concerns regarding postoperative SRS: interphysician variability in delineating target volume around irregular surgical cavities, a theoretical risk of intraoperative tumor cell spillage at the time of surgical resection to an area beyond the immediate tumor bed, and radiation necrosis [62, 63]. Neoadjuvant SRS is carried out on a well-defined target, with intact blood supply, and permits dose reduction as the goal is to treat microscopic disease rather than gross tumor.

Asher et al. [62] published a retrospective and prospective single-institution study on 47 patients (51 lesions) with one to three BM with mass effect or symptomatic lesion, treated with neoadjuvant SRS followed by surgery. They demonstrated its safety and efficacy with promising results. In that study, the median tumor diameter was 3.04 cm (ranging 1.34–5.21 cm), the median volume was

8.49 mL (ranging 0.89–46.7 mL), there was a median of one day (ranging 0–17 days) elapsed between SRS and resection, and a median dose of 14 Gy (ranging 11.6–18 Gy) was prescribed to the 80% IDL (PTV equal to GTV, no expansion margins added). At a median follow-up of 12 months, overall survival and local control at 12 months were 60% and 85.6%, respectively. Local failure was statistically associated with lesions >10 mL and >3.4 cm, most of which were found to have dural attachment or in proximity to veins. Salvage WBRT was given in less than 15% of the patients for either local or distal recurrence. There was no documentation of adverse effects, RN, or leptomeningeal (spread of cancer to the leptomeninges or cerebral spinal fluid) failures.

A multi-institution retrospective analysis published by Patel et al. [63] compared outcomes and toxicities of pre-op- and post-op-SRS. A total of 180 patients underwent surgical resection for 189 BM, 37% of which received pre-op SRS and 63% post-op SRS. Although GTV was similar between both groups (8.3–9.2 mL), pre-op SRS had lower median PTV margin (0 vs. 2 mm) and lower peripheral dose (14.5 Gy vs. 18 Gy) due to differences in planning technique (no margin expansion from GTV and dose reduction of 20% compared with standard dosing for pre-op SRS). Pre-op SRS was delivered within 48 h of planned surgery. After median imaging follow-up of 11.1 months for all patients (and 24.6 months, for those alive at analysis), there was no difference in overall survival, local or distant intracranial control. Significantly higher rates of leptomeningeal dissemination and symptomatic RN were associated with post-op SRS. Considering these results, authors recommended a prospective clinical trial to compare the two modalities.

17.6.5 SRS Alone for Four or More Brain Metastases

The prospective multi-center non-randomized trial JLGK0901 reported by Yamamoto et al. [49, 50] is so far the only prospective study analyzing the efficacy of SRS alone in patients with up to 10 BM with a goal of demonstrating that overall survival of patients with five to ten BM is non-inferior to that of patients with two to four BM. Lesions were limited to <10 mL in volume, <3 cm in largest diameter, and ≤15 mL in total cumulative volume. SRS prescription dose at the lesion periphery was 22 Gy for tumor volumes <4 mL and 20 Gy for volumes 4–10 mL, with the ability to adjust the dose by +/− 2 Gy. Brainstem lesions were given a separate dose schedule which was also volume dependent. Although the study showed a significant overall survival advantage in patients with a single BM compared with patients with two to four (13.9 vs. 10.8 months), survival was the same between patients with two to four compared with five to 10 (10.8 months for both) meeting the non-inferiority criterium. The rates of local intracranial control at 12 months were significantly worse for single BM (87%) compared to either 2–4 (93%) or 5–10 (94%). Overall salvage rates with SRS, WBRT, and surgery were 38%, 9%, and 2%, respectively. Rates of neurological death ranged from 6% to 10%, with no significant difference between treatment groups. Functional status preservation (KPS ≥70 preservation at 12 months) and neurocognitive changes (MMSE 3-point deterioration from baseline at 12 months) showed no difference between groups. Rates of CNS toxicity (NCI CTCAE grade 3 or more) were similar and below 5% in all groups.

Based on the indirect evidence provided by this study, the authors concluded that SRS up to 10 BM is a suitable alternative to WBRT.

Several meta-analyses have since been reported comparing the use of WBRT and SRS alone or in combination, all of which corroborate results from the individual large trials. The meta-analysis by Sahgal et al. [64] which included JROSG99-1, EORTC 22952-26001, and MDAAC [46, 52, 53] evaluated SRS with or without WBRT for patients presenting with one to four BM. Results confirmed that local control favored addition of WBRT in all age groups, but for age ≤50, SRS alone statistically favored survival (with no significant difference in older patients), and for that age group, the addition of WBRT did not impact distant intracranial failure (although it did statistically impact older patients).

17.6.6 Is Number or Volume the Limit to SRS?

There is mounting evidence that the total amount of treated brain volume might be a better guide to decide on the benefit of SRS over WBRT.

Yamamoto et al. [65] published a retrospective case-matched study, using the propensity score matching method applied to prospectively accumulated data from a Japanese institution. The study compared treatment results after GKRS alone for patients with two to nine vs. 10 or more BM. Patients included had mostly new BM, good KPS (KPS ≥80% in 75%) and good neurocognitive function and excluded are those with meningeal dissemination or an anticipated survival time ≤3 months. The study showed similar rates of post-SRS median overall survival, neurological death-free survival, neurologic death, neurological deterioration, or SRS-related complications. However, it showed significantly lower cumulative incidence of local recurrence (HR 0.425) and repeat SRS for new lesions (HR 0.732) in the 10 or more BM group. Authors concluded that carefully selected patients with 10 or more BM are not unfavorable candidates for SRS alone and recommended a RCT.

A decade ago, a report by Bhatnagar et al. [66] introduced the concept that total treatment volume (sum of the volume of all treated metastases), rather the number of metastases, should be used as a selection criterium for radiosurgery. This was based on a retrospective study of patients with four or more BM who underwent GKRS as a single treatment session at the University of Pittsburgh Center for Image Guided Surgery which showed that total treatment volume was one of the statistically significant factors associated with survival, whereas the number of metastases was not.

A retrospective analysis by Banfill et al. [67] showed that patients with a total treated volume of metastases <5 mL or from 5 to 10 mL lived statistically longer than patients with a volume >10 mL. There was no survival difference between patients with a single metastasis vs. multiple metastases. A largest lesion less than 5 mL was a positive prognostic factor.

However, in a retrospective analysis of a prospectively collected database on BM, patients treated with GKRS or CKRS, comparing patients with newly diagnosed 1–4 BM vs. 5 or more BM (similar median intracranial tumor volumes between 1.7 and 1.8 mL), Knoll at al. [68] showed that the number of intracranial BM statistically correlates with overall disease burden (number of major involved organ systems) and disease status (uncontrolled vs. not), hence a surrogate for systemic disease. Although statistically correlated to overall survival on univariate analysis, after matching and controlling for these variables on multivariate analysis, the number of BM or the total intracranial tumor volume was no longer prognostic for overall survival. Multivariate model showed only ECOG PS and systemic disease status to be correlated with survival. Authors concluded SRS is a reasonable option for patients with multiple BM, especially patients with otherwise localized and controlled extracranial systemic disease.

Several clinical trials are underway, trying to push the upper limit number of BM to 15–20, and are described in the last section of this chapter.

17.6.7 Preservation of Neurocognitive Function and Quality of Life with SRS Alone

Concerns about late adverse effects of WBRT on cognitive neurofunction have generated increasing interest in SRS, which minimizes the dose and volume of radiation exposure to healthy tissue by providing very focal treatment (quick dose fall-off around the target).

Although it is difficult to distinguish the impact of systemic disease and cancer treatment (cytotoxic drugs given systemically for non-CNS tumor primaries might also have cognitive side-effects known as “chemobrain”), previously reported from 13% to 70% [61] on cognitive function, or to assess cognitive function itself, several large studies have tried to assess its deterioration or preservation in treatment arms that compare SRS alone or postoperative SRS to WBRT.

An early pilot MDACC study by Chang et al. provided a prospective analysis of various cognitive domains in patients treated with SRS alone [60]. The study employed rigorous neuropsychological assessments by faculty and trained staff from the section of neuropsychology, and the tests were selected because they were widely used, standardized psychometric instruments that had previously demonstrated sensitivity to the neurotoxic effects of cancer treatment in other clinical trials. The study included patients with one to three newly diagnosed BM all ≤4 cm with SRS doses per RTOG 9005 (median 20 Gy, ranging 14–21 Gy to the 80% IDL). Most patients had some degree of neurocognitive dysfunction in at least one domain at baseline; however, most long-term survivors had stable or improved neurocognitive function performance across multiple domains of learning and memory (80%), motor dexterity (60%), and executive function (60%).

In 2011, the International Cancer and Cognition Task Force (ICCTF) recommended a minimum set of tests to be included in neuropsychological assessment and criteria for the definition of cognitive impairment or change, along with guidelines for designing a study [61]. In 2018, in light of the increased use of neuroimaging in studies of cancer and treatment-related cognitive dysfunction, the ICCTF published recommendations with regard to neuroimaging study design, scanner considerations, and sequence selection, focusing on concerns relevant to cancer populations [69]. The reader can consult this reference for more details.

Various large RCTs used the MMSE as a surrogate of neurocognitive testing although it is an insensitive measure. As shown in Table 17.2, the MMSE was utilized in RTOG 9508, JROSG-99-1, and JLGK0901 [49–51, 53, 54]. In RTOG 9508 and JROSG-99-1, which compared combinations of WBRT and SRS, the MMSE failed to detect a statistical difference between treatment arms.

A recent systematic review by Schimmel et al. [70], which included studies investigating SRS alone in one of the study arms vs. a combination of WBRT and SRS, with exclusion of postoperative SRS, analyzed studies on cognitive effects of SRS with formal neuropsychological testing and those that relied on the MMSE solely. Studies that used the MMSE instead of formal neuropsychological testing showed that improvement or stability occurred more often than a decline in MMSE scores after treatment with SRS alone. The addition of SRS to WBRT vs. WBRT alone, in patients with one to three BM did not cause significant differences in change of MMSE.

On the other hand, large RCTs such as MDACC single institution (Chang et al.), NCCTG Alliance N0574 (Brown et al.), and NCCTG N107C/CEC.3 (Brown et al.) utilized formal neurocognitive assessment meeting the minimal requirement by the ICCTF. The tests and a description of the domain assessed are summarized in Table 17.3 [52, 55, 58] with a summary of the most significant test results in Table 17.2. Based on these studies, the addition of WBRT to SRS or the use of WBRT instead of SRS is thought to significantly impact neurocognitive function. This finding is supported by the systematic review by Schimmel et al. [70].

QOL was also a measure from most large RCTs using various tools. The most commonly used tool was FACT-BR, a patient-reported outcome measure used to assess health-related quality of life in patients undergoing cancer therapy. The impact of cancer therapy is measured in various domains: physical, social, family, emotional, functional well-being, and the quality of the relationship with the physician [71]. MDACC single-institution (Chang et al.), NCCTG Alliance N0574 (Brown et al.), and NCCTG N107C/CEC.3 (Brown et al.) trials all showed results favoring a deterioration in QOL when treatments involved addition of WBRT to SRS or the use of WBRT instead of SRS; however NCCTG Alliance N0574 is the only trial which showed a significant deterioration at 3 months, measuring with FACT-BR alone. NCCTG N107C/CEC.3 did show a significant decline in FACT-BR for physical well-being subscore at 3 and 6 months.

Based on these randomized trials, SRS is an effective treatment to minimize the risk of neurocognitive decline and preserve QOL in patients with BM.

17.6.8 Survivorship

Because of advances in systemic therapies (chemotherapy and cancer targeted therapies), patients have been able to live longer. SRS offers superior neurocognitive preservation and QOL over WBRT. Now, physicians have no well-defined guidelines regarding the maximal number of BM to treat during the patient's lifetime.

Pham et al. [72] presented the case of two patients who each developed more than 10 BM over the course of their life at an academic cancer treatment institution. The first patient was a 78-year-old woman with BRAF mutation-positive melanoma metastatic to the brain, left adrenal gland, and spleen, who underwent three SRS sessions for a total of 17 intracranial targets (16 unresected BM and one surgical cavity) over the course of two years. Those lesions were found on the initial and the serial brain scans as her intracranial disease progressed on systemic therapy. The patient tolerated all treatments very well and, 2 years after the last intervention, she was still neurologically asymptomatic with excellent performance status, travelling cross-country and working, while on maintenance pembrolizumab.

Another similar case was a 44-year-old woman with metastatic BRAF-mutated melanoma to the brain and lungs who underwent nine SRS sessions for a total of 37 intracranial lesions over the course of 2 years with two surgical resections. Her intracranial disease also progressed on various systemic therapies. Once again, the patient tolerated all the treatments very well, and 1 year after the last intervention, she was neurologically asymptomatic, with excellent performance status, traveling with a very active lifestyle, while on maintenance pembrolizumab.

Both examples illustrate the benefits of SRS on preservation of performance status and QOL in patients who remained highly functional. When patients find appropriate systemic treatment specific to their disease and are willing to undergo careful brain imaging surveillance, it is possible to postpone WBRT.

17.6.9 Progression and Recurrence

Although SRS offers excellent rates of local control, patients treated with SRS are usually placed on close serial surveillance with various planes of contrast-enhanced MRIs to monitor the size of BM after SRS, to assess the response to treatment, and to detect local as well as distal recurrences. During the months after SRS treatment, a brain MRI appears typically abnormal and can show signs of local regression of the treated lesions or post-treatment radiation effect [73] on surrounding normal tissue (T1-weighted enhancement and/or T2 FLAIR edema). When treatment effect shows radiographical findings like those of a local recurrence, it is called tumor pseudoprogression, a term commonly used in post-treatment of high-grade gliomas associated with an increase in lesion size. As reported by Patel et al. although treated BM can be stable or smaller in size during the first 36 months post-SRS, about one-third of them can undergo transient increase in volume [74].

Post-radiation treatment effects can be divided into pseudoprogression or RN [73]. Pseudoprogression can appear several weeks up to 3 months after radiation treatment, whereas RN may appear 3 months to several years after radiation therapy. RN, which will be discussed later in this chapter, involves a space-occupying necrotic lesion with mass effect and neurological dysfunction.

Brain images are typically reviewed by an SRS specialized multidisciplinary team including a neuroradiologist for consensus. For asymptomatic patients, more frequent serial imaging is typically chosen. However, biopsies are sometimes necessary to confirm progression.

Treatment options for recurrent SRS-treated tumors are surgical resection and thermal ablation using laser interstitial thermal therapy (LITT). For distant brain recurrence, salvage options include SRS, partial brain irradiation, and WBRT. There is no consensus for dosage fractionation and time interval for reirradiation.

Minniti reported on repeated salvage SRS in patients with various cancer primaries (39% NSCLC, 21% breast cancer, 26% melanoma,

and 14% other) who had previously received single-fraction SRS, with recurrent/progressive BM. [75]. All 43 patients with 47 lesions, median KPS of 80 (range 60–100), initiated dexamethasone therapy the first day of treatment at doses of 4–8 mg per day and maintained high doses of steroids for 1 week. While the PTV was generated from GTV (identified on 1 mm thin-slice gadolinium enhanced axial MRI) with 1–2 mm expansion, doses of LINAC-based SRS were 8 Gy × 3 fractions for lesions <2 cm and 7 Gy × 3 fractions for lesions ≥2 cm in largest diameter, prescribed to the 80–90% IDL to achieve 95% PTV coverage by the planned dose. Median time interval between radiation treatments was 17 months (range 6–56 months). At a follow-up of 19 months, median survival was 10 months, the 1- and 2-year overall survival rates were 37% and 20% with local control rates of 70% and 60%, respectively. Local control was better for breast and NSCLC primaries compared to melanoma. The causes of death were systemic disease in 58% and brain disease in 26% of the patients. The rate of RN was 19% and the RTOG grade 2 or 3 CNS toxicity rates in setting of RN were 14% combined. Authors conclude that a second course of SRS at doses of 21–24 Gy in 3 daily fractions was feasible with acceptable local control and risk of neurological toxicity.

In another retrospective study by Choi et al. [76], 23 patients (48% NSCLC, 35% breast cancer, 17% SCLC) initially underwent WBRT (median dose 30 Gy in 3 Gy fractions, range 23.4–30 Gy), SRS (median dose 16 Gy in 1 fraction, range 12–24 Gy), or partial brain radiation with three-dimensional conformal radiotherapy (3DCRT, with dose of 30 Gy in 3 Gy fractions). Patients were reirradiated due to radiographic progression with neurologic symptoms, at which time more than 50% had KPS <30 (mean 42.2, median 30). The relative number of patients in RPA classes I to III were 13%, 4%, and 83%, respectively. Mean time interval between the two courses of radiation was 13.6 months (median 11.1, range 1–38 months). For the second course of radiation, the median dose of WBRT was 27.5 Gy (range 12–30 Gy), median dose of 3DCRT was 30 Gy (range 25–30 Gy), and the dose of SRS was 16 Gy in one fraction. Patients who initially received WBRT (56.5% of all patients) were retreated with any of the three radiation techniques, most frequently 3DCRT; those initially treated with 3DCRT received either another course of 3DCRT or WBRT; and those who initially received SRS were retreated with either WBRT or 3DCRT. Overall, the mean post-reirradiation KPS was 52.7 (median 60), the neurologic symptom resolution rate was 47.8%, the rate of palliative efficacy (defined as relief of neurological symptoms or stable symptoms) was 82.6%, and the overall survival was 3.2 months. No patients experienced RN after the second course of radiation, and only 1 patient (4.3%) experienced treatment related grade 3 CTCAE headache. Patients who experienced aggravated neurological symptoms (17.4%) after reirradiation were RPA class III and had primary disease progression. There was a statistically significant correlation between KPS ≥60 vs. KPS <60 before reirradiation, and median survival of 16 vs. 3 months. Authors concluded that brain reirradiation is likely to benefit patients with KPS ≥60 prior to retreatment and stable extracranial disease.

17.7 Management of SRS Complications

SRS can cause both acute and late neurological side effects.

The most common acute radiation injury is caused by transient (and reversible) edema which can start as early as 12–48 h after treatment. For this reason, patients are counseled to avoid travelling (driving and flying) and staying home for 48 h. Acute side effects include new onset of headache, dizziness, nausea, vomiting, or seizures. These symptoms can be treated or prophylactically treated with a short course of corticosteroids. The decision on initiation dose and duration of corticosteroids is based on the patient's comorbidities and anti-convulsants if needed for seizures.

The most common and serious complication of SRS is cerebral tissue death called radiation

necrosis or radionecrosis (RN), a permanent radiation injury that may be irreversible, and symptomatic (roughly 50%), caused by avascularization at the site of the SRS target, with typical onset between 6 months and 2 years after treatment. Rates of incidence depend on the cumulative amount of radiation received, the amount of radiation received in 1 session, tumor diameter (hence volume of brain receiving radiation), the presence and type of concurrent systemic therapy received, and the criteria used to diagnose and define RN.

RN is diagnosed via histologic confirmation which is the gold standard. However due to morbidity of biopsy or surgical resection, it is often made based on clinical symptoms (which correlate with the area of brain involved) or radiographically.

17.7.1 Risk Factors

Low incidence rates of RN have been reported, between 1.5% and 4.5%, in large phase III RCTs [46, 53, 55] discussed earlier, although rigorous techniques were not established to track development or lack of symptoms. However retrospective studies have reported rates greater than 30%, illustrating the importance of definition and duration of follow-up. In a retrospective study by Kohutek et al. [77] looking at the impact of tumor diameter, prior WBRT, prescription dose, and histology, on long-term incidence of RN (diagnosed pathologically or radiographically) in patients who received single-fraction LINAC-based SRS, actuarial incidence was 17.2% at 12 months and 34% at 24 months, 67% of whom were symptomatic. On this study, tumor diameter was the only significant factor on multivariate analysis: rates at 12 months were 2.9% for ≤0.5 cm, 6.6% for 0.6–1.0 cm, 19.1% for 1.1–1.5 cm, and 37.8% >1.5 cm. Rates of symptomatic RN followed the same trend. Another study by Minniti et al. [78] of prospectively followed patients treated with LINAC-based SRS yielded overall rate of 24% of the rated lesions (10% symptomatic and 14% asymptomatic) with median time to necrosis of 10–11 months. When the brain volume receiving 12 Gy in a single fraction was >8.5 mL, the rate of RN was >10%, and authors recommended use of hypofractionated SRS (3 fractions) especially if located in or near eloquent areas.

Targeted therapy and immunotherapy may also increase the risk of RN as evidenced by a retrospective study by Colaco et al. [79] . In 180 patients treated with GKRS for BM, rates of RN were 37.5% for immunotherapy alone, 25.0% for targeted therapy alone, and 16.9% for chemotherapy alone. The rates were significantly higher for immunotherapy alone and lowest for chemotherapy alone.

17.7.2 Treatment

RN can be self-limited and treated conservatively with observation; however in symptomatic cases, several modalities are available, as shown in a review by Patel et al. [80], and include corticosteroids, surgery, bevacizumab, HBO, pentoxifylline (PTX), and vitamin E (VitE).

Corticosteroids are first-line therapy, which are effective treatment by blocking the inflammatory process in symptomatic patients and should be given at the lowest dose to avoid side effects such as psychiatric, gastrointestinal, and metabolic disturbances. Care is taken in tapering the medication at resolution of symptoms to avoid the development of secondary adrenal insufficiency.

In cases of refractory to steroids, surgical interventions such as resection of involved tissue (which confers the advantage of histological diagnosis confirmation) or LITT, an ablating technique, are invasive; however they have shown symptomatic improvement and ability to wean off steroids.

HBO was reported to be beneficial in managing patients with RN [81] and is under investigation in a prospective clinical trial NCT02714465 initiated in 2016, where patients who have received GKRS and subsequently developed RN are treated with HBO. Patients undergo regular neurological assessments scored by Rankin Scale (patients with Rankin Scale >5 are excluded at recruitment) and receive at least 24 HBO ses-

sions. If RN regresses on MRI, treatment is suspended; otherwise they receive up to 40 HBO sessions.

Bevacizumab has also been shown to benefit patients, as best illustrated by a placebo-controlled randomized double-blind study by Levin et al. [82] of bevacizumab 7.5 mg/kg given every 3 weeks for 2 cycles in patients who had undergone radiation for head-and-neck carcinoma, meningioma, or low- to mid-grade glioma and who had radiographic or biopsy proof of RN. All patients who received bevacizumab whether in the original arm or by crossover had both radiological response and improved neurologic symptoms. Patients who never received bevacizumab had neither radiological response nor improved neurologic symptoms.

Oral PTX and VitE combination therapy has also been prescribed for adverse radiation effects [83]. A prophylactic phase II trial NCT01508221 to assess the use of PTX and VitE (PTX 400 mg TID and VitE 400IU BID starting the first day after the last SRS treatment) for prophylaxis of RN in patients with metastatic BM treated with 1–5 fractions of SRS was investigated by the University of Cincinnati, and data is to be published.

Table 17.4 Typical metrics relevant to SRS planning

Metric	Description/ relevance	Equation
Conformity (or conformality) index (CI), RTOG definition	Ratio of volume receiving the full prescription dose to the target volume	*PIV/TV*
Target coverage index	Fraction of target volume enclosed by the prescription isodose volume	$PIV \cap TV/TV$
Plan selectivity index (SI)	Fraction of prescription isodose volume enclosed by the target volume	$PIV \cap TV/PIV$
Dose gradient index (GI)	Ratio of volume receiving half the prescription dose to volume receiving the full prescription dose	$V_{50\,\%\,Rx}/PIV$
V_{12Gy}	Volume of normal brain receiving ≥12 Gy	

PIV prescription isodose volume (volume receiving 100% of the prescription dose), $V_{50\%Rx}$ volume receiving 50% of the prescription dose, *TV* target volume

17.8 Radiotherapy Technique and Planning

The benefit of SRS is that it highly conforms to the shape of the radiosurgical target while delivering a clinically insignificant dose to the surrounding tissues. A high single dose is given. Dose homogeneity inside the target area is secondary.

17.8.1 Treatment Plan Metrics

A set of metrics listed in Table 17.4 is traditionally defined to assess for the quality of SRS treatment plans [84, 85]. They are useful in comparing possible plans for the same patient, but also to compare the capabilities between different platforms (GKRS, CKRS, LINAC, or particle).

The conformity (or conformality) index (CI) is a measure of how well the volume of a radiosurgical dose distribution conforms to the size and shape of a target volume (TV). Using the RTOG definition, it is the ratio of the prescription isodose volume (PIV or volume receiving the full 100% of prescription dose) over TV. The goal is a value <1.5, knowing that unity is ideal, and undercoverage is a value lower than 1, and overtreatment a value greater than 1.

The CI definition is relevant only if the TV is fully enclosed by the PIV; therefore the target coverage index is usefully defined as the fraction of TV within the PIV, with goal of 100%.

The plan selectivity index (SI) is defined as the fraction of PIV enclosed by the TV and is inversely related to the target coverage index. A low selectivity index correlates with excessive normal brain tissue receiving the prescription dose.

Also defined is the dose gradient index (GI), the ratio of the volume of brain tissue receiving 50% of the prescription dose divided by the PIV. It is useful in comparing plans of similar conformity to assess steepness of dose fall-off. A value of 3.0 is considered satisfactory.

The volume of brain receiving ≥12 Gy (V_{12Gy}) is a surrogate of risk of RN as discussed

in a previous section. It is usually maintained between 5 and 10 mL.

17.8.2 Target Volume Delineation

The use of tight margins and the nature of sharp dose fall-off distribution around the target make target delineation accuracy of utmost importance to avoid local treatment failure. Volume recommendations are presented in Table 17.5.

17.8.2.1 Intact (Unresected) Brain Metastases

In the case of intact (unresected) BM, the GTV is simply defined as the contrast-enhancing lesion defined preferentially on fine-slice T1-weighted sequence MRI (over CT scan). Based on results from the randomized trial NCT01017497 published by Kirkpatrick et al. [86] using LINAC-based SRS which investigated the optimal PTV (GTV plus 1 vs. 3 mm margin expansion) and outcomes such as local control, rates of RN, neurocognition, and QOL, a 1 mm expansion was found to offer the highest rate of local control and minimal morbidity.

17.8.2.2 Postoperative Cavity

Postoperative cavity contouring conventional wisdom was, until recently, based on the work of Soltys et al. using CKRS published in 2008 [87] which recommended a 2 mm expansion margin around the resection cavity borders visualized on postcontrast MRI. These were used in NCCTG N107C/CEC.3 by Brown et al. [58] without attempt to target the surgical access tracks for deep lesions. The MDACC trial by Mahajan et al. of postoperative SRS vs. observation for patients with resected BM [57] was analyzed for patterns of failure and published on a separate ASTRO abstract which showed that 25% of the local failures were at the margin, all of which had had preoperative dural involvement [88].

In 2018, Soliman et al. published expert consensus contouring guidelines for postoperative completely resected surgical cavities for adjuvant SRS [88] using ten cases of patients from a prospective institutional registry. Each patient represented a variety of BM regions within the brain (supra- and infra-tentorial, deep and superficial, and dural or venous sinus contact) and was contoured by 10 radiation oncology experts. The recommendations, summarized in Table 17.5, are notable because the clinical target volume

Table 17.5 Target volume delineation recommendations

Target	GTV	CTV	PTV	Reference
Unresected BM	Contrast-enhancing lesion on T1-weighted sequence MRI	n/a	GTV + 1 mm	Kirkpatrick et al. [86]
Postoperative completed resected cavity[a]	n/a	– Entire contrast-enhancing surgical cavity and surgical tract seen on postoperative MRI – 5–10 mm margin along the bone flap beyond the initial region of preoperative tumor contact (if initial tumor was in contact with the dura) – 1–5 mm margin along the bone flap (if initial tumor was *not* in contact with the dura) – 1–5 mm margin along the sinus (if initial tumor was in contact with a venous sinus)	CTV + 0 mm	Soliman et al. (2018) [88]
Postoperative completed resected cavity	n/a	– 2 mm expansion margin around the resection cavity borders visualized on postcontrast MRI	CTV + 0 mm	Soltys et al. 2008 [87]

[a]Include fusion of the preoperative MRI

(CTV) should not only encompass the preoperative volume but also include changes seen on postoperative MRI along with potential areas of microscopic disease. For the definition of the CTV, consensus was to (i) fuse the preoperative MRI to assist in volume delineation, (ii) include the entire contrast-enhancing surgical cavity and the entire surgical tract (regardless of the preoperative location of the tumor) visualized on postoperative axial T1-weighted sequence MRI, (iii) add a 5–10 mm margin along the bone flap beyond the initial region of preoperative tumor contact if initial tumor was in contact with the dura (otherwise the margin is 1–5 mm), and (iv) add a 1–5 mm margin along the sinus if the initial tumor was in contact with a venous sinus. As these recommendations have not been validated by clinical outcomes and patterns of recurrence, Soliman et al. recommended clinical judgment on a case-by-case basis.

In a recent abstract by Jhaveri et al. [89] based on retrospective data of patients treated with postoperative SRS (LINAC-based, frame and frameless, single-fraction and hypofractionated dosing) investigating the optimal PTV on local recurrence and symptomatic RN postoperatively, it was found that expanding the PTV margin beyond 1 mm did not improve local recurrence, although it significantly increased the risk of symptomatic RN.

17.8.3 Organs at Risk

The maximal dose tolerance to normal brain tissue depends on the number of fractions. For single-fraction SRS, the maximal dose to the optic pathway is typically between 8 and 10 Gy, and 10 and 15 Gy to the brainstem. For five-fraction SRS, the maximal dose to the optic pathway is typically between 20 and 25 Gy, and 23 and 31 Gy to the brainstem.

17.8.4 Treatment Planning

In the case of GKRS units, the radiation dose has historically been prescribed to the 50% IDL, which corresponds to the steepest dose fall-off outside the target. However, since the automation of GKRS units and the use of multiple isocenters (each exposure is referred to as a "shot" of radiation), the dose can be prescribed to a wider range of IDLs as part of an optimization of the treatment plan quality which includes variables such as coverage index, plan selectivity, and gradient index, defined above.

When using Leksell GammaPlan®, treatment planning can be carried out in a forward fashion (user individually chooses the shot location, the sector combination set, and the relative weight of each shot within each target), inverse planning (the software provides a shot number, location, collimator combination, and relative weight for each shot) or a hybrid of forward and inverse planning.

Figure 17.6 depicts the treatment plan of a patient who presented with a single $1.8 \times 2.0 \times 2.5$ cm^3 BM of ovarian origin in the midbrain tectum, using Leksell GammaPlan®. She was prescribed 18 Gy to the 50% IDL, as per RTOG protocol 9005 [16]. The plan, which involved 27 shots and all the collimator sizes, had target coverage index 1.00, plan selectivity index 0.88, and gradient index 2.71. All plane views (axial, coronal, and sagittal) demonstrate how conformal the plan is, as evidenced by the 50% IDL (green) with respect to tumor target (red).

Figure 17.7 illustrates part of the treatment plan of a patient who had 20 BM of breast cancer origin treated over 2 GKRS sessions and who presented with 11 new BM on her routine surveillance brain MRI. Leksell GammaPlan® allows one to visualize her previously treated targets (delineated in red and showing the 50% IDL in blue). This feature is useful to determine whether a lesion is new or was previously treated and if it is an in-field or out-of-field recurrence.

17.8.5 Treatment Platform Comparison

Over the last 2 decades, considerable effort has been invested in improving the conformity of LINAC-based SRS in the hope to compete with

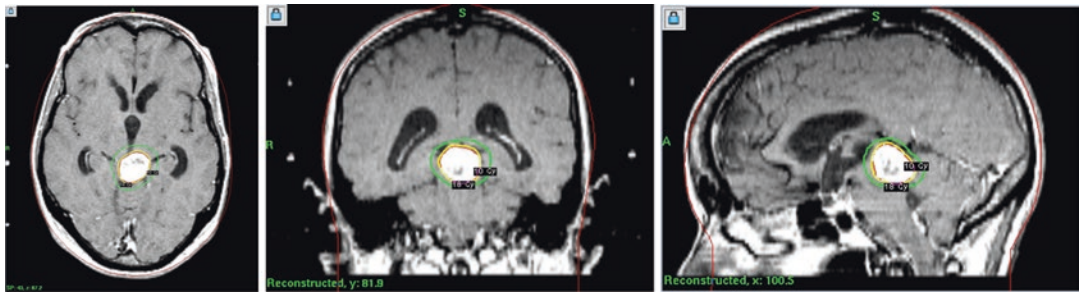

Fig. 17.6 Single 1.8 × 2.0 × 2.5 cm^3 BM of ovarian origin in the midbrain tectum; treatment plan with Leksell GammaPlan® version 10.2.0 for Leksell Gamma Knife® by Elekta; fiducial markers seen as white dots on the edges of the figures; target delineated (red line); prescription dose of 18 Gy at the 50% IDL (yellow), 10 Gy IDL (green), maximal dose 36 Gy; collimators used: 4, 8, and 16; number of shots: 27; target coverage 1.00; selectivity 0.88; gradient index 2.71; left to right: axial, coronal, and sagittal planes

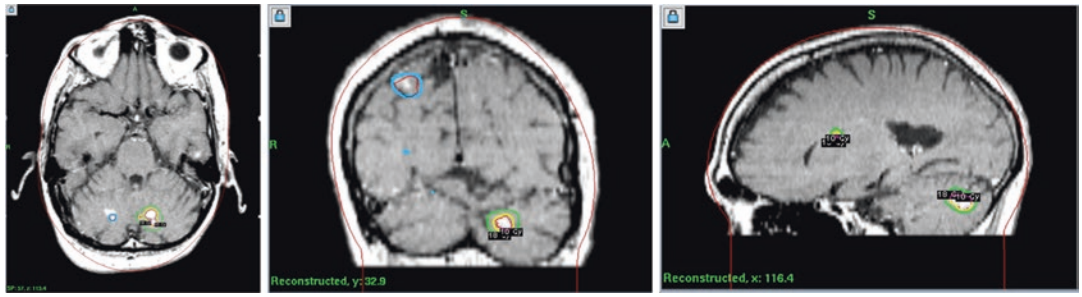

Fig. 17.7 Left cerebellar metastasis in patient with 11 diffuse BM (20 BM previously treated with GKRS over two sessions) of breast origin; treatment plan with Leksell GammaPlan® version 10.2.0 for Leksell Gamma Knife® by Elekta; target delineated (red line); prescription dose of 18 Gy at the 50% IDL (yellow), 10 Gy IDL (green), maximal dose 36 Gy; collimators used, 4 and 8; number of shots, 5; target coverage 1.00; selectivity 0.54; gradient index 3.03; previously treated targets delineated (red line) surrounded by 50% IDL (blue); left to right: axial, coronal, and sagittal planes

GKRS platforms as LINACs are more available geographically. Significant advancements took place with the introduction of VMAT in 2007. VMAT, during radiation treatment delivery, allows simultaneous variation of the gantry rotational speed, the treatment aperture shape via movement of the MLC leaf position, and the radiation dose rate (intensity).

The first benefit of VMAT is significantly reducing treatment time, especially in FFF mode (as already discussed earlier in this chapter). Dose rate of GKRS using new cobalt sources result in values of approximately 363 MU/min vs. 1400–2400 MU/min (MU, or monitor units, are directly related to dose) in a 6–10 MV LINAC in FFF mode. Until recently, the main criticism of VMAT plans in the treatment of multiple brain lesions was the low-dose spread (or low-dose spill) over normal brain tissue compared to GKRS delivery. However, after more investigation, the introduction of different couch angles (sometimes referred to as "couch kicks") during treatment, which allows radiation to enter the skull from more angles, has provided positive evidence to help resolve this concern. The advent of HyperArc™ is also promising in providing highly conformal, non-coplanar treatment plans.

17.9 Future Directions

As discussed in this chapter, SRS can provide excellent local tumor control in patients with resected or unresected BM and preserve neuro-

cognitive function owing to rapid dose fall-off to adjacent brain tissues. Large prospective RCTs have provided unequivocal level I evidence.

Several clinical trials are currently in process to continue to push the applicability of SRS:

Re-investigating dose escalation: NCT02645487, taking place at the University of Texas Southwestern Medical Center, is a new phase I dose-escalation study similar to RTOG 9005 in patients with BM receiving SRS without WBRT. SRS is given with 3 Gy incremental doses in each size group, starting at 24 Gy in lesions ≤1 cm, up to 30 Gy, with the goal of determining the maximal tolerated doses within 90 days from the date of procedure.

Pushing the upper limit number of BM to 15–20:

- NCT02953717 (CAR-Study B) in the Netherlands is a prospective RCT comparing SRS (volume-dependent doses from 18 to 25 Gy delivered with GKRS) to WBRT (20 Gy in 5 fractions) in patients with 11–20 newly diagnosed BM with cognitive decline at 3 months as primary outcome using HVLT-R Total Recall score (verbal learning and memory test) as neuropsychological assessment [90].
- NCT01592968 currently ongoing at MDACC is a phase III prospective RCT comparing SRS (12–24 Gy range, depending on lesion largest diameter on MRI) to WBRT (30 Gy in 10 fractions) in patients with 4–15 non-melanoma BM, with local tumor control and cognitive decline at 4 months (measured using HVLT-R score compared to baseline) as primary endpoint.
- Recently announced [91] is the upcoming NCT03550391 phase III prospective RCT lead by the North American Canadian Cancer Trials Group (CCTG), comparing SRS (doses 18–22 Gy in single fraction) to WBRT (30 Gy in 10 fractions with memantine 10 mg given twice daily) in patients with 5–15 BM. Primary outcomes include overall survival and neurocognitive progression-free survival (drop in 2 of the 6 neurocognitive tests).
- NCT03075072 in Boston by the Dana-Farber Cancer Institute and Brigham and Women's Hospital is a phase III prospective RCT comparing WBRT (30 Gy in 10 fractions with hippocampal sparing approach, when possible) to SRS (1–5 fractions) in patients with 5–20 BM. The primary endpoint is QOL measured by the MD Anderson Symptom Inventory-Brain Tumor (MDASI-BT).

Investigating the effect of tumor treating fields: NCT02831959 also known as "METIS" trial, sponsored by NovoCure Ltd., is for NSCLC patients with 1–10 BM treated with SRS alone or SRS followed by treating fields (150 kHz). The primary outcome is time to intracranial progression, while secondary outcomes include time to neurocognitive failure (decline measured using HVLT-R free recall, delayed recall, and delayed recognition, COWAT, and TMT Parts A and B).

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18 Whole Brain Radiotherapy (WBRT) for Brain Metastases

Frédéric Dhermain

18.1 WBRT 'For All Patients' Was the Gold Standard in the 1980s, Despite a Well-Known Neurotoxicity

WBRT was the historical reference in the management of metastatic patients with brain metastases (BMs) both acting *as a palliative tool for symptomatic patients and also by effectively preventing the risk of developing new BMs, including the postoperative setting* [1]. To be noted and until the early 2000s, median overall survival (OS) of these patients was usually between 6 and 9 months, and consequently *neurocognitive status and quality of life* were evaluated with 'basic' tools such as the Karnofsky Performance Status (KPS), the MMSE (Mini-Mental Status Exam) or the EORTC QLQ (Quality of Life Questionnaire)-Brain Neurologic (BN-20) module, also due to the lack of time devoted to this clearly 'palliative' care.

However, *post-WBRT toxicity was already well documented*, with a continuum of three periods due to evolving anatomical and functional injuries. An 'acute' phase of headache, fatigue and nausea could be followed by an 'early-delayed' period of attention and memory problems with an associated hypersomnia, prolonged up to 6 months, hopefully regularly reversible. For the rare patients still alive after 12 months, a late phase of irreversible decline with no plateau was possible, including ataxia, incontinence and dementia in less than 5% of cases [2, 3].

18.2 Prophylactic Cranial Irradiation (PCI) Is a Model for Evaluation of WBRT Efficacy and Toxicity

The largest phase 3 study of PCI versus no PCI included a selected population of non-small cell lung cancer (NSCLC) stage III patients presenting a high risk of BMs (with *a normal brain MRI* at baseline) with *a primary neurocognitive* endpoint. Even if the WBRT scheme was carefully delivered (30 Gy in 15 fractions and 3 weeks), the Hopkins Verbal Learning Test (HVLT) showed a significantly greater decline in immediate recall ($P = 0.03$) and delayed recall ($P = 0.008$) in the PCI arm, both at 6 and 12 months [4]. Again in (stage III) NSCLC patients, a very recent publication showed that PCI decreased significantly the risk of symptomatic BM at 24 months, but with an increase of neurotoxicity and no better survival [5]. Even in small cell lung cancer (SCLC) patients, if PCI is still offered as a standard to patients with *a limited disease* after response to first-line therapy [6], its indication in

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patients with *extensive disease* is now debated, regarding a recent Japanese trial where WBRT did not result in longer survival versus a strict observation *plus systemic MRI follow-ups*, in contrast with the initial publication of Slotman; a prospective trial is planned to confirm this [7–9].

18.3 Conventional WBRT Is Always Neurologically Detrimental, with No Definitive Effect on Survival

In patients with up to 4 BMs and a life expectancy of more than 6 months, all but one phase III trials comparing WBRT with active follow-up and or radiosurgery (RS) report similar results: a comparable overall survival (OS) despite a better intracranial control, but in the same time, *a higher incidence of neurocognitive decline in the WBRT arms*, depending on the battery of test used (the more refined the test was, the more evident was the neurotoxicity). The first trial in 2004 from Andrews et al. only used the Karnofsky Performance Status (KPS) as an assessment of neurocognition; consequently no significant difference was measurable [10]. Later, Chang proposed a more subtle test, the Hopkins Verbal Learning Test (HVLT) as a primary endpoint which demonstrates a huge difference: an early decline of more than 5 points was observed in 52% of patients receiving WBRT + RS versus only 24% of those with RS alone [11]. Even if the EORTC trial showed in 2013 an only modest decline in the QLQ-30/BN 20 [12], the Brown trial using a complete assessment of cognitive outcome reported *a more frequent cognitive decline at 3 months*: 92% for the WBRT + RS arm versus 63% after RS alone. Furthermore, *the 16% of 'long survivors'* (living more than 1 year) were also analysed, and executive function was significantly higher in patients receiving RS, despite a higher rate of intracranial failures [13]. More recently, questioning the role of WBRT versus immediate RS of the cavity *in the post-operative setting*, Brown et al. again showed that quality of life and cognitive outcome (using HVLT-R immediate and delayed recall) were better preserved in the RS arm [14], including patients assessed at 12 months. Interestingly, and *in the same post-operative context*, a Japanese study tested the role of *immediate WBRT* versus *a delayed salvage with RS* in a (positive) phase III non-inferiority randomized trial, where OS was the primary and cognitive function a secondary endpoint, *but only evaluated with MMSE*. Probably because of this choice, they failed to demonstrate a clear significant difference between arms, even if 16.4% of patients in the WBRT arm experienced grade 2–4 cognitive dysfunction after 91 days, whereas only 7.7% of those in the RS arm did [15]. To be noted and all along these large trials, *the median OS of the whole population* studied regularly *progressed* from 6–9 months initially to 10–12 months in the more recent one, *reflecting possibly the positive impact of new systemic therapies* on survival.

For *patients with a poor performance status*, asking the role of WBRT (delivered in 5 fractions of 4 Gy in 1 week, without hippocampal sparing) *versus* best supportive care in a prospective randomized trial (QUARTZ), authors showed that *the median survival of these patients was particularly limited* (less than 3 months) with no measurable clinical benefit favouring WBRT [16]. However, an improved survival was indeed shown (post hoc) *for a subgroup of patients*, particularly those younger than 60 years with a trend for a better outcome in those with a higher performance status and a controlled primary [17].

For patients with 'multiple' BMs (more than 4–5, up to 15–20) and in contrast to those with a 'limited' bulk of intracranial disease, *a clear advantage of RS on WBRT is still to be demonstrated.* Results of several series suggest that starting with RS and delaying WBRT would not compromise ultimate intracranial control and survival. However it's important to underline that *the key study of Yamamoto* presented *a very large retrospective* 'case-matched' study of RS for patients with 'oligo' versus 'multiple' BMs, suggesting a comparable survival [18]. However, inclusion criteria were very strict, limiting the total cumulative tumour volume to less than 15 cc, this selection bias being reflected by the very favourable median survival nearing 1 year. Existing data for this group of patients are indeed mainly retrospective and subject to selection bias, showing essentially that RS is technically 'feasible'. Consequently, *it*

will be essential to take attention to the ongoing phase III studies evaluating prospectively RS vs WBRT in patients with 4 or more BM, including patients with a total cumulative bulk of intracranial disease up to 30 cc. It could be anticipated that there will be with time increasing difficulties of recruitment, linked to the larger diffusion of RS and stereotactic radiotherapy (SRT) among centres in many countries**.**

18.4 Will Hippocampal Avoidance (HA) and Memantine Be the 'Saviours' of WBRT?

Intensity-modulated radiation therapy **(IMRT) and** ***tomotherapy*** techniques are increasingly available, capable to (1) deliver *in the same schedule*, two different levels of dose (one in the whole brain *and* an extra dose very precisely within BMs), and (2) *in the same time* spare newly identified 'organs at risk' as the hippocampus areas, strongly suggested as key in the memory process ([19, 20]; Fig. 18.1). In the RTOG 0933 study, *a single-arm phase II* study of HA WBRT, results on the HVLT-delayed recall were significantly improved at 4 months, but compared to 'historical controls'. This comparison might be suboptimal in this situation, because early detection of BM has improved over time with the diffusion of high-resolution MRI. Furthermore, aside from the hippocampus, *general cognitive function likely has multiple areas in the brain*, and sparing only these small even important sites may not avoid all the appropriate targets for cognition located in the grey and white matter [21]. Consequently, this possibility to decrease, at less in part, the neurotoxicity of WBRT is still the object of a hot debate, versus the concept of 'on-demand RS', which could be considered as the best way to fully spare hippocampi.

Using memantine **as a 'cognition-enhancing' agent,** the RTOG 0614 study compared patients receiving WBRT (37.5 Gy in 15 fractions of 2.5 Gy in 3 weeks) versus WBRT + memantine (as a preventive agent), regardless of numbers of BMs. As a primary endpoint, the HVLT-delayed recall test showed less decline in the memantine arm at 24 weeks compared to placebo (but $p = 0.59$ was not significant), and *time to first cognitive decline significantly favoured memantine*, with 21% relative reduction in failure. The effect began at 8 weeks from WBRT and was maintained

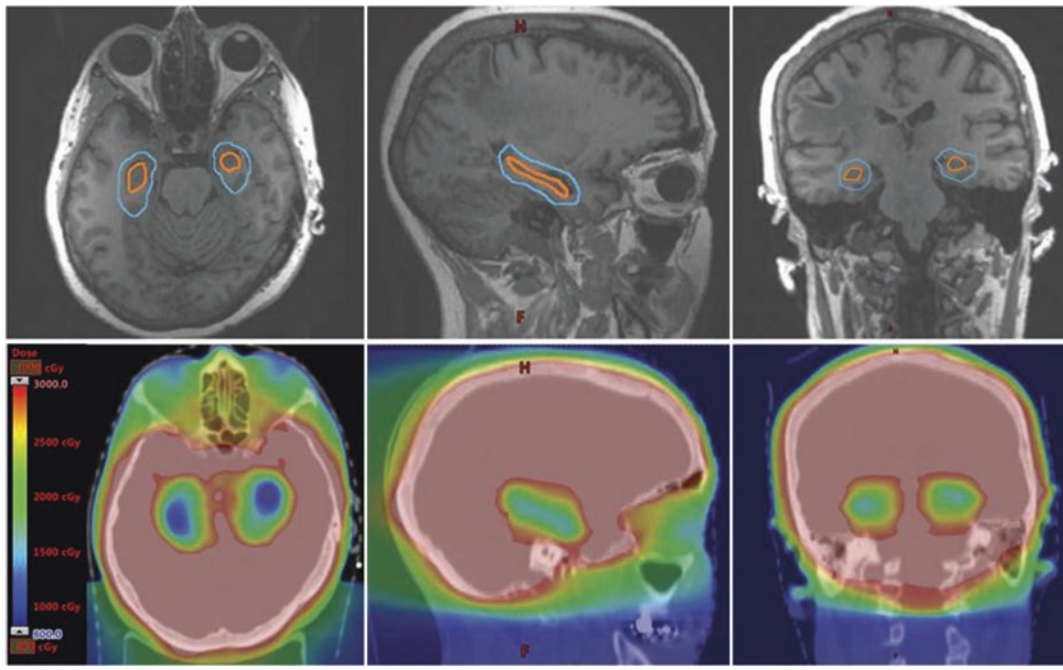

Fig. 18.1 TOP line: visualization of contoured hippocampi (in orange) and areas around to be spared (3 mm expansion). BOTTOM line: final dosimetric plan, with the full planned dose in red, the hippocampi areas in blue and green

even after memantine discontinuation at 6 months. Because patients in the memantine arm had better processing speed and executive function, this was considered as a 'positive trial': in the USA, this drug is now regularly associated with WBRT, but not in Europe where the indication is not validated.

The next step is to ask the question of hippocampal sparing *in a prospective way*: *the ongoing NRG CC001 phase III trial* is indeed investigating *memantine and WBRT with or without HA*, and with an endpoint of neurocognitive failure, positive results will be possibly presented this year 2018.

Finally, the currently accruing phase III trial NCT 03075072 is testing WBRT, with HA when possible, compared to exclusive RS/SRT (in 5 fractions) for patients with 5–20 BMs (none with a maximum diameter beyond 5 cm), and the primary endpoint will be quality of life.

18.5 New Molecular-Oriented and Dynamic Tools Will Better Predict Survival and the Risk of New BM

In our modern 'molecular-oriented' therapeutic context, the graded prognostic assessment (GPA) scores were updated to better adapt therapeutic strategy to a more 'personalized' expected survival. As proposed in breast and lung cancer patients, a disease-specific GPA (DS-GPA) index is also available for metastatic melanoma patients *(see Sperduto chapter in this book).* In the same effort to predict if a patient with BMs will be a 'long survivor', potentially exposed to long-term neurotoxicity of WBRT, it is also of great importance to *predict the risk of new distant BM*. Recently, the *intra-CNS total 'cumulative' volume* appeared to be more adapted than the total number of BMs or the maximum size of BM (one dimension). Several arbitrary thresholds were proposed to differentiate patients with a 'limited' intracranial disease (15 cc in the Yamamoto paper) from those with a 'bulky' cumulative volume of BMs (more than 30 cc), clearly not amenable to RS/SRT.

Finally, simply *evaluating the dynamics of appearance of new BMs* (when *and* how many) could be a personalized reflect of the natural history of BMs, to better predict the risk of an early indication of WBRT, excluding from the 'frontline on-demand RS/SRT' paradigm the subgroup of rapidly evolving patients [22]. All these tools must be taken into account for a given patient in a multifaceted point of view.

18.6 In the End, Are They Still Good (But Rare) Indications for WBRT?

Even if the indications of WBRT *frontline* are strongly decreasing, *it seems important not to exclude 'by principle' this option.* There are still some clinical situations where 'debulking' surgery or radiosurgery for multiple BMs is not recommended in practice or not feasible: we present in Table 18.1 a list of radio-clinical

Table 18.1 Factors favouring the option of whole brain radiotherapy

	Comments
Clinical	
KPS 70 or more	
Symptoms	Headache, seizures, dizziness, minor focal deficit
DS-GPA	Intermediate prognostic (between 6 and 12 months)
Nomogram for prediction of new BM after SRS	High risk for new BM after RS
Radiological	
Number of BMs	More than 8–10
Dynamic/Velocit	BMs rapidly growing/ new BMs at 3–6 months interval
Large BM	More than 30 mm axis
Oedema	If large BM and/or near an eloquent area
Bulky disease	Total cumulative volume >30 cc
Leptomeningeal	Mostly 'nodular' and/or focally symptomatic
Histo-molecular	
General	Low response rate of BMs on systemic treatment
NSCL	Non-actionable profile
Melanoma	BRAF not mutated
Breast	Triple-negative status

and biologic parameters which could balance the decision in favour of WBRT, if possible always with hippocampal avoidance. *WBRT could be typically discussed* for *symptomatic but still healthy* patients, presenting a 'wild-type' molecular profile or *progressing* under targeted drugs/immunotherapy, with *a rapidly evolving history* of numerous BMs, with some of them presenting *a large volume* and a perilesional oedema (see Fig. 18.2). If the expected prognosis is 'intermediate', using the DS-GPA score, in example between 6 and 12 months, *WBRT will rapidly control symptoms* without worsening the neurological status, which is a potential risk after radiosurgery, either at short term (increasing the mass effect) or at long term (with the risk of symptomatic radionecrosis) [23]. Furthermore, WBRT will *effectively*

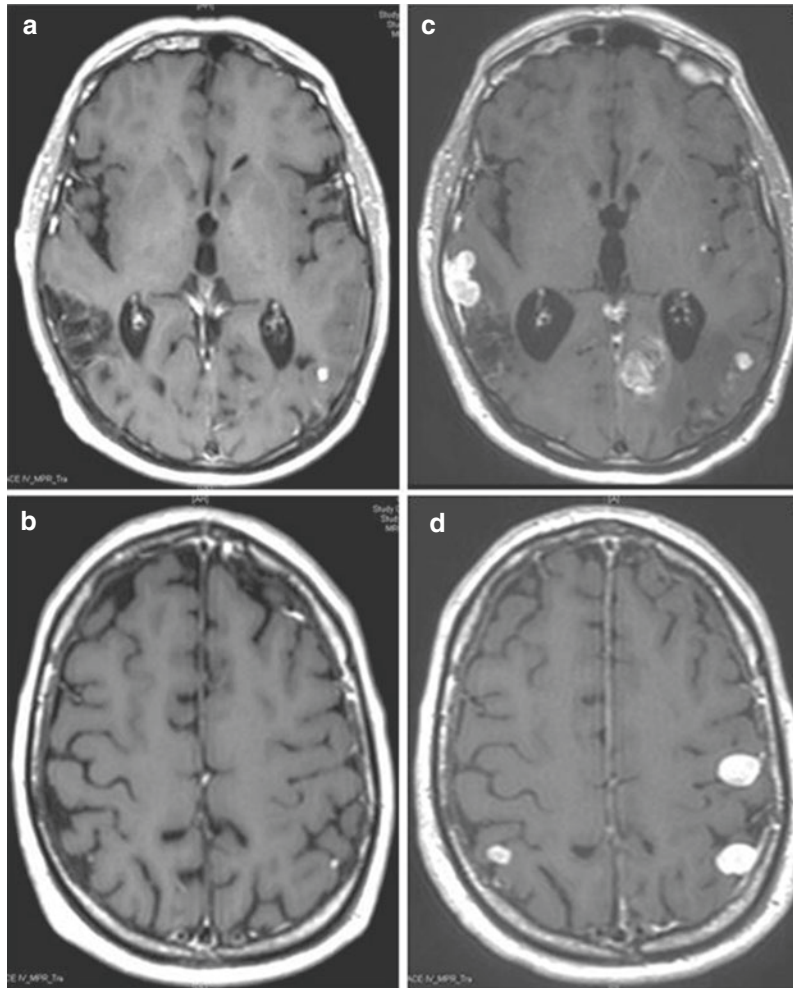

Fig. 18.2 A 56-year-old patient, still in good health and stable extra-cranially, progressed rapidly intracranially under anti-BRAF therapy for a metastatic disease from a melanoma resected 3 years ago. During the follow-up, he developed at a 3 months interval resistant headaches and dizziness, with eight new brain lesions (**a** and **b** then **c** and **d**). The multidisciplinary staff decided to switch for a checkpoint inhibitor, but taking into account the bulky intracranial status (25 cc in total) and the delay for immunotherapy effect, *whole brain radiotherapy (10 fractions of 3 Gy, 2 weeks) was proposed and delivered* to the patient, with a good palliative effect. A new brain MRI was planned 6 weeks after, for eventual stereotactic boosts on large lesions, on the condition of controlled intracranial status

prevent the risk of new distant BM, which was shown as very high in this situation of intracranial 'bulky disease'. Finally, after a 6–8 weeks rest period, a new MRI could be performed: if intracranial 'control' is confirmed, a complementary session of RS or SRT could be delivered on the largest BMs, especially in a context of stable extra-cranial metastatic disease. An option to select patients for 'early WBRT' is based on the individualized risk prediction of development of new brain metastases after SRS alone [24, 25]. If patients are at high risk for a rapid development of new distant BMs, WBRT could be considered as an early and more effective salvage versus expensive iterative RS sessions.

18.7 Perspectives

For the very next future, there will still be some remaining indications for WBRT, possibly adding memantine and hippocampal sparing, in a subgroup of carefully selected patients discussed in a multidisciplinary staff. Special attention should be paid to the results of ongoing prospective trials testing WBRT versus RS/SRT in patients with multiple BMs to more solidly indicate (or not) this therapeutic option.

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19 Combining Radiosurgery and Systemic Therapies for Treatment of Brain Metastases

Veronica Chiang and Stephanie Cheok

19.1 Introduction

The recognition of the benefit of concurrent use of chemotherapy with radiation to enhance the tumor-killing properties of each of these treatment modalities dates back to the 1950s. Chemoradiation remains in use today outside of the brain for conditions such as neoadjuvant therapy for gastrointestinal cancers and sole therapy for non-operative lung cancers. For treatment of brain metastases, combining chemotherapy with whole brain radiation therapy (WBRT) has resulted in improved efficacy of treatment but also in unacceptable rates of severe normal tissue toxicities without additional survival benefit [1]. Therefore, for decades, WBRT with or without surgery was performed first and chemotherapy was put on hold or delayed for as long as 4–6 weeks [2].

Three main changes have occurred over the past two decades that have revolutionized the treatment of brain metastases: (1) The introduction of screening for brain metastases—the use of magnetic resonance imaging (MRI) of the brain to screen or survey for new brain metastases in patients with cerebrotropic primary cancers such as lung cancer, breast cancer, and melanoma. More than 50% of brain metastases can be small and asymptomatic when they are diagnosed, and therefore the need to hold all other therapy to treat the brain metastasis first is not always necessary [3]. (2) The introduction of radiosurgery—toxicities related to radiation and chemotherapy are due to the adverse effect of these treatments on normal cells. With the highly conformal, single-dose nature of radiosurgical treatment, the amount of normal brain, skull, and scalp receiving high-dose radiation is significantly decreased. This reduction allows for the possibility of increased local toxicity and therefore the possibility for reconsidering concurrent delivery of therapy. (3) Finally, the introduction of new systemic therapies such as immunotherapy and targeted therapies have different mechanisms of action on tumor and normal cells altogether and possibly different interactions in the setting of radiation. To understand the relative roles of radiation and systemic therapies in treatment of brain metastases today, it is important to first understand the efficacy and toxicity of each treatment tool alone and then in combination in order to best decide in what sequence treatments should be best administered.

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19.2 Targeted Therapy and Radiation

Targeted therapies introduced over the past decade have revolutionized the treatment of cancer patients with metastatic disease. Targeted therapies are drugs that inhibit specific molecular and tumorigenic pathways essential for the growth and proliferation of cancer cells. As a group, these agents are small molecules and many seem to be able to cross the blood–brain barrier better than chemotherapeutics. Once initiated, they have a rapid onset of activity within the central nervous system, and efficacy of drug on brain metastases is high. Unfortunately, as with systemic disease burden, duration of control of disease remains limited due to the development of mutational escape pathways in the cancer cells. Dosing of targeted agents is usually oral, and there is no data to suggest that steroid use is at all detrimental to the efficacy of these drugs.

19.2.1 Breast Cancer

Brain metastases occur in 10–20% of breast cancer patients. The main therapeutic targets in breast cancer are HER2 and EGFR—members of the ErbB family of receptor tyrosine kinases. Both gene amplification and overexpression of the receptors can be seen in breast cancer. Brain metastases can occur in as many as 50% of patients with HER2-positive breast cancer. One of the first targeted therapy agents was trastuzumab—a monoclonal antibody that binds to HER2 and induces an immune-mediated response. The reduction in HER2 activity mediates antibody-dependent cellular cytotoxicity and inhibition of the MAPK and PI3K/Akt pathways leading to growth suppression. Clinical use of trastuzumab over the past 30 years has markedly improved extracranial disease control [4]. However, with a cerebrospinal fluid (CSF) to serum ratio of 1:420, trastuzumab does not penetrate across the blood–brain barrier (BBB) in concentrations high enough to be effective in the treatment of brain metastases and may possibly further result in selection for the development of metastatic disease in the brain [5, 6]. Lapatinib is a later generation tyrosine kinase inhibitor that targets both HER2 and EGFR. CSF levels of this drug are about 10% of peripheral concentrations, prompting the LANDSCAPE trial, a phase II trial looking at the combination of lapatinib and capecitabine on previously untreated brain metastases. Of 42 evaluable patients, best CNS response was complete response in 2 patients, partial response in 22 (52%), stable disease in 15 (36%), and progression in 3 (7%). Median time to CNS progression however was 5.5 months allowing the study to conclude that use of combined drug alone at best delayed WBRT [7].

There are few studies on the combined effects of radiation therapy (RT) and either trastuzumab or lapatinib for treatment of brain metastases. It has been suggested that WBRT may transiently disrupt the BBB as CSF levels of trastuzumab increased to a CSF/serum ratio of 1:49 after radiation [6, 8]. Unfortunately, a prospective trial investigating the combination of WBRT with trastuzumab specifically for brain metastases (NCT01363986) was prematurely terminated due to slow recruitment. In the most recent retrospective study by Sperduto et al. (2013) looking at breast cancer subtype as a predictor for brain metastasis patient outcome, HER2-positive patients were significantly more likely to need both WBRT and radiosurgery (SRS) during their disease course [9]. Further, in a retrospective study by Yomo et al. (2013), 40 HER2-positive and 40 HER2-negative breast cancer patients underwent treatment with lapatinib and SRS for treatment of brain metastases [10]. Analysis on a per-lesion basis showed that the combination of lapatinib and SRS resulted in better local control than with SRS alone. However, the benefit was lost on the per-patient analysis. On the other hand, multiple retrospective studies do not report increased toxicity from the combined use of drug and WBRT or SRS. In view of this data, the 2018 ASCO Clinical Practice Guidelines continue to recommend local therapies in the form of surgery and/or radiation as first-line treatment for HER2-positive breast cancer brain metastases independent of systemic therapy [11].

19.2.2 Melanoma

Brain metastases occur in >70% of melanoma patients. Targeted therapies in melanoma inhibit the BRAF and MEK pathways. BRAF is a serine-threonine kinase belonging to the MAPK pathway, and an estimated 50% of melanomas harbor a mutation in this protein. MEK inhibitors (MEKi) can also be used to affect the MAPK pathway, and multiple MEKi are also available for use in combination with BRAF inhibitors (BRAFi) for the treatment of metastatic melanoma. Compared with dacarbazine, a chemotherapeutic, the use of BRAFi and MEKi agents has also significantly improved survival in patients with metastatic melanoma [12, 13]. Used alone for the treatment of brain metastases, it has been shown that use of vemurafenib can result in an overall partial response of intracranial disease but again with only a few months of local control [14]. The combination of dabrafenib and trametinib has yielded better intracranial responses with an objective response in 44–59% of patients with brain metastases. Similar to the breast cancer literature, however, median duration of response of dabrafenib/trametinib ranged from 4.5 to 8.3 months in cohorts varying by symptomatology of brain metastases and prior local CNS therapy resulting in most patients requiring local therapy for salvage [15].

With regard to timing of radiation, initial studies looking at adding vemurafenib to WBRT showed that vemurafenib was a potent radiosensitizer causing high rates of acute dermatitis and radiation recall inflammatory changes in the brain. Similar toxicity however has not been reported with the combination of vemurafenib and SRS [16]. Further, in a study by Ly et al. (2015), in patients with BRAF mutant melanoma brain metastases, the use of a BRAFi at the time of SRS resulted in 1-year lesional control rates of 85% compared with only 51.5% in those not receiving BRAFi ($p = 0.0077$) [17]. Finally, in a large cohort study by Kotecha et al., local failure was lower in the SRS plus BRAFi group and lowest when BRAFi was administered within 4 weeks of SRS [18].

Several studies also raise concerns about an increased risk of radiation necrosis when combining SRS with BRAFi therapy, but these findings have not been confirmed in subsequent studies [18, 19]. No national consensus guidelines have been created for the treatment of melanoma brain metastases but based on the above data. Our institutional policy is for all patients with brain metastases receiving BRAFi to undergo SRS if lesion size and number are amenable to SRS. For those patients in whom initial local therapy requires WBRT, BRAFi/MEKi combination can be initiated and SRS could be considered if CNS disease significantly decreases in total volume. Continued progression of disease requires WBRT salvage. Guidelines released by the Eastern Cooperative Oncology Group (ECOG) recommend holding drugs for at least 1 day before and after SRS and 3 days before and after fractionated radiation to avoid radiation-related toxicity [20].

19.2.3 Lung Cancer

Brain metastases occur in about 30% of lung cancer patients. The detection of molecular markers in non-small cell lung cancer (NSCLC) can significantly affect treatment paradigms and prognosis in patients with brain metastasis. Targeted therapeutics are currently available for EGFR-mutated and ALK-rearranged NSCLC. Epidermal growth factor receptor (EGFR) is a transmembrane protein and is part of the HER/*erb*B family of receptor tyrosine kinases. Ninety percent of mutations occur as an exon 19 deletion or exon 21 substitution. The treatment of EGFR mutant NSCLC has been revolutionized by the introduction of tyrosine kinase inhibitors (TKIs), and multiple retrospective, prospective, and randomized controlled trials have proven the efficacy of first- and second-generation TKIs in treatment of primary lung disease as well as metastatic disease in the brain [21, 22]. Osimertinib, a third-generation irreversibly-binding TKI designed originally to be used as salvage for EGFR-mutant lung cancers developing T790M resistance mutation, has been found in addition to have significantly

greater CNS penetration in preclinical studies [23]. Recent data shows that use of osimertinib as first-line treatment of lung adenocarcinomas with EGFR-exon 19 deletion or L858R resulted in significantly longer survival when compared with standard first-generation TKI (18.9 months vs. 10.2 months). Median duration of response was also significantly longer with osimertinib (17.2 months vs. 8.5 months), and overall response rate remained around 80% for all agents [24].

This prolonged progression-free survival in lung cancer patients with brain metastases makes management of this disease different from that of melanoma and breast cancer patients. Treatment of brain metastases with TKI alone can result in CNS control duration in the order of 11–14 months. In addition, the landmark randomized study NCT01724801 comparing icotinib alone versus WBRT at first diagnosis of brain metastasis not only showed longer intracranial control with icotinib alone (10 months vs. 4.8 months) but also significantly fewer adverse events (8% vs. 38%) [25]. Further, a phase II study comparing WBRT alone versus WBRT plus erlotinib showed that use of erlotinib was the most important prognostic factor for prolonged survival [26]. Given the clinical success and good tolerability of daily drug administration, TKIs alone have recently been recommended then as first-line therapy for brain metastases with use of radiation delayed until salvage is required [25].

Despite these recommendations, the literature remains divided on the optimal first-line management strategy for EGFR-mutant lung cancer brain metastases. All completed comparative studies of TKI monotherapy versus upfront radiation plus TKI are retrospective and so far only study the use of first-line TKIs. Data that supports use of TKI alone for treatment of brain metastases assert that additive WBRT does not improve survival outcomes and comes at a cost of post-radiation effects: neurocognitive decline and radiation necrosis. Byeon et al. reviewed 59 patients treated with combination TKI and WBRT or SRS compared with 62 patients treated with TKI only (gefitinib or erlotinib). There was no significant difference in intracranial progression-free survival (16.6mos for RT group vs. 21mos for TKI alone) or three-year survival rates (71.9% vs. 68.2%) [27]. Jiang et al. compared 116 patients receiving TKI monotherapy (erlotinib/gefitinib/icotinib) and 51 undergoing combined TKI and hypofractionated conformal RT and also found no improvement in progression-free survival (6.9mos for RT vs. 7.4mos for TKI alone) and in fact found a worsened survival rate in the RT group (21.6mos for RT vs. 26.4mos for TKI alone) [28]. Lastly, a series by Sung et al. of 81 patients did find improvement in intracranial disease control in the combination TKI and radiation group, but no improvement in overall survival [29].

In contrast, results from a multi-institutional retrospective study analyzing 351 patients showed that upfront RT (WBRT and SRS) and TKI resulted in improved intracranial disease control and increased median overall survival when compared with use of erlotinib alone despite the RT subgroups having larger and more symptomatic brain lesions as well as less favorable Graded Prognostic Assessment (ds-GPA) scores prior to initiation of treatment [30]. The patients were then subdivided into those receiving WBRT versus SRS, and it was found that while duration of intracranial disease control was improved with upfront RT regardless of type (23 and 24mos for SRS and WBRT, respectively, vs. 17mos for TKI alone), median overall survival was markedly increased in the SRS group (46mos for SRS vs. 30mos for WBRT vs. 25mos for TKI alone). This survival benefit has now been confirmed by multiple studies as summarized in a recent meta-analysis of 12 non-comparative observational studies by Soon et al. (2015) that showed that upfront cranial irradiation improved 4-month intracranial progression-free survival and improved 2-year overall survival although toxicities also occurred at a higher rate after RT. [31] Several prospective trials in China comparing gefitinib monotherapy and gefitinib plus upfront RT are in progress, although accrual has been problematic. NCT02338011 is a study comparing gefitinib alone to gefitinib plus WBRT. It was scheduled to complete accrual by November 2017 but has as yet not concluded. NCT0271401

is a randomized multicentered study comparing intracranial progression-free survival in patients receiving any TKI versus TKI plus WBRT. This trial opened in August 2015 and is not expected to complete accrual until December 2021. With the recent introduction of osimertinib for first-line use in lung cancer treatment, NCT03497767 was recently opened. This study plans to compare 12-month intracranial progression-free survival in 80 patients randomized to receive either osimertinib only versus osimertinib and SRS at first diagnosis of brain metastases. Secondary outcome measures will include need for salvage WBRT, local and distant brain failure, extracranial progression, and overall survival.

All of the above data addresses first-line treatment of TKI-naïve patients with EGFR-mutant adenocarcinoma of the lung with brain metastases. Given the conflicting results but possible advantage of combining TKIs with SRS for improved overall survival, our institutional policy is to recommend upfront SRS along with initiation of TKIs in those patients with brain metastases of number and size appropriate for SRS treatment. Given that the data for WBRT seems less clear, WBRT has been withheld until use as salvage at time of CNS failure. What is not addressed well by the literature is evidence to guide treatment at time of TKI failure resulting in CNS progression. Patient management in this situation is therefore individually assessed.

Also not well addressed by the literature is the role of RT in patients with anaplastic lymphoma kinase (ALK) rearranged lung cancer. While this constitutes a very small percentage of the lung cancer population, the second- and third-generation ALK inhibitors alectinib and ceritinib used alone have been shown to have a 50–70% overall response rate in the first-line treatment of brain metastases [32–34] and have also demonstrated efficacy as salvage therapy [35]. While there are no studies comparing the use of an ALK inhibitor (ALKi) alone versus ALKi plus SRS, there have also been no studies documenting adverse effects to the use of combined drug and radiosurgery. Our institutional policy also remains the treatment of brain metastases in patients with ALK-mutation lung cancer with SRS and/or WBRT concurrent with the use of ALKi.

19.3 Immunotherapy and Radiation

Immunotherapy alone for treatment of brain metastasis is also a relatively novel treatment concept. The presence of the blood–brain barrier (BBB) and the concept of CNS immune privilege resulted in previous exclusion of patients with active brain disease from immunotherapy trials. However immune privilege is not absolute and not only have T cells been shown to cross the BBB and patrol the CNS but tumor-infiltrating lymphocytes are often found within the stroma of brain metastases—albeit in highly variable concentrations [36]. This discovery and many similar experiments have led to the development and extension of immunotherapy use to patients with brain metastasis. Clinically approved checkpoint inhibitors target CTLA4, PD-1, and PD-L1.

19.3.1 CTLA-4 Inhibitors

CTLA4 is a transmembrane receptor expressed on the surface of activated T cells that acts as a negative regulator of T-cell activation thereby decreasing the response of T cells to antigen-presenting cells. CTLA-4 inhibitors are also known as checkpoint inhibitors because they potentiate the activation of T-cells and inhibit the T-cell regulatory pathway. Ipilimumab, an IgG-1 monoclonal antibody, was the first immune checkpoint inhibitor to be approved for use in melanoma patients. In the metastatic melanoma population, response rates of 10–20% have been reported systemically and median overall survival (OS) in responders is about 11.4 months [37]. Few studies have looked specifically at the effect of ipilimumab on melanoma brain metastases, but many studies have been reported showing effect as a secondary outcome. An initial phase III trial published by Hodi et al. (2010) reported that compared with gp100, ipilimumab patients had a good response in their melanoma brain metastases (MBM) [38].

Of note, patients with untreated brain metastases were excluded from this trial and all patients also received local therapy to their brain metastases. In addition, two anecdotal studies reported good responses in MBMs using ipilimumab alone when brain metastases were missed prior to initiation of drug [39, 40]. Margolin et al. (2012) prospectively studied the efficacy of ipilimumab in patients with MBMs and reported that for new or re-growing MBMs, treatment using ipilimumab alone resulted in lesional control rates of 18% in patients with small asymptomatic lesions and only 5% in patients with larger symptomatic lesions. Median OS was 7 months vs. 3.7 months, respectively [41]. Ipilimumab alone therefore remains insufficient to treat MBMs.

While no prospective studies have been performed to study the combined effect of ipilimumab and RT, multiple retrospective series have been published comparing standard of care RT only compared to RT plus CTLA-4 inhibitors. Data from studies by Knisely et al. (2012), Silk et al. (2013), and Skrepnik et al. (2017) were able to show that by controlling CNS disease using a combination of ipilimumab and RT, and more specifically SRS, median overall survival durations of 21.3, 18.3, and 35.8 months, respectively and local control rates of around 95% were possible [42–44]. Interestingly, in the study by Silk et al., the administration of ipilimumab after RT also resulted in statistically better local control and longer survival than if ipilimumab was used prior to RT. [43] This was confirmed in the study by Kiess et al. (2015) who showed that local control and median OS was improved if SRS was used during (median OS 65% at 1 year) or before (56%) ipilimumab administration compared with after (40%) [45]. The study by Skrepnik et al. also showed that local and distant CNS control was improved if SRS was delivered within 30 days of immunotherapy versus Schoenfeld et al. who showed persistent benefit if drug was administered within 3 months of SRS [42, 46]. Further, An et al. (2017) looked at timing of SRS at multiple time points after ipilimumab treatment completion and showed that while median OS was not affected, overall CNS control was worse if greater than 5.5 months had passed before SRS was performed [47].

Ipilimumab alone is no longer used for first-line treatment of patients with metastatic melanoma but its role in combination with SRS for CNS control might still be considered in cases where CNS disease predominates over systemic burden.

19.3.2 PD-1/PD-L1 Inhibitors

Programmed cell death protein 1 receptor (PD-1) is also a surface protein expressed by activated T cells that typically binds to the ligand, PD-L1, on the surface of the antigen-presenting cell. This interaction results in inhibition of further T-cell activation. Inhibitors of either PD-1 or PD-L1 can then function as immune checkpoint inhibitors and facilitate T-cell activation. While PD-1 is only found on the T-cell, PD-L1 has been found on many tumor types including breast cancer, melanoma, lung cancer, and several of the genitourinary and gynecological cancers. In view of this, many clinical trials are open today using checkpoint inhibitors as either first- or second-line therapy for metastatic disease, and much data is being accumulated documenting beneficial effects of these agents on survival of cancer patients [48]. Two PD-1 blockers are approved for clinical use—pembrolizumab and nivolumab. In comparison with ipilimumab, the phase III KEYNOTE-006 study (NCT01866319) showed that pembrolizumab provided superior response rates (36%), as well as improved length of median OS, progression-free survival (PFS), and lower rates of adverse effects in patients with metastatic melanoma. In this study median OS was not reached at time of publication [49].

Initial trials of these drugs excluded patients with melanoma brain metastases. Given the known efficacy of ipilimumab alone for MBMs, however, NCT02085070 was opened to study the effect of pembrolizumab alone for the treatment of melanoma and NSCLC brain metastases. On interim analysis, a response rate of 22% was seen for MBMs and 33% for NSCLC brain metastases. Responses were durable and mostly concur-

rent with systemic response, but in comparison to the local control rates of 93–97% achievable using SRS, our institutional recommendation remains that local therapy be used for the treatment of brain metastases in these patients [3, 50].

In parallel to the advancement of systemic agents, there has also been an evolution in the thinking about the use of different forms of radiation for brain metastases. Given the concern for neurocognitive decline after WBRT in those patients with longer expected survival, first-line and salvage treatment for brain metastases has become SRS when possible [51, 52]. Several unique features arise with the use of combined SRS and immunotherapy. Firstly, compared with chemotherapies where toxicities precluded use of chemotherapy concurrently with WBRT, there appear to be minimal toxicities to the concurrent use of SRS and immunotherapy [53, 54]. Timing of immunotherapy and SRS therefore no longer requires significant coordination. Secondly, in comparison with ipilimumab which was administered over a 4-week block, but rarely repeated or used as maintenance, anti-PD1 agents are given as maintenance every 2 or 3 weeks (depending on the agent) for the remainder of the patient's life, unless limited by toxicity. Interactions between the effects of immunotherapy and radiosurgery can then occur both acutely and also in a delayed setting.

Many studies have looked at survival in MBM patients receiving both anti-PD1 therapy and radiosurgery. The first by Ahmed et al. (2016) included 26 patients who received radiation within 6 months of nivolumab with a median overall survival of 11.8–12.0 months. Of interest, they also found that median OS was improved (not reached) at end of study in those patients whose MBMs were resected prior to SRS [54]. Many other studies have confirmed similar median OS lengths of around 12–18 months for patients treated with SRS and anti-PD1 agents [55, 56]. Analysis of the largest data set of 1104 patients with MBMs from the National Cancer Database showed that median OS was 11.1 months in those treated with RT and immunotherapy compared with 6.2 months in those treated with RT alone. Treatment with immunotherapy and SRS specifically were both independent factors associated with improved OS [57].

In addition to studying survival, Acharya et al. (2017) showed that the combination of immunotherapy (any agent) and SRS resulted in significant reduction of distant intracranial failure compared with SRS alone or SRS in combination with BRAF/MEK inhibitor (1-year local control 60% for SRS + immunotherapy versus 11.5% for SRS alone versus 10% for SRS + targeted therapy) [58]. In contrast, Rahman et al. (2018) reported that patients getting concurrent SRS and immunotherapy (within 30 days) had a higher rate of developing intracranial progression within 60 days of SRS (54.3% compared with 30.8% non-concurrent) [56]. Larger population studies may be required to determine the actual risk of distant failure.

Given the previously encouraging results of concurrent ipilimumab and SRS, Qian et al. (2016) studied the radiographic response of different checkpoint inhibitors relative to SRS for MBMs. They found that concurrent use of immunotherapy (regardless of agent) and SRS for MBMs (administered within 4 weeks of each other) resulted in a significantly greater reduction in median percent volume reduction in lesion volume at all points of follow-up out to 6 months compared with non-concurrent treatment [59]. In addition, median volume reduction was also greater for anti-PD1 agents than for ipilimumab. In comparison, Rahman et al. looked at overall patient response. In their study, patients received either concurrent ipilimumab (68.6%, 24 of 35), pembrolizumab (20.0%, 7 of 35), combined ipilimumab and nivolumab (5.7%, 2 of 35), or nivolumab alone (2.9%, 1 of 35). Interestingly, patients on concurrent immunotherapy and SRS were found to be more likely to have early intracranial progression within 60 days, but non-early progressors had greater progression-free survival at 1 year [56]. In contrast, Yusuf et al. (2017) showed that the administration of immunotherapy peri-SRS significantly predicted freedom from distant brain failure, and Anderson et al. (2017) showed that in 21 patients treated with concurrent SRS and pembrolizumab, 70% of lesions exhibited complete or partial response

at first imaging follow-up (median 57 days post SRS) compared with only 32% of lesions treated with concurrent SRS and ipilimumab and 22% treated without immunotherapy [53, 60]. While the differences in overall CNS control may be related to differing patient populations, it is clear that concurrent immunotherapy and SRS results in better local lesional control of SRS-treated lesions, and this advantage might in fact enable longer survival.

More recently the CHECKMATE trial (NCT01844505) has shown even more promising systemic results for the use of combined anti-CTLA4 and anti-PD1 agents in melanoma patients. At 18 months interim analysis, ipilimumab combined with nivolumab (ipi/nivo) resulted in longer PFS than using either agent alone with median duration of response not reached for 57.6% of patients receiving combination therapy compared with 22.3 months for nivolumab alone and 14.4 months for ipilimumab alone. In addition, the ipi/nivo combination appears to result in a comparable overall intracranial response rate of 57% in the treatment of MBMs with a complete response rate of 26% [61]. With this improved efficacy of CNS control, the largest concern with this combination has now become the issue of treatment toxicity. Many studies have been published reporting rates of radiation necrosis ranging from 5% to 20% after combined immunotherapy and SRS depending on the clinical definition used for radiation necrosis [55, 62–64]. In the only two studies to compare rates of radiation necrosis across patients receiving chemotherapy, targeted therapies, and immunotherapies, Colaco et al. reported that patients receiving immunotherapy were at highest risk for developing post-SRS imaging changes of lesional regrowth or symptomatic radiation necrosis (OR 2.40, $p = 0.03$), and Martin et al. reported a 2.56 times increased rate of symptomatic radiation necrosis across all brain metastasis histologies versus an almost 4 times increased rate for MBMs [62, 65]. What is not clearly addressed are the ranges of SRS doses used in these studies. The only report where dosing is clearly discussed is in a study by Skrepnik et al. (2017) where most metastases were treated with a margin dose of 21 Gy. In this study, an radiation necrosis rate of 20.7% was reported [42]. Given that known risk factors for development of radiation necrosis include increased treatment volume, increased treatment dose, and re-treatment with SRS [66] and anecdotal cases of excellent local response of MBMs to SRS doses as low as 12 Gy in the setting of immunotherapy have been seen at our institution, the three parts of our institutional policy for combined anti-PD1and SRS therapy are: (1) given the possibility of high likelihood of improved CNS local control as well as improved survival, patients with brain metastases receiving immunotherapy should also be treated using SRS concurrently where possible, (2) to surveil for brain metastases frequently in order to find lesions when they are small and (3) to lower the dose prescribed as much as possible to limit toxicity.

Immunotherapy agents are also increasingly being used for cancer types other than melanoma. No literature has been published specifically looking at the combined effects of immunotherapy and SRS in these other cancer types. Our own institution recently completed a retrospective analysis of NSCLC patients treated with SRS for brain metastases while receiving anti-PD1 agent, and preliminary results do not suggest either an improved survival or local benefit to the combination of these treatments [Leksell Gamma Knife Society abstract from Dubai meeting 2018].

19.3.3 Antiangiogenesis

Antiangiogenic agents have been widely used in the treatment of aggressive primary brain tumors such as WHO grade III and VI gliomas. However, their use has been limited for many years in metastatic CNS disease due to a perceived risk of intracerebral hemorrhage as reported in a patient with unrecognized metastatic hepatocellular carcinoma brain metastasis occurring two weeks after being given a dose of bevacizumab in 1997. Bevacizumab is a humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF) and prevents it from reaching the endothelium and therefore inhibiting neovascular proliferation. Other agents in this group include sunitinib and sorafenib—drugs used predominantly currently for renal cell cancer treatment. Contrary to popular belief then, a study by Besse

et al. (2018) recently showed that in 187 patients with occult brain metastases identified across multiple drug trials, risk of intracerebral hemorrhage was independent of bevacizumab therapy [67]. A renewed interest therefore has now arisen to combine bevacizumab with chemotherapies to enhance anti-tumor effect although its use continues to be debated.

Bevacizumab is also not routinely used concurrently with RT for treatment of brain metastases, and there is little data to advise if there is benefit to combining antiangiogenic agents with SRS. Two trials are currently open looking at this question for brain metastases:

1. NCT02672995—A phase 1 dose-escalation trial looking at combining bevacizumab and fractionated SRS to determine if maximal safe dose of SRS can be increased to improve response rate, time to progression, and decrease adverse effects of SRS
2. NCT00981890—A phase 1 study combining sunitinib with concurrent SRS

The tolerance and efficacy of concurrent bevacizumab and whole brain radiation therapy, however, was prospectively assessed in the REBECA trial [68]. Nineteen patients were enrolled, including 13 breast and 3 lung cancer patients, all with brain metastasis. WBRT was delivered 15 days after starting bevacizumab. There were no dose-limiting toxicities, and 10 out of 19 patients had a measurable intracranial response in 3 months, a similar rate to WBRT alone.

A newer indication for bevacizumab has been for the treatment of radiation necrosis (RN), a late complication particularly of SRS. While the pathophysiology behind the development of RN is not completely understood, it is currently thought that it is possibly initiated by an auto-reactive injury response to normal brain cells surrounding the treated tumor. Hypoxia in irradiated tissue is thought to promote VEGF overproduction, which results in fragile angiogenesis, increased capillary permeability, edema, and eventual necrosis. Gonzales et al. in an early study of 8 patients showed radiographic improvement with significant reduction in post-contrast and FLAIR volumes on MRI with following bevacizumab [69]. This observation was confirmed in a placebo-controlled randomized double-blind trial including 14 patients with radiographic or biopsy-proven radiation necrosis [70]. At a median of 10 months, all patients in the cohort on bevacizumab had reduction of lesion volume and clinical symptoms and none of the patients of the placebo patients showed a benefit. Given this class I evidence of efficacy, the largest use of bevacizumab today at our institution is for the treatment of radiation necrosis rather than in conjunction with radiation for efficacy of tumor control.

19.4 Conclusion

The landscape for the treatment of brain metastasis is rapidly evolving with advances in targeted and immunotherapy. As these agents improve, important questions arise: What is the optimal treatment for each brain metastasis cancer subtype? With the increased specificity and BBB penetration of systemic therapy, is monotherapy sufficient? And finally, what is the role of local therapy?

Radiation for focused control of intracranial disease control is a pillar of brain metastasis management. The synergistic effect of radiation, SRS in particular, with TKIs and immunotherapies provides an attractive option for a difficult-to-treat disease, which often portends a poorer prognosis. However, recommendations are shifting. For example, in EGFR-mutant NSCLC, some institutions are moving away from radiation as a first-line treatment in lieu of TKI monotherapy. On the other hand, radiation continues to be a mainstay in treatment in breast cancer and melanoma brain metastasis. With the potential of SRS to improve both intracranial disease control and overall survival across cancer subtypes, our institution continues to provide upfront or early radiation therapy in conjunction with systemic treatments.

Ongoing studies looking not only at the efficacy and toxicities of drug and radiation interaction but also the sequence in which they are administered for treatment of brain metastases, in the setting of stability or progression of systemic disease, are critical as new and better drugs are being approved.

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Brain Metastases from Lung Tumors

20

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20.1 Introduction

Among metastatic primary tumors to the brain, those from the lungs are among the most common, owing both to their high incidence and their underlying biology [1]. Broadly, primary neoplasms of the lungs can be classified into two histologic subtypes—small cell and non-small cell. Among non-small-cell tumors, there are three primary histologic subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, accounting for 85% of all lung cancers [1]. Small-cell cancers are comprised of cells with neuroendocrine characteristics, accounting for 15% of all lung cancers [1–3]. In addition to the histology, the course of the two subtypes and the treatment differs significantly [4]. However, among both cancer types, there is a predilection towards metastatic disease in the brain, with 10–30% of NSCLC patients exhibiting brain metastases during their course [5]. Ten to 25% of the NSCLC patients with metastatic disease can have brain metastases at presentation.

Owing to the high prevalence of lung cancer, much work has been done on characterizing the molecular alterations that are critical to the development of these tumors [6]. The study of these molecular alterations has led to an understanding of "driver mutations" that propel the growth of cancer cells. Excitingly, this has led to the development of targeted agents in the form of small-molecule inhibitors and monoclonal antibodies for the mutant protein product, which have shown significant promise in delaying the onset of therapeutic resistance, increasing average survival [7]. As a result of this increased survival of patients with primary tumors, as well as the more advanced and sensitive cerebral imaging modalities available, the incidence of metastatic disease from lung primary cancer is increasing. Moreover, this increase in metastatic disease burden also extends to the CNS, and there has been an increase CNS metastases noted since the advent of these therapies [8].

Traditionally, brain metastases from lung cancer have been treated with a combination of surgical and radiotherapies, and the presence of metastases has been shown to confer a poor prognosis, in general [9]. However, with an increased understanding of the underlying biology, prognostication has also evolved. More specifically, the Lung-molGPA (molecular graded prognostic assessment) has been recently updated to include

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molecular markers associated with lung cancers. This was based on effort data from 2186 patients with NSCLC and brain metastases, of which 1521 were adenocarcinoma and diagnosed between 1985 and 2005. The authors incorporated reported gene and molecular alteration data for patients with NSCLC and brain metastases. The authors identified the following significant clinical variables in their prognostic model: patient age, Karnofsky performance status, extracranial metastases, number of brain metastases, and, in patients with adenocarcinoma, the presence of EGFR and ALK alterations [9]. The authors of this study found that the presence of these alterations conferred a better prognosis, although this could only be stated for those with adenocarcinoma, as other histologic subtypes did not have routine genotyping. The overall median survival in the whole lung cancer cohort is 12 months, and those with NSCLC-adenocarcinoma and Lung-molGPA scores of 3.5 to 4.0 had a median survival of nearly 4 years.

20.2 Neurosurgical Resection and Radiotherapy

Neurosurgical resection and radiotherapy management of brain metastases have been covered in detail in other sections/chapters of this book. In lung cancer, the general principles of surgery are followed, as in other brain metastases, where patients with solitary metastases may undergo surgical resection when such lesions are causing mass effect, and in brain metastases of size greater than 3.5–4 cm where the role of radiosurgery is limited. Surgical resection may be attempted if the locations of metastases are amenable to resection in the case of limited metastatic disease and if there are fewer than 3 metastatic lesions. However, there is no significant benefit of surgery compared to SRS in oligometastatic disease, and these two modalities are thought to be equivalent in terms of local control. The combination of radiation and surgery is also an approach that has shown promise. Postoperative SRS, in a trial of 132 patients, compared with observation postoperatively, increased local control significantly, with hazard ratio of local recurrence 0.46 ($p = 0.015$) in a study by Mahajan et al. [10]. The addition of WBRT to postoperative management has not been shown to provide any benefit above SRS and has only been shown to increase the risk of neurocognitive side effects [11].

20.3 Chemotherapeutics

20.3.1 Traditional Chemotherapeutics

The use of traditional chemotherapeutics in the management of metastatic (and primary) oncologic disease in the CNS has been significantly limited due to the poor ability for these drugs to cross the blood–brain barrier (BBB), often limited by molecular weight or lipid solubility [12]. Indeed, temozolomide, which is among the only chemotherapeutic agents with significant BBB penetration, and while it is an efficacious treatment for primary brain tumors, it shows little efficacy in the treatment of brain metastases from lung cancer. A phase II study by the EORTC, published in 2003, involved 12 chemotherapy-naive patients with brain metastases from NSCLC, treated with single-agent temozolomide. Due to disease progression, most patients received only 1–2 cycles of the 6 planned cycles of temozolomide, and it was concluded that there was little therapeutic benefit of temozolomide, if any, in the treatment of metastatic NSCLC [13]. A later phase II trial, published in 2005, involved patients who were heavily pretreated (having tolerated at least one chemotherapy and WBRT), treated with temozolomide for five cycles. This study involved 30 participants with NSCLC metastatic to the brain, and of this cohort, 80% had progressive disease, 10% had stable disease, and 10% had an objective response after five cycles of temozolomide treatment, and no patients discontinued therapy due to temozolomide toxicity, suggesting that it may be a viable option in this subset of patients [14]. With the emerging role of immunotherapy and targeted therapies, the role of traditional chemotherapy has been more limited and restricted for the management of the patients with lung cancer and brain metastases.

20.3.2 Targeted Therapies

The discovery of molecular drivers of various NSCLC tumors has significantly changed the field of treatment options, with small-molecule inhibitors of various aberrant pathways significantly extending survival for certain patient subgroups. In this subsection, we review the mutations, their targeted therapies, and the evidence for their efficacy in treating brain metastases. Among the most common of these activating mutations is in the KRAS oncogene, mutated in approximately 30% of all cases of NSCLC, resulting in uncontrolled cellular proliferation [15]. However, at the present time, there are no targeted therapies for this mutation [15].

The most promising evidence for the efficacy of targeted therapies comes from EGFR-mutated and ALK-rearranged tumors. More specifically, the EGFR mutation is present in 15% of cases of primary NSCLC, and patients with these tumors are thought to have a higher burden of brain metastases, but also better prognosis for brain metastases than those without the mutation [16, 17]. First-generation EGFR inhibitors that have been studied include gefitinib and erlotinib, and due to the development of resistance to these agents (commonly the T790M mutation in EGFR mutant tumors), second- and third-generation inhibitors were developed, including afatinib and osimertinib [18, 19]. Evidence for their efficacy in brain metastases from primary EGFR-positive NSCLC initially came from smaller cohort studies showing good response rates for both intra- and extracranial metastases in these patients. Initial reports which included a 2003 case series of four patients reported that two patients had long-lasting benefit noted in intracranial metastases from NSCLC while on gefitinib, and a later 2004 report of two Japanese women also reported a good response of intracranial metastases to gefitinib, and a similar case report of a 60-year-old patient with metastatic NSCLC treated with erlotinib emerged in 2007 [20–22]. These promising case reports then prompted larger-scale investigation into the role of EGFR inhibitors, and one Japanese study examined 57 patients who had received gefitinib during the treatment of their NSCLC, and 14 of these patients had brain metastases. In 6 of 14 patients, partial or complete response was observed, and the remaining 8 had stable disease. This report also demonstrated that 7 of 14 patients had response in extracranial tumors, and this set of 7 patients included 6 patients who had objective response in the brain as well [23]. The first prospective trial of gefitinib in brain metastases from NSCLC came from Ceresoli et al. in 2004, where this group analyzed 41 patients with measurable brain metastases treated with gefitinib. Twenty-seven of these patients were pretreated with chemotherapy, and 18 had prior WBRT. Partial response was observed in 10% of cases, stable disease in 17% of cases, with a partial response duration of median 13.5 months [24]. This was exciting and demonstrated an improvement over the historical benefit seen with traditional chemotherapeutics as discussed in the previous section. Interestingly, when study participants were further stratified by smoking status, response rates improved significantly. In a trial of 23 Korean never-smokers without any prior treatment for brain metastases, the response rate of synchronous intracranial metastases was observed in 74% of patients (17 of 23) [25]. Because of the association with these demographic variables and primary tumor EGFR status, it was hypothesized that mutational status plays a key role in determining even response of brain metastases to EGFR treatment. A later study by Porta et al. in 2011 reported that among 17 patients with EGFR mutations, objective response to erlotinib was observed in 82.4%, and among 52 patients without or uncertain EGFR mutations, there were no responses of brain metastases observed ($p < 0.001$) [26].

After the success of the first-generation tyrosine kinase inhibitors (TKIs) in brain metastases, several studies examined the efficacy of EGFR TKIs with radiation therapy. In a phase II study of 40 patients with NSCLC, brain metastases were treated with erlotinib 150 mg orally once daily for 1 week, then concurrently with WBRT, followed by maintenance dose irrespective of *EGFR* status [27]. Overall response rate of 86% in 36 patients was seen; however, only 17 patients in the study had confirmed *EGFR* status, and 9 patients had *EGFR* mutations. Median overall survival of

19.1 months was seen in those with EGFR mutations compared to 9.3 months in patients without *EGFR* mutations. In another phase II clinical trial of 80 patients, 40 subjects were randomized to erlotinib with WBRT, and another 40 were treated with placebo with concurrent WBRT [28]. After treatment with WBRT, patients were continued on erlotinib or placebo until disease progression. Median OS of 3.4 and 2.9 months was seen in the erlotinib and placebo arms, respectively; however, only one patient in the erlotinib arms had the EGFR mutation.

In addition to erlotinib, osimertinib has also begun to be examined for potential clinical benefit in the scenarios when the EGFR mutation present carries the T790M mutation, rendering first-line chemotherapies ineffective. A trial by Mok et al. in 2017 examined 419 patients with EGFR T790M mutation-positive NSCLC, to either osimertinib or pemetrexed with platinum chemotherapy [18]. Among each of the patients considered in the trial, their tumors had advanced while on first-line EGFR therapy. In this trial, osimertinib was found to extend PFS statistically significantly compared to standard chemotherapy, to 10.1 months versus 4.4 months, HR 0.30 (0.23–0.41, 95% CI, $p < 0.001$). In this trial, it was also noted that among 144 patients with CNS metastases, in subgroup analysis, the median PFS was 8.5 months for those receiving osimertinib versus 4.2 months for those receiving pemetrexed, HR 0.32 (0.21–0.49, 95% CI).

Likewise, ALK rearrangements have been shown to occur in roughly 5% of cases of NSCLC, and in primary tumors with this activating mutation, inhibitors of ALK have shown promise in extending survival. In patients with brain metastases from these primary tumors, a systematic review and pooled analysis of 21 studies published in 2008 encompassing 1016 patients showed that the objective response rate to ALK inhibitors for patients with ALK-rearranged NSCLC and brain metastases who were treatment naive was 70.3%, and for treated patients was 78.2% [29]. However, because these therapies are highly targeted, they promote the development of resistance, and the clinical manifestation of this resistance is often reported as the development or progression of intracranial lesions during targeted therapy [30]. Despite the issue of chemotherapeutic resistance, these results suggest that, as in the case of EGFR inhibitors, for preselected patient groups harboring the driver mutation, targeted therapy can be efficacious for brain metastases in prolonging survival, regardless of treatment status.

In particular, recent clinical trials have examined the effectiveness of these ALK inhibitors, and further evidence is emerging for their role in treating metastatic CNS disease. An open-label phase 3 randomized control trial comparing pemetrexed +/− cisplatin to crizotinib in ALK-mutated NSCLC was published by Solomon et al. in 2014 and studied 343 patients with no previous systemic treatment for advanced disease [31]. PFS in the crizotinib group was significantly longer, 10.9 months versus 7.0 months, HR 0.45 (0.35–0.60, 95% CI, $p < 0.001$). In further analysis of this cohort, the intracranial disease control rate (IC-DCR) was measured. This revealed that of the 343 initial patients, 23% had brain metastases at baseline, and in these patients, IC-DCR was significantly higher in crizotinib-treated patients at 12 weeks as compared to standard chemotherapy, 85% versus 45%, $p < 0.001$, and at 24 weeks as well, 56% versus 25%, $p = 0.006$.

In another trial, led by Crinò et al., the ALK inhibitor ceritinib was examined for efficacy in a phase II trial of 140 patients with ALK-mutated NSCLC, who had previously received two or more previous treatment regimens, which included crizotinib [32]. The results of this trial showed that, overall, PFS was median 5.7 months (5.4–7.6 months, 95% CI), and among the 100 patients enrolled with brain metastases at baseline, the investigator-assessed intracranial response rate was 45% (23.1%–68.5%, 95% CI). These results are again encouraging and suggest that there may be potential benefit in second-line therapy for ALK-mutated tumors, even in patients with brain metastases.

A third clinical trial studying alectinib was published in 2017 and involved 303 patients randomly assigned to alectinib or crizotinib [33]. The rate of PFS was significantly higher in the alectinib-treated group as compared to the crizo-

tinib group, with hazard ratio for disease progression or death being 0.47 (0.34–0.65, 95% CI). In this study, 12% of patients in the alectinib group had CNS progression versus 45% of patients in the crizotinib group, yielding a hazard ratio of 0.16 (0.1–0.28, 95% CI).

Lastly, a trial involving brigatinib published in 2018 suggests that it may be a superior initial choice for ALK-mutated NSCLC as compared to crizotinib. This trial, by Camidge et al., studied 275 patients who were not previously treated with an ALK inhibitor and ALK-mutation-positive randomized to either brigatinib or crizotinib therapy [34]. Progression-free survival was significantly longer in the brigatinib group, with hazard ratio for disease progression or death 0.49 (0.33–0.74, 95% CI). In addition, the rate of intracranial response among these patients was 78% in those treated with brigatinib (52–94%, 95% CI) versus 29% in the crizotinib-treated group (11–52%, 95% CI).

Together, these four studies suggest that ALK inhibition not only has an effect on primary tumor response and progression free survival but also has a measurable and statistically significant effect on brain metastases. Importantly, these results suggest that there is a role for crizotinib and brigatinib initially and also a potential for superior therapy with alectinib and ceritinib (in the case of crizotinib failure) for treating these tumors, though further validation and randomized controlled trials to determine the most efficacious strategy remain to be done.

Less common driver mutations identified in patients with NSCLC are those occurring in MET (3%), BRAF (2%), ROS1 rearrangement (2%), Her2/MEK overexpression (2%), and the RET gene fusion (1%) [35]. For each of these, targeted molecular inhibitors of the aberrant gene product or pathway have been developed and have shown efficacy in clinical studies for patients with these mutations with these primary tumor types. However, larger-scale studies supporting their use in patients with NSCLC brain metastases are lacking. Thus, evidence for their efficacy comes from smaller case series or case reports. For instance, a case report was recently published describing a patient with BRAF-mutant primary NSCLC and brain metastases responding well to vemurafenib [36].

For some of these small-molecule inhibitors, the pharmacology of their transport into the CNS may be a limiting factor to their use in treating brain metastases. Interestingly, the RET inhibitor vandetanib is not transported by P-glycoprotein-based transporters and is therefore thought to have very poor CNS penetration. However, when combined with the mTOR inhibitor everolimus, penetration across the blood–brain barrier may be improved. A case report of a patient treated with concurrent vandetanib and everolimus with metastatic NSCLC to the brain reported that this combination of chemotherapies resulted in a reduction of intracranial disease burden and resulted in systemic response as well [37]. Novel strategies to improve CNS concentrations of targeted inhibitors, such as the combination of everolimus with vandetanib, may have benefit and improve survival in subgroups of patients with less common driver mutations such as these, but further study with larger cohorts, and in a prospective manner, will be required to ascertain this.

20.4 Emerging Role of Immunotherapies

Immunotherapies are among the most promising novel class of therapeutics now being employed against neoplastic diseases. Effectively functioning to reverse the immune evasion strategies employed by tumors, this class of drugs re-enables the body's immune system to target the tumor. Indeed, these strategies have proven successful, with recent clinical trials leading to their adoption as fist-line agents in certain NSCLC tumors [38]. The penetration of these agents across the blood–brain barrier has yet to be expressly determined, but as we will discuss below, there are recent reports and ongoing trials that indicate that patients with brain metastases may derive benefit from these treatments, and benefit has been shown in metastatic melanoma [39].

The first immune checkpoint inhibitors approved for the treatment of primary NSCLC were antibodies against program cell death-protein-1 (PD-1), namely, nivolumab and pembrolizumab. These inhibit a negative regulatory response of cytotoxic T cells, by preventing the ligand program cell death-ligand-1 (PD-L1) from binding PD-1. Nivolumab was approved in 2014 and is indicated for NSCLC that progressed on platinum-based chemotherapy or as first line in combination with ipilimumab [40, 41]. Pembrolizumab was approved in 2018 by the FDA as first-line therapy in patients with EGFR- or ALK-negative metastatic NSCLC with high PD-L1 expression (tumor proportion score ≥50%) [42]. A third antibody recently developed and active in this pathway is durvalumab, which instead inhibits PD-L1 and, as reported in the PACIFIC trial, extends progression-free survival for patients with stage II NSCLC, in tumors not amenable to surgical resection [43].

All of the aforementioned clinical trials excluded patients with brain metastases, but there are encouraging signs from preclinical studies that suggest that these therapies may play an important role for the treatment of brain metastases. Much of the data supporting the use of immunotherapies in the treatment of patients with metastatic disease to the brain has come from studies involving primarily patients with metastatic melanoma, and these have had encouraging results [44–46]. One phase II trial studied pembrolizumab in treating patients with NSCLC and melanoma brain metastases. In this trial, patients from the Yale Cancer Center, with measurable (5–20 mm), untreated, or progressive brain metastases, neurologically asymptomatic, were enrolled in an open-label study involving treatment with pembrolizumab [47]. Those taking corticosteroids were excluded from this study. Thirty-six patients were enrolled in this trial (18 melanoma, and 18 NSCLC), and of the NSCLC cohort, 16/18 (89%) had no prior treatment for brain metastases. Partial response was reported in 6/18 (33%) NSCLC participants, and 4/18 (22%) of NSCLC patients had complete intracranial response. No significant adverse effects were reported for the NSCLC cohort of patients. Following the success for this trial, multiple other studies involving brain metastases and immunotherapies in patients with NSCLC are underway. For instance, NCT02681549 is a phase II study evaluating the efficacy of pembrolizumab with bevacizumab in patients with untreated brain metastases from melanoma or NSCLC, with estimated completion date in May 2021.

Combination therapies involving immunotherapy and radiotherapy are also being investigated in the treatment of intracranial metastatic disease from NSCLC. Based on preclinical studies suggesting a potential interaction between the immune system and radiation response, these trials seek to take advantage of this effect by effectively using checkpoint inhibitors as synergistic radiosensitizers. NCT02978404 is a phase II clinical trial evaluating the combination of nivolumab and SRS in the treatment of brain metastases from metastatic renal cell carcinoma and NSCLC. Trial results are expected in June 2020. NCT02858869 is a phase I clinical trial designed to study the combination of pembrolizumab and SRS from patients with metastatic disease to the brain from melanoma or NSCLC. This trial has estimated completion date October 2020. NCT02696993 is a phase I and II clinical trial recruiting presently at MD Anderson Cancer Center, evaluating the safety and efficacy of nivolumab given either with radiation alone or with radiation and ipilimumab together for patients with NSCLC. Estimated primary completion date for this study is December 2020.

20.5 Conclusions

Overall, lung cancer is among the most common primary cancer, and an increased understanding of the molecular basis of disease has facilitated the development of novel chemotherapeutics for this disease. As we have discussed in this chapter, these therapies are increasingly showing efficacy in treating brain metastases for the target populations of patients whose primary tumor harbors the same mutations. Indeed, the traditional treatment modalities of neurosurgery and SRS have key roles in

the treatment of oligometastatic disease, but small-molecule inhibitors and combinations with immunotherapy are also promising treatments for metastatic lung cancers. In particular, multiple clinical trials will complete in 2020, and at this time further data about the combinations of immune checkpoint inhibitors and SRS will become available and potentially further change the practice of how metastatic lung tumors to the CNS are treated.

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Current Treatment Strategies in Breast Cancer Brain Metastases

21

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21.1 Introduction

Up to 15% of all patients with metastatic breast cancer (MBC) will develop brain metastases (BM) during their course of disease, making MBC after lung cancer the second most common cause of BM among solid malignancies [1]. Incidence of MBC BM has been rising over the last years commonly attributed to the tremendous progress of systemic therapy. This resulted in prolonged overall survival (OS) of MBC patients with human epidermal growth factor receptor 2 (HER2)-positive and hormone receptor (HR)-positive disease [2, 3] and a shift to more aggressive courses of MBC in patients recurring after optimal adjuvant treatment [4]. Further, advanced imaging methods including magnetic resonance imaging (MRI) are more broadly available, and patients presenting with only minor neurological symptoms receive earlier imaging. Screening of asymptomatic patients and in consequence the more frequent diagnosis of a- to oligosymptomatic patients might be further attributing to the increasing incidence of breast cancer (BC) BM patients. Prognosis of patients with BM remains poor with median OS times ranging from 2 to 16 months and differs greatly depending on the BC subtype [1].

In daily clinical practice, BC subtypes are classified as luminal, triple-negative and HER2-positive as defined by the expression of the oestrogen (ER) and/or progesterone receptor (PR) and HER2 overexpression as defined by immunohistochemistry and/or *HER2/neu* gene amplification [5, 6]. These subtypes have a significant impact on clinical prognosis [7]. Treatment of different BC subtypes differs substantially since endocrine therapy (ET) is the standard of care for luminal disease and HER2-targeted treatment plays a pivotal role in HER2-positive BC. Chemotherapy remains the backbone of treatment for triple-negative breast cancer (TNBC) patients, although interim results of the recently presented phase III trial Impassion 130 suggest a progression-free survival (PFS) and potential OS benefit if a programmed cell death ligand 1 (PD-L1) inhibitor is combined to chemotherapy in the first-line setting. Nevertheless, patients with triple-negative tumours are at great-

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est risk for being diagnosed with BM followed by patients with HER2-positive disease [8]. In addition to BM incidence, brain metastases-free survival (BMFS) was shown to differ between subtypes as well [9].

Treatment decisions in BM patients should be based on clinical characteristics such as Karnofsky performance score, age, number of BM and the status of extracranial disease combined in well-verified graded prognostic assessment score [10]. Local therapy (surgical resection, stereotactic radiosurgery (SRS) and whole-brain radiotherapy (WBRT)) remains the mainstay of treatment, especially for symptomatic patients with a need for rapid symptom relief [10, 11]. By contrast, about 20% of BC patients are diagnosed with asymptomatic BM which may have a better prognosis [12]. For these patients, systemic treatment has become an attractive alternative approach since long-term toxicity of WBRT can be postponed. In certain areas of BM, the blood–brain barrier (BBB) is disrupted and replaced by a blood–tumour barrier with higher fenestration of the endothelium allowing bigger molecules to penetrate into the brain parenchyma [13, 14]. Meanwhile, systemic anti-HER2 treatment was shown to achieve reasonable intracranial response rates, to prolong OS and to delay WBRT in asymptomatic patients with HER2-positive MBC BM [15–17]. In addition, in patients with symptomatic progressive BM on high cortisol doses, antiangiogenic therapy with the vascular endothelial growth factor (VEGF) targeting antibody bevacizumab may decrease oedema and allow for tapering corticosteroid therapy, thereby reducing treatment-related toxicity and improve quality of life [18].

21.2 Screening and Prevention

21.2.1 Screening

Historically, BM are diagnosed due to disease-related symptoms such as seizures, headache, nausea, emesis, vertigo and visual impairments. This may correlate with higher disease load at diagnosis and worse performance status compared with early detection, resulting in shorter survival. Supporting the notion that early BM detection in an a- to oligosymptomatic stadium may be beneficial, a recent comparison of 349 BC patients with newly diagnosed BM with 659 patients with non-small-cell lung cancer (NSCLC) revealed that BC patients presented with metastases of larger size, had more numerous lesions, were more likely to be symptomatic at presentation, and had higher risk of death due to neurologic reasons (37.3% vs 19.9%; $p < 0.001$) as well as a shorter time to neurologic death (HR = 1.54; $p = 0.01$) [19]. These data therefore suggest that early diagnosis of BM may be beneficial.

In the absence of randomized trials, cohort studies compared the effect of screening for BM with the standard non-screening approach in MBC [20, 21]. One analysis reported on 80 patients with HER2-pos. MBC without neurological symptoms who were screened for the presence of BM; in the 29 patients with occult BM, immediate WBRT was performed. The outcome of these patients was compared to a control group of 52 patients treated over the same time period who had received WBRT because of symptomatic BM. While the rate of patients dying from cerebral disease progression was lower in the screening population (16% vs. 48%; $p = 0.009$), OS from diagnosis of BM did not differ between the two groups (9 and 8.8 months, respectively). These results were mirrored by a study comparing the outcome of a screening cohort with a historic control group [20]. Out of 41 screened HER2-pos. MBC patients, 22% were diagnosed with occult BM. In the screening population, 16.7% died from BM progression as compared with 46.3% of non-screened BM patients; again, OS from BM diagnosis was comparable between the two groups (6.8 and 6.1 months, respectively). Of note, these studies were conducted before modern (i.e. brain-specific) systemic treatment approaches were developed.

In the LANDSCAPE study, upfront systemic therapy with the HER2-targeting tyrosine kinase inhibitor (TKI) lapatinib plus capecitabine yielded a response rate of 65.9% (95% CI 50.1–79.5) in patients with newly diagnosed BM and resulted in

a time to radiotherapy of 8.3 months [17]. As WBRT is associated with clinically relevant late toxicity [22], this secondary endpoint is regarded as clinically relevant. Of note, more than 40% of patients accrued to this study had no neurologic symptoms at diagnosis, suggesting the inclusion of a screening population. Therefore, the availability of specific systemic treatment options casts doubts on the traditional non-screening approach, and in the absence of randomized clinical data, screening in MBC patients at high risk for developing BM may be considered.

21.2.2 Prevention

Due to their low molecular weight, small molecule TKIs such as the first-generation, reversible HER2-TKI lapatinib were believed to pass the BBB, generating an opportunity of BM prevention. The phase III CEREBEL study randomized 540 patients (61% with prior trastuzumab exposure) to trastuzumab in combination with capecitabine or lapatinib plus capecitabine, but was terminated early due to poor accrual [23]. The incidence of BM as first site of relapse was defined as the primary study endpoint. All patients were required to have a brain MRI at baseline and patients with asymptomatic BM were excluded. Overall, no significant difference in the rate of patients with newly diagnosed BM was detected between the two study arms (3% lapatinib/capecitabine vs. 5% trastuzumab/capecitabine; treatment difference −1.6%; 95% CI −2% to 5%; $p = 0.360$); secondary endpoints (PFS; OS) favoured trastuzumab treatment, while numerically less serious adverse events were observed in patients receiving lapatinib plus capecitabine. Considering the activity of lapatinib plus capecitabine in newly diagnosed asymptomatic multiple BM as indicated in the LANDSCAPE study, these results suggest that due to the exclusion of patients with asymptomatic BM, CEREBEL excluded the population potentially achieving the largest benefit from lapatinib; in addition, these results are in line with experimental data suggesting that despite its low molecular weight, lapatinib does not cross an intact BBB to a clinically relevant extent [24].

The phase III CLEOPATRA study compared the former standard of care of docetaxel plus trastuzumab for the first-line treatment of HER2-positive MBC with docetaxel plus dual HER2 inhibition with trastuzumab plus pertuzumab [25]. In this study, combined antibody therapy yielded a clinically relevant prolongation of progression-free survival (PFS) from 12.4 to 18.5 months (HR 0.62; 95% CI 0.51–0.75; $p < 0.001$); in addition, OS was significantly prolonged as well [26]. A post hoc analysis revealed no significant difference in the overall rate of patients being diagnosed with BM as first site of disease progression between the two groups (12.6% docetaxel/trastuzumab/placebo vs. 13.7% docetaxel/trastuzumab/pertuzumab, n.s.) [27]; on the other hand, BMFS was significantly longer in patients receiving dual HER2 inhibition (BMFS 11.9 vs. 15.0 months; 95% CI 0.39–0.85; $p = 0.0049$). Overall, these outcomes suggest that, currently, systemic therapy cannot prevent the development of BM but better systemic treatment at least offers the chance for a delay of BM due to improved extracranial disease control.

21.3 Local Therapy of BC BM

Radiotherapy is still a very important treatment option for patients with BM. Neurocognitive decline is one of the major problems in long-term survivors with brain tissue atrophy, leukoencephalopathy and dementia. This is more often observed in patients with multiple BM and WBRT than in patients with oligo- or single metastases and SRS. Different radiotherapy treatment options can be offered to patients with BC BM according to extent of disease and performance status of the patients. To choose the adequate treatment for patients with BM, prognostic score models as recursive partition analysis (RPA score) and graded prognostic assessment (GPA score) have been developed [28].

21.3.1 WBRT

WBRT has been for a long time the golden standard for patients with BC BM. Development of distant metastases in the brain can be reduced, applying a homogenous dose to the entire brain tissue. There is an increase of median OS for 3–4 months after WBRT compared to 1 month without treatment and 2 months with corticosteroid treatment alone. The most common dose applied is 30 Gy in 10 fractions within 2 weeks. The actual indications for WBRT treatment are multiple BM in combination with disseminated disease, poor function and meningeosis carcinomatosis. If possible, WBRT with the "classical" opposed field technique should be avoided in case of longer life expectancy of the patient [29].

Based on the knowledge that most of the BM are described in more than 1 cm distance to both hippocampi, new treatment planning concepts performing WBRT with hippocampus sparing and neurocognitive follow-up are under evaluation [30]. Intensity-modulated radiotherapy (IMRT) with field-in-field dose application or volumetric-modulated arc therapy (VMAT) allows homogenous dose distribution to the whole brain, avoiding irradiation of both hippocampi without increasing risk of relapses. In regular follow-up controls, the neurocognitive status of theses patients has to be carefully evaluated [31].

21.3.2 WBRT Plus Boost

There are a lot of retrospective evaluations of WBRT in combination with SRS as a boost. Randomized controlled studies reported a significant survival benefit in patients with single metastasis and combined treatment. There might be as well a benefit in patients with oligo-metastases and good performance status treated with WBRT and SRS. Due to the increased integral dose, there is a higher risk of toxicity after WBRT and SRS [32].

To reduce the toxicity of a single shot boost after WBRT the combination of WBRT performed with IMRT or VMAT with a daily integrated boost to the site of metastases and hippocampus sparing can be a new treatment option in future studies. The goal of this treatment is not only to optimize local control of the metastases but also to reduce the number of intracranial distant relapses without neurocognitive decline.

21.3.3 SRS

SRS is a treatment option established at the Gamma Knife, at a LINAC and CyberKnife. Originally SRS is a high precision therapy with high doses of 18–20 Gy or more applied in a single fraction. After SRS, local control ranges between 70% and 80% for new and recurrent BM within a year. Size of the metastases treated with SRS should be smaller than 2–2.5 cm and they should not be located in eloquent areas. The number of metastases should be less than 5 at one time. With increasing size and number of metastases, the risk of development of an oedema after high-dose single shot radiotherapy increases, and to avoid neurological symptoms, corticosteroid treatments are obligatory. In the Aoyama study, the risk of distant recurrence in the brain during the first year was 63.7% in the SRS arm alone and 41.5% in the combined WBRT and SRS arm. Salvage therapy is more often required after SRS. The big advantage of SRS is the option to repeat the SRS several times for a limited number of new metastases and to postpone WBRT. The median OS is reported in both groups without a significant difference [33, 34].

21.3.4 Radiotherapy with Concomitant Chemotherapy or Targeted Therapy

A concomitant treatment with chemotherapy and radiotherapy should be avoided if possible. More toxic short- and long-term side effects are generated due to the open BBB. However, a combination of targeted therapy with radiotherapy seems to be possible without increasing toxicity.

21.4 Systemic Treatment of HER2-Positive BM

21.4.1 Lapatinib as Systemic Therapy for Progressive BM

A prospective single-arm phase II trial evaluated the role of lapatinib in patients with HER2-positive BC BM whose disease had progressed on prior local treatment consisting of WBRT in 95% of all subjects [35]. This population was heavily pretreated as 81% had received at least two prior lines of trastuzumab-based therapy. Overall, 242 patients were included; after amending the protocol, patients progressing on single-agent lapatinib were allowed to continue therapy with the combination of lapatinib plus capecitabine (n = 51; 50 patients evaluable for response). Response rate in patients on single-agent lapatinib was 6% (defined as a ≥50% reduction in the volumetric sum of all measurable central nervous system (CNS) lesions), and 21% had a reduction in their CNS lesions of ≥20%. PFS in the overall population was 2.4 months and was significantly longer in patients with disease shrinkage ≥20% (HR 0.51; 95% CI 0.36–0.72); OS was 6.4 months. In the lapatinib/capecitabine extension cohort, 20% of patients experienced a ≥50% reduction in the volumetric sum of all measurable CNS lesions, and 40% experienced disease shrinkage of ≥20%; PFS in this cohort was 3.65 months. As expected, the most common adverse effects were diarrhoea and rash on single-agent lapatinib and hand-foot syndrome and diarrhoea with the combination of lapatinib and capecitabine. In summary, this study is to date the largest prospective evaluation of systemic therapy in progressive HER2-positive BC BM and has defined the combination of lapatinib plus capecitabine as a potential treatment standard in this setting.

21.4.2 Lapatinib as Upfront Systemic Therapy

Based upon the activity of lapatinib and capecitabine in progressive BM, Bachelot et al. evaluated this combination as upfront therapy in previously untreated BM patients [17]. LANDSCAPE was designed as prospective single-arm phase II trial; in total, 45 patients with HER2-positive BC and newly diagnosed BM were included; as previously described, more than 40% of all patients had no neurological symptoms at diagnosis. CNS response rate was specified as the primary study endpoint and again defined as a 50% or greater volumetric reduction of CNS lesions in the absence of increased steroid use, progressive neurological symptoms or progressive extracranial disease. At a median follow-up of 21.2 months, CNS response rate in this selected population was 65.9% (95% CI 50.1–79.5) and PFS 5.5 months (95% CI 4.3–6). Other relevant secondary endpoints included time to WBRT (8.3 months; 95% CI 5.4–9.1) and OS (17.0 month; 95% CI 13.7–24.9). On the downside, 49% of all study subjects experienced grade 3/4 adverse events indicative of relevant toxicity, while no quality-of-life data are available. Despite this, LANDSCAPE is an important trial indicating the feasibility of an upfront systemic treatment approach in BC BM.

21.4.3 Trastuzumab-DM1

Trastuzumab passes an impaired BBB at the site of BM, while similar to lapatinib, no significant uptake of radioactively-tagged trastuzumab in healthy brain tissue was observed [36]. In addition, there is currently no proof of direct activity of trastuzumab monotherapy in newly diagnosed or progressing BM. This led to growing interest regarding the potential activity of trastuzumab-DM1 (T-DM1), an antibody-drug conjugate linking the anti-microtubule agent DM1 to trastuzumab.

The phase III EMILIA trial compared T-DM1 with lapatinib plus capecitabine in the second-line setting and in first-line patients progressing on adjuvant trastuzumab or within 6 months since the end of adjuvant immunotherapy; inclusion of patients with stable BM after local therapy was allowed [37]. In the overall population, T-DM1 was associated with a significant and clinically relevant advantage over lapatinib plus

capecitabine in terms of PFS (9.6 vs. 6.4 months; HR 0.65; 95% CI 0.55–0.77; $p < 0.001$) and OS (30.9 vs. 25.1 months; HR 0.68; 95% CI 0.55–0.85; $p < 0.001$). In patients with stable BM at baseline ($n = 95$), superiority of T-DM1 was maintained, although, not surprisingly, OS in absolute numbers was shorter in both arms (26.8 vs. 12.0 months; HR 0.38; $p = 0.008$) [38].

Meanwhile, several reports and case series suggested clinically relevant activity of T-DM1 in newly diagnosed or progressive BM. In a population of ten patients with HER2-positive BM, T-DM1 was administered as upfront therapy for newly diagnosed BM ($n = 2$) or upon progression of BM after prior local therapy ($n = 8$) [16]. Thus, this analysis allowed for an appraisal of the direct activity of T-DM1 in BM. A partial remission as defined by RANO BM response criteria (decrease in the sum of longest diameters of CNS target lesions of at least 30% sustained for at least 4 weeks in the absence of new lesions, increased corticosteroid dose and/or clinical deterioration [39]) was observed in three patients (PR, 30%), while disease stabilization of ≥6 months was reported in two additional subjects, resulting in a clinical benefit rate (complete remission, partial remission, stable disease ≥6 months) of 50%. In addition, two further patients experienced stable disease ≥3 months but <6 months. Of note, activity was not restricted to patients with newly diagnosed BM as one of the two responders and both patients with SD ≥6 months had progressive BM at baseline. At a median follow-up of 8.5 months, intracranial PFS was 5 months (95% CI 3.69–6.32), and median OS from initiation of T-DM1-based treatment had not been reached. Another retrospective study included 39 patients from five French centres [40]. Patients had received a median of two prior HER2-directed treatment lines for metastatic disease, and 36 patients had received prior local therapy as well, consisting mostly of WBRT (72%). In this pretreated population, a response rate of 44% was reported; median PFS was 6.1 months (95% CI 5.2–18.3). These clinical data are supported by a preclinical model of trastuzumab or T-DM1 at equivalent doses in female nude mice with BM [41]. Median survival in mice bearing BM generated with the luminal B/HER2-positive BT474 cell line was 28 days for trastuzumab and 112 days for T-DM1 (HR 6.2; 95% 6.1–85.84; $p < 0.001$). In addition, a significantly higher rate of tumour cell apoptosis was observed in the T-DM1 group.

In summary, these clinical and preclinical data suggest that T-DM1 harbours clinically relevant activity in MBC BM; the prospective phase II KIARA (Kadcyla In pAtients with bRAin metastasis) trial (NCT03203616) intended as prospective verification of this concept, however, was recently stopped due to poor accrual. Concurrent administration of T-DM1 and radiosurgery, on the other hand, may not be advisable as a rate of irradiation necrosis of 50% was observed in another small retrospective case series [42].

21.4.4 Other Systemic Treatment Approaches for HER2-Positive BM

Neratinib is a second-generation (irreversible) TKI of HER2 and epidermal growth factor receptor (EGFR). In the prospective, randomized, open-label phase III study NEfERT-T, 479 patients with HER2-pos. MBC were randomized to first-line therapy with paclitaxel either in combination with trastuzumab or neratinib [43]. The primary endpoint, PFS, was not different between the two arms (12.9 vs. 12.9 months), and grade 3/4 diarrhoea was more commonly observed in the neratinib group (30.4% vs. 3.8%). The participation of asymptomatic patients with a prior history of CNS metastases was allowed; in addition, asymptomatic patients with newly diagnosed BM were also eligible. At baseline, BM were present in 2.5% and 5.1% of patients in the neratinib and trastuzumab arms, respectively, and CNS progression was recorded in 8.3% of patients in the neratinib and 17.3% in the trastuzumab group (HR 0.48; 95% CI 0.29–0.79; $p = 0.002$). A competing risks model suggested that the 2-year estimated cumulative incidence of BM was 10.1% in patients receiving neratinib and therefore significantly lower compared with trastuzumab (20.2%; $p = 0.002$). While these results are intriguing and apparently in contradiction to CEREBEL, the design of the study does

not allow to clarify whether differences were due to a true prophylactic effect of neratinib or caused by the small imbalances between the two arms in terms of baseline BM rates; in addition, neratinib may be superior to trastuzumab regarding activity against pre-existing BM.

The direct activity of neratinib in HER2-positive BC BM was evaluated in a multicohort prospective phase II trial (TBCRC022) including 40 patients whose BM had progressed on prior local therapy (78% WBRT) [44]. In this study, however, activity of single-agent neratinib was disappointing with a CNS response rate of 8%; median PFS was 1.9 months. Another cohort of this phase II study evaluated the combination of neratinib and capecitabine (with upfront loperamide prophylaxis) [45]. Thirty-seven patients with progressive BM were included. A CNS response rate of 49% (95% CI 32–66%) was reported; PFS and OS were 5.5 and 13.5 months, respectively, indicating relevant clinical activity. On the downside, grade 3 diarrhoea was observed in 32% of patients despite prophylaxis.

Tucatinib (ONT-380) is a third-generation HER2 TKI. In contrast to lapatinib and neratinib, this drug has only minor inhibitory activity against EGFR resulting in a lower diarrhoea rate [46]. In a joint analysis of two phase Ib studies investigating different tucatinib-based combinations, the rate of patients with prolonged PFS (defined as PFS ≥16 months) was evaluated [47]. Overall, 22% of this heavily pretreated population achieved prolonged disease control. Of note, 50% of these patients had BM at baseline suggesting that the role of tucatinib in BC BM should be further investigated.

21.5 Systemic Treatment of BM Beyond the HER2-Positive Subtype

21.5.1 Chemotherapy

As early as 1986, Rosner et al. reported on a series of 100 consecutive BC patients treated with conventional chemotherapy for symptomatic BM with responses observed in 50% of all subjects [48]. Although this study was performed in an unselected population of different BC subtypes, no MRI was available for response assessment, and mainly historic chemotherapy regimens such as CFP (cyclophosphamide, 5-FU and prednisone) or CFP-MV (CFP, methotrexate and vincristine) were used; this study established that conventional chemotherapy offered activity in BC BM. In line with these data, single-agent high-dose methotrexate (MTX) yielded a response rate (RR) of 33% in BC patients as well [49].

In a phase II study of patients with BM from different primary tumours, 56 BC patients were treated with upfront cisplatin and etoposide [50]. Response rate (RR) was 37.5% with seven patients achieving complete response. While these results are of interest, again no information was provided regarding BC subtypes, and one third of the BC patients had not received any prior systemic therapy, suggesting the presence of a selected population. In another prospective phase II study, single-agent topotecan was administered in 24 BC BM patients as upfront chemotherapy [51]. Out of 16 patients evaluable, six had a complete or partial response. A similar study, however, yielded contradicting evidence; here, the activity of single-agent topotecan as first-line therapy in an unselected population of 30 MBC patients was low (RR 6%; PFS 2.3 months) [52]. Overall, these data suggest that single-agent topotecan is not a preferred treatment option in this setting.

Temozolomide (TMZ) is well-established in the treatment of primary brain tumours due to its ability to pass the BBB [53]. As TMZ has no significant activity against BC, however, only minimal activity of single-agent TMZ was observed in patients with BC BM (reviewed in [54]). In contrast, the combination of TMZ with capecitabine or cisplatin yielded response rates of 40% and 18%, respectively, but this may rather indicate the activity of the combination partner [55, 56]. Supporting this notion, Morikawa et al. administered a single dose of capecitabine 1.250 mg/m^2 to eight patients scheduled for neurosurgical resection of BM 2–3 h before the planned intervention [57]. A clinically significant—albeit highly variable—concentration of capecitabine and its metabolites within the

resected BM was observed. As outlined above, the potential activity of capecitabine in BM is also emphasized by the high response rates obtained with the combination of lapatinib and capecitabine in HER2-positive BC BM making capecitabine an attractive option for the treatment of BC BM.

A preclinical model analysed the permeability of paclitaxel and doxorubicin into BM [58]. In more than 2000 experimental BM, the uptake of ^{14}C-paclitaxel and ^{14}C-doxorubicin into BM was greater compared with healthy brain tissue but less than 15% of the uptake in extracranial metastases. Again, high variability in terms of tissue concentrations of these agents was observed between different metastases and within single BM; in addition, cytotoxic concentrations were only reached in a minority of lesions.

Activity of etirinotecan pegol (EP) was compared with treatment by physician's choice (eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or nab-paclitaxel) in pretreated patients who had received at least two prior chemotherapy regimens for metastatic disease in the prospective randomized phase III BEACON study [59]. OS was defined as the primary study endpoint and was not different between the two arms; a pre-planned subgroup analysis, however, reported a significant benefit in favour of EP in patients with liver metastasis (HR 0.73; 95% CI 0.59–0.89) and brain metastasis (HR 0.51; 95% CI 0.30–0.86). As a biological background, preclinical models suggested that EP may be able to cross the blood–tumour barrier, leading to preferential accumulation and retention in BM [60]. Based upon these results, EP is currently being evaluated in patients with stable BM within the ATTAIN trial (NCT 02915744). In order to fully assess the potential effect of EP in BM, however, studies in patients with newly diagnosed or progressive BM are strongly encouraged.

21.5.2 Endocrine Therapy

Two thirds of all BC belong to the luminal subtype defined by hormone receptor (HR) expression [61, 62]. These patients will usually develop BM less frequently compared to HER2-positive BC or TNBC with an incidence of about 7%; in addition, luminal BM typically occur late during the course of disease [9, 63]. As only limited data exist regarding the efficacy of ET in BC patients with BM, local therapy remains the treatment backbone to date [1]. So far, only case reports suggested that tamoxifen may offer intracranial activity [64–66]. Furthermore, two case reports indicated improved OS results when letrozole and anastrozole were administered after diagnosis of BM [67, 68]. Recently, results of a retrospective analysis conducted in a large single-centre cohort of 198 luminal BC patients with BM reported that continuing ET after diagnosis of BM is significantly associated with a longer OS [69]. While these data cannot prove a direct activity of ET in BM, results still warrant further evaluation of this approach in prospective trials.

Adding cyclin-dependent kinases (CDK) 4/6 inhibitors to endocrine therapy has increased PFS and response rates over ET alone to a clinically relevant extent in HR-positive/HER2-negative MBC [70]. While the CDK4/6 inhibitors palbociclib and abemaciclib both reached concentrations in rodent brains sufficient for enzyme inhibition, abemaciclib brain concentrations were reached at lower doses, and the drug may remain on target for a longer period of time [71]. This suggests that abemaciclib may be the preferred CDK4/6 inhibitor for trials of BC BM treatment and prevention as the brain distribution of palbociclib seems to be limited by the activity of efflux pumps [72]. Based upon these assumptions, a phase II clinical trial of abemaciclib in patients with newly diagnosed BM or BM progressing after prior local therapy in patients with HR-positive/HER2-negative and luminal B/HER2-positive BC is currently ongoing (NCT02308020) (www.clinicaltrials.gov); preliminary results suggested activity in the HER2-negative subset [73].

21.6 Leptomeningeal Carcinomatosis

BC is the most common cause of leptomeningeal carcinomatosis (LMC) among solid tumours [74]. In contrast to parenchymal BM, LMC is

more common in HR-positive and triple-negative BC as compared with the HER2-positive subtype [75]; lobular disease appears to be overrepresented among patients with LMC [76]. Clinically, LMC shows fast and profound clinical deterioration and is associated with short survival despite local, systemic and intrathecal treatment [77, 78].

Limited clinical data regarding the optimal treatment approach is available, and the majority of studies included patients of different BC subtypes or different solid tumours. Currently, radiotherapy remains the mainstay of treatment, while the role of intrathecal and systemic therapy is less well defined. In a multivariate model, a prospective observational study including 118 BC patients with LMC identified performance status and systemic therapy after LMC diagnosis as the only factors significantly associated with OS [79]. The same group analysed specifically the role of intrathecal chemotherapy in LMC patients as well [75]. In a series of 140 prospectively observed consecutive LMC patients, systemic therapy prolonged survival, while radiotherapy and intrathecal therapy had no impact on OS, although both methods alleviated neurological symptoms. Fifteen patients had received intrathecal liposomal cytarabine, and OS was not different from patents treated with intrathecal MTX. These results are well in line with a randomized study comparing intrathecal MTX with liposomal cytarabine in patients with LMC from different primary tumours [80]. Response rates and survival were comparable between the two arms, although the time to neurological deterioration favoured the liposomal cytarabine group (58 vs. 30 days; $p = 0.007$). In a phase II study of liposomal cytarabine in 56 BC patients, median survival was 88 days (range 1–515+ days), and 1-year survival rate was projected to be 9% [81], indicating limited clinical activity. However, in a recently presented randomised trial, intrathecal liposomal cytarabine significantly prolonged progression of LMC when added to systemic therapy in BC patients with newly diagnosed and untreated LMC [82]. Considering the combination of intrathecal chemotherapy and radiotherapy, a randomized study conducted in 35 BC patients observed no significant differences in terms of activity; neurological toxicity, however, was significantly higher in the combination group [83]. In contrast, several case reports and case series reported relatively favourable outcomes with intrathecal administration of chemotherapy [84, 85] or targeted agents such as trastuzumab [86]. Moreover, also systemic immunotherapy like pembrolizumab, a PD-1 inhibitor, might be active in BC patients with LMC [87]. In summary, it may be reasonable to assume that the potential benefit of intrathecal treatment is restricted to patients without LMC plaques as the penetration of intra-CSF agents into such plaques is limited.

21.7 Summary and Outlook

Despite recent advances, there is still an unmet clinical need for developing new treatment approaches given the limited survival prognosis of BC patients with BM. The combination of CDK4/6 inhibitors with standard endocrine therapy was shown to prolong PFS in ER-positive/HER2-negative MBC patients by blocking cell-cycle progression [70]. Among this class of drugs, abemaciclib was suggested to cross the BBB to a clinically relevant extent and may therefore be active in BM [71]. Furthermore, immune-checkpoint inhibitors had interesting activity in PD-L1-positive, TNBC patients, which has further been increased by adding chemotherapy [88, 89]. Of note, immune inhibitory pathways such as PD-L1 are upregulated in the tumour inflammatory microenvironment of BM [90, 91] and may therefore provide a potential treatment target in the large group of TNBC patients with BM. Consequently, targeted therapies such as CDK4/6 inhibitors and immune-checkpoint inhibitors are of high clinical interest and clearly should be considered in future trials of systemic treatment for BC patients with BM.

In summary, the interest in optimizing the management of patients with BC BM has increased in recent years. While local treatment still plays a pivotal role in the management of BM, systemic therapy was recently shown to yield clinically relevant activity. With novel treatment approaches upcoming, a further improvement in the outcome of patients with this devastating complication is expected.

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Management of Melanoma Brain Metastasis

22

C. Boutros and C. Robert

In the past decades, local therapies including surgery, whole-brain radiation therapy, and stereotactic radiosurgery were considered the pillar of metastatic brain metastasis (MBM) management, although their benefit in terms of overall survival was never demonstrated. Advances in understanding the biology and molecular pathways implicated in melanoma biology and consecutive improvements in metastatic melanoma treatment using anti-BRAF-based targeted therapies for BRAFV600-mutant melanoma as well as immune checkpoint immunotherapy have generated considerable interest in evaluating these novel systemic therapies in treating MBM (Table 22.1).

22.1 Targeted Therapies

In the phase 2 BREAK-MB study, the BRAF inhibitor dabrafenib showed a clinical activity and an acceptable safety profile in patients with BRAFV600E-mutant melanoma with brain metastases [1]. Among 172 patients enrolled in the study, 74 patients had not received previous local treatment for brain metastases (cohort A) and 65 had progressive brain metastases after previous local treatments (cohort B). The overall intracranial response was achieved independently of whether previous local treatment for brain metastases was administered or not (in 39 and 31% of patients, respectively). The median progression-free survival (PFS) was around 16 weeks in both cohorts, and the overall survival (OS) was greater than 31 weeks. Fewer patients with BRAFV600K-mutant melanoma achieved an overall intracranial response than did those with BRAFV600E-mutant melanoma (in 7% and 22% of patients treated in the cohorts A and B, respectively). The most discriminating prognostic factor was the concentration of serum lactate dehydrogenase at baseline: in both cohorts, patients with high LDH had lower response rates and shorter median progression-free survival as well as overall survival. Adverse events (AEs) of all grade occurred in 82% of patients. Grade 3 or 4 AEs occurred in 22% of patients. Overall, 26% of patients had pyrexia of any grade and 6% had cutaneous squamous-cell carcinoma due to the

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Table 22.1 Review of the clinical studies evaluating systemic therapies for melanoma brain metastases: evaluation of intracranial responses, median overall survival (OS), and progression-free survival (PFS)

References	Study type	Study population	Number of patients	Treatment	Intracranial response	Median OS	Median PFS (months)	Median follow-up (months)
Long et al.	BREAK-MB (phase 2)	**Cohort A:** no previous local treatment **Cohort B:** previous local treatment	**Cohort A:** 89 **Cohort B:** 83	Dabrafenib	**Cohort A:** 39% **Cohort B:** 31%	**Cohort A** (Val600Glu BRAF mutant): 33.1 **Cohort A** (Val600Lys BRAF mutant): 16.3 **Cohort B** (Val600Glu BRAF mutant): 31.4 **Cohort B** (Val600Lys BRAF mutant): 21.9	Longer than 16 weeks	At least 4 months
Davies et al.	COMBI-MB (phase 3)	**Cohort A:** BRAFV600-E, asymptomatic, no previous local treatment. **Cohort B:** BRAFV600-E, asymptomatic, with previous local treatment **Cohort C:** BRAFV600D/K/R, asymptomatic, with or without previous local brain therapy **Cohort D:** a BRAFV600D/E/K/R, symptomatic, with or without previous local brain therapy	**Cohort A:** 76 **Cohort B:** 16 **Cohort C:** 16 **Cohort D:** 17	Dabrafenib + trametinib	**Cohort A:** 58% **Cohort B:** 56% **Cohort C:** 44% **Cohort D:** 59%	**Cohort A:** 10.8 **Cohort B:** 24.3 **Cohort C:** 10.1 **Cohort D:** 11.5	**Cohort A:** 5.6 **Cohort B:** 7.2 **Cohort C:** 4.2 **Cohort D:** 5.5	8,5
Margolin et al.	BMS-734016 (phase 2)	**Cohort A:** asymptomatic, without corticosteroids **Cohort B:** symptomatic, with stable doses of corticosteroids	**Cohort A:** 51 **Cohort B:** 21	Ipilimumab	**Cohort A:** 16% **Cohort B:** 5%	**Cohort A:** 7.0 **Cohort B:** 3.7	**Cohort A:** 2.7 **Cohort B:** 1.3	At least 3 months

Di Giacomo et al.	NIBIT M1 (phase 2)	Asymptomatic	86	Ipilimumab + fotemustine	40%	12.7	3.0	39.9
Long et al.	ABC (phase 2)	**Cohort A and B:** asymptomatic, no previous local treatment **Cohort C:** failed local therapy or symptomatic	**Cohort A:** 36 **Cohort B:** 27 **Cohort C:** 16	Cohort A: ipilimumab + nivolumab Cohort B: nivolumab Cohort C: nivolumab	Cohort A: 44% Cohort B: 20% Cohort C: 6%	6-month: **Cohort A:** 76% **Cohort B:** 59% **Cohort C:** 44%	6-month: **Cohort A:** 50% **Cohort B:** 29% **Cohort C:** 0	17
Tawbi H et al.	CheckMate 204 phase 2	Asymptomatic	94	Ipilimumab and nivolumab	57%	Not reached OS rate: 82.8% at 9 months	Not reached PFS rate: 56.6% at 9 months	14
Goldberg et al.	Small phase 2	Asymptomatic, untreated	23	Pembrolizumab	22%	17	2	34

paradoxical activation of the MAPK pathway. The three most frequent serious adverse events were pyrexia (in 6% of patients), intracranial haemorrhage (in 6% of patients; one considered to be treatment-related), and squamous-cell carcinoma (in 6% of patients).

The combination of dabrafenib and the MEK inhibitor trametinib improved the OS when compared with dabrafenib monotherapy in advanced melanoma without brain metastases [2, 3]. Similarly, this combination was evaluated in patients with BRAFV600-mutant MBM in the phase 2 COMBI-MB study (41). Among 125 patients enrolled in the study, 76 patients had a BRAFV600E-positive, asymptomatic MBM, without previous local brain therapy (cohort A); 16 patients had a BRAFV600E-positive, asymptomatic MBM, with previous local brain therapy (cohort B); 16 patients had a BRAFV600D/K/R-positive, asymptomatic MBM, with or without previous local brain therapy (cohort C); and 17 patients had a BRAFV600D/E/K/R-positive, symptomatic melanoma brain metastases, with or without previous local brain therapy (cohort D). Patients in cohorts A, B, and C had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and patients in cohort D, an ECOG performance status of 0, 1, or 2. The intracranial response was achieved in 58%, 56%, 44%, and 59% of patients in cohort A, B, C, and D, respectively. Extracranial responses were obtained in 55%, 44%, 75%, and 41% of patients in cohort A, B, C, and D, respectively. Overall responses were observed in 58%, 56%, 44%, and 65% in cohort A, B, C, and D, respectively.

The median PFS was 5.6 months and the median OS was 10.8 months in the cohort A. AEs of any grade were observed in 98% of patients, with 48% reporting one or more grade 3 or 4 AE. The most frequent grade 3 or 4 AEs were pyrexia (in 3%) and headache (in 2%). The most frequent serious adverse events attributed to the treatment were pyrexia for dabrafenib (in 6% of patients) and decreased ejection fraction for trametinib (in 4% of patients). Dose interruptions and reductions attributed to AEs were observed in 50% and 22% of patients, respectively. Discontinuations occurred in 10% of patients, mostly due to decreased ejection fraction (in 3%).

Altogether, targeted therapy demonstrated an efficacy in MBM, but the intracranial response rates as well as the survival benefit are not as high or prolonged than in patients with metastatic BRAF-mutant melanoma without brain metastases where response rates are around 70% and median overall survival around 33 months [3].

22.2 Immunotherapy

Ipilimumab improved OS in advanced melanoma [4, 5]. In a phase 3 study, ipilimumab was administered with or without a glycoprotein 100 (gp100) peptide vaccine and was compared with gp100 alone in patients with previously treated metastatic melanoma [5]. In this study, 11% of patients treated with ipilimumab had brain metastases. Hazard ratios for death in patients with brain metastases were similar to those of patients without brain metastases (0.76 [0.38–1.54]). In the phase 2 BMS-734016 study, ipilimumab showed activity in patients with advanced melanoma and small, asymptomatic brain metastases [6]. This study enrolled 72 patients with 51 patients neurologically asymptomatic and not receiving corticosteroid treatment at study entry (cohort A) and 21 symptomatic patients on a stable dose of corticosteroids (cohort B). The intracranial disease control was achieved in 24% and 10% of patients in cohort A and B, respectively. The median OS was 7.0 months in cohort A and 3.7 months in cohort B. In cohort A, the OS was 55% at 6 months, 31% at 12 months, and 26% (14–39) at 24 months. In cohort B, the OS was 38% at 6 months, 19% at 12 months, and 10% at 24 months. The most frequent AEs were fatigue, diarrhoea, nausea, headache, rash, and pruritus. The most frequent grade 3 AEs were diarrhoea, fatigue, dehydration, hyperglycaemia, and increased concentrations of serum aspartate aminotransferase. The most common neurologic events possibly attributed to ipilimumab

were grade 1 and 2 headache and dizziness. One patient had grade 4 brain haemorrhage attributed to metastatic melanoma and possibly to ipilimumab.

Ipilimumab combined to fotemustine was evaluated in the phase 2 NIBIT-M1 study, because fotemustine could cross the blood-brain barrier and act against MBM [7]. Eighty-six patients were included in the study. Among them, 20 patients had brain metastases. Patients with neurologic symptoms requiring immediate local intervention were excluded. Fifty percent of patients with asymptomatic MBM achieved immune-related disease control; 25% had partial or stable intracranial response, and 25% had complete intracranial response by scan. With a median follow-up of 39.9 months, the median OS and the 3-year survival rates were 12.9 months and 28.5% for the whole study population and 12.7 months and 27.8% for patients with brain metastases, respectively [8]. Median immune-related (ir) progression-free survival (irPFS) was 4.5 and 3.4 months, respectively, for the whole population and for patients with brain metastases; median brain PFS was 8.3 months in the whole population and 3.0 months in patients with brain metastases. Eighty-seven percent of the whole population had all grade AEs, whereas 55% had grade 3 or 4 AEs with the most frequent being myelotoxicity (thrombocytopenia in 24% patients and neutropenia in 19%). Grade 3 or 4 elevation of alanine aminotransferase or aspartate aminotransferase was observed in 24% patients.

The follow-up phase 3 NIBIT-M2 study was subsequently initiated to evaluate fotemustine versus the combination of fotemustine and ipilimumab versus the combination of ipilimumab and nivolumab in untreated, asymptomatic MBM [9]. Results are pending.

The activity of ipilimumab in combination with nivolumab versus nivolumab monotherapy in MBM was evaluated in the phase 2 ABC study, based on the improved response rates and progression-free survivals of these drugs in clinical studies [10]. Among the 66 patients enrolled in the study, 50 patients were asymptomatic and had not received previous local treatment for brain metastases. Half of them received the combination of nivolumab and ipilimumab (cohort A) and half received nivolumab monotherapy (cohort B). Sixteen patients with neurological symptoms and/or with leptomeningeal disease or who had failed local therapy received nivolumab monotherapy (cohort C). 44%, 20% and 6% of patients achieved intracranial response in cohorts A, B, and C, respectively. The 6-month OS was 76%, 59%, and 44% in cohorts A, B, and C, respectively. The intracranial response in cohort A was 53%, whereas it was 16% in patients previously treated with BRAF inhibitors. These results suggest that nivolumab combined to ipilimumab had reduced activity in patients who progressed on BRAF inhibitors. Grade 3 or 4 AEs in cohorts A, B, and C were 68%, 40%, and 56%, respectively.

The safety and efficacy of the combination of nivolumab and ipilimumab was further evaluated in the phase 2 CheckMate 204 study [11] on 75 patients with asymptomatic MBM who received the combination. With a median follow-up of 6.3 months, the intracranial objective response rate was 56% with 19% of patients in complete response, 37% in partial response, and 8% with a stable disease for more than 6 months. Intracranial and extracranial responses were largely concordant. The median time to intracranial response was 2.8 months. With a median follow-up of 9.2 months, the intracranial response rate was 55% including 21% complete responses. Median PFS was not reached. The 6-month PFS was superior to 60%. AEs of any grade occurred in 96% of patients and grade 3 or 4 AEs in 52% of patients. The most frequent AEs were cutaneous (in 76%), general (in 60%), digestive (in 59%), endocrine (in 39%), and nervous (in 37%). Headache was the most frequent AEs (in 25%) and it was grade 3 or 4 in 4% of patients.

Pembrolizumab alone was evaluated in a small phase 2 study. Patients with melanoma or non-small-cell lung cancer and untreated brain metastases were included [12]. Among the 18 patients with melanoma who were treated with pembrolizumab, 22% achieved a durable brain metastases response. Neurological responses were durable (4.0 months [n = 2], 7.0 months [n = 1], and 10.0 months [n = 1] at the time of

data cutoff). All responses were ongoing at the time of data analysis. The best systemic response was complete or partial response in 22 of patients (2 complete responses and 2 partial responses). The safety profile of pembrolizumab was acceptable, with mostly grade 1 or 2 AEs; although 6% of patients in the melanoma cohort had a grade 3 elevation of aminotransferases, 17% had clinically significant neurological AEs including transient grade 3 cognitive dysfunction and grade 1 or 2 seizures.

Combination of targeted therapy or immunotherapy with radiotherapy (all brain or stereotactic radiosurgery, SRS) has not been prospectively evaluated.

Some uncontrolled retrospective studies suggest that combining targeted therapy immune checkpoint immunotherapy with radiotherapy is safe and effective in patients with MBM [13–15]. Controlled prospective studies are urgently needed to evaluate these combinations.

22.3 Clinical Study Design Issues

Clinical trials evaluating MBM as compared to those performed on patients with extracranial melanoma metastases pose several problems due to the vulnerability of the patients, specific clinical evaluation issues, and potential drug interactions with anti-epileptic agents and/or corticosteroids.

First, it is now well known that immunotherapy may result in unusual responses manifested by an initial transient increase in tumour burden before response or the appearance of new lesions in patients with responding baseline lesions that lead to the development of the immune-related response criteria (irRC), including the bidimensional tumour measurement and the measurements of new target lesions [16]. Recently, immune-based therapeutics (iRECIST) criteria have been proposed to provide consistency in design and data collection in immunotherapy studies and ultimately validate guidelines [17]. In iRECIST, new lesions are evaluated as per RECIST 1.1. but are reported separately on the case report form and are not included in the sum of lesions for target lesions identified at baseline, and disease progression has to be confirmed. This approach allows delayed responses that occur after pseudoprogression to be identified. Additional efforts have been made with the development of the immune-modified RECIST (imRECIST) criteria based on studies evaluating atezolizumab data from studies [18]. imRECIST includes unidimensional tumour measurement with up to five target lesions (two per organ as per RECIST v1.1). New lesions are added to the total tumour burden with the sum of the target lesions when measurable. Moreover, progression in non-target lesions does not define progressive disease. The median PFS and disease control rates obtained using imRECIST are longer and higher, respectively, than when using RECIST v1.1.

Concerning MBM, it is important to mention that recommendations for the evaluation of response and progression criteria of brain metastases have been developed by the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) working group [19]. MRI and CT scans were allowed for tumour evaluation. Two to five target lesions were allowed provided that they had two perpendicular diameters superior to 10 mm. Complete response required the disappearance of all lesions for at least 4 weeks without corticosteroids. Partial response required a $\geq$30% decrease in the sum of longest diameter of target lesions defined at baseline, sustained for at least 4 weeks, with stable or decreased doses of corticosteroids. Progressive disease was defined as $\geq$20% increase in the sum of longest diameter of target lesions and at least one lesion increasing in size by 5 mm or more. An increase in corticosteroid doses without clinical deterioration did not indicate progression. These new radiologic criteria allow a uniform evaluation of clinical responses and will hopefully facilitate study designs as well as more objective evaluation of patients' benefit.

In conclusion, we now have systemic therapies that are effective for treating MBM. The most promising treatment seems to be the combination of nivolumab and ipilimumab, albeit associated with a high rate of adverse events. The objectives are now to develop more clinical trials

for MBM and to evaluate new drugs and combinations with a priority on exploring the optimal designs to combine or sequence systemic therapies with SRS.

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Miscellaneous Metastases

23

Andrew Dhawan and David Peereboom

23.1 Introduction

As discussed in the previous subsections of this book, CNS metastases arise primarily from the breast, lung, and melanoma primary tumors, but they can arise from virtually any tumor type, though less commonly. This chapter focuses on the most common of these less common primary tumors metastatic to the CNS. In particular, we begin with a discussion on renal cell carcinoma (RCC), followed by discussions on the presentation and management of metastatic CNS disease from thyroid cancers, gastrointestinal cancers, germ cell tumors, gynecologic tumors, and hematopoietic malignancies.

For each of these tumor types, we endeavor in this chapter to discuss the current standard of care in management, as well as the relevant evidence. In general, the management of metastases for each of these tumor types is related to (i) their pattern of dissemination in the CNS, (ii) patient performance status, (iii) their responsiveness to chemotherapy and radiation, and (iv) patient preferences. Understanding the variation between each of these for these primary tumor types for their CNS metastases is the key to understanding their management. Much of the evidence for the treatments comes from retrospective studies, as the number of patients with CNS metastases from these uncommon sites is small, limiting the statistical power of any prospective study. Evidence for the treatments presented comes from the largest data sets, the most recent evidence, and those studies which have influenced practice patterns significantly.

23.2 Renal Cell Carcinoma

As mentioned above, following neoplasms of the breast, lung, and melanocytes, RCC is the next most common primary tumor to metastasize to the brain. Data from four relatively large studies estimate the incidence at 5.5–11% of all patients with RCC, and with a male predominance, and 1–2-year average survival [1–4].

No standardized guidelines or protocols currently exist for the management of RCC brain metastases. Moreover, despite the fact that the primary tumor in RCC is often radioresistant itself, SRS is highly effective in the treatment of brain metastases from this primary tumor [5]. In one retrospective study of 2312 RCC CNS metastasis patients of whom 35% received SRS, intracranial radiation was associated with statistically significantly improved overall survival [5]. In addition, SRS provides effective tumor control in approximately 96% of patients, associated with a median survival of 15 months [6]. More recently, a report by Barata et al. presented at

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the 2018 American Society of Clinical Oncology Genitourinary Cancer Symposium reported that in a cohort of 95 patients with metastatic clear cell RCC (some of whom were also treated with concurrent systemic therapy), 85% of patients achieved local control with SRS [7]. The efficacy of radiation in this disease appears to be limited to SRS, with an earlier report by Mori at al. in 2000 addressing the question of whether whole-brain radiation therapy (WBRT) could improve survival alongside SRS in metastatic RCC [8]. This study analyzed 52 brain metastases in 35 patients, of whom 28 patients also underwent whole-brain radiotherapy [8]. WBRT did not prevent the development of new remote tumors, and SRS alone showed good tumor control [8]. That is, the addition of WBRT to SRS did not prolong survival in this cohort of patients [8]. This lack of benefit of WBRT suggests that there is relative radioresistance of RCC to external beam radiotherapy.

Often patients with metastatic clear cell RCC that have CNS metastases also have a burden of disease at other metastatic sites, necessitating the use of systemic therapy for these sites [9]. Moreover, an increased understanding of the genomic drivers of clear cell RCC helps guide the choice of systemic therapy, although the role of these drivers as potential targets in the treatment of CNS metastases has not been studied extensively [9]. A recent review presented a decision-making algorithm for the treatment of metastatic clear cell RCC, which involves first considering a cytoreductive nephrectomy if kidney is present, as well as a metastasectomy, if possible [9]. Following this, first-line chemotherapies, including bevacizumab and interferon alpha, high-dose IL-2, pazopanib (tyrosine kinase inhibitor), sunitinib (tyrosine kinase inhibitor), or temsirolimus (mTOR inhibitor), can be used [9]. Second-line and later agents include axitinib (tyrosine kinase inhibitor), cabozantinib (tyrosine kinase inhibitor, specific to c-Met and VEGFR2), lenvatinib (VEGFR1-3 inhibitor) and everolimus (mTOR inhibitor), or nivolumab (anti-PD1) [9]. Other agents include everolimus and sorafenib (tyrosine kinase inhibitor) [9]. The question of the interaction of these agents with other treatments for patients with brain metastases was recently addressed by Barata et al., who reported that, in the setting of patients with CNS metastases undergoing SRS, systemic therapy could be continued and that these patients do not experience harm for undergoing both SRS and chemotherapy concurrently [7]. Of note, this study included patients taking systemic therapies, including more novel agents such as PD1 inhibitors, alongside VEGF inhibitors and mTOR inhibitors, which themselves may add benefit to the treatment of CNS metastases [7]. Interestingly, Chen et al. reported that, in a cohort of 260 patients with brain metastases from renal carcinoma, non-small-cell lung cancers, and melanomas, SRS combined with immune checkpoint blockade was associated with decreased incidence of new brain metastases and a favorable overall survival [10]. However, this result attained statistical significance only in a pooled analysis, and just 12.6% of study participants had RCC, which did not provide enough discriminatory power to show any benefit [10]. Certainly, however, this remains an area of significant research interest, and future studies also looking at dosing regimens for combined modality treatments, as well as larger patient cohorts, may provide more insight.

Prognostic factors for patients with metastatic RCC to the CNS were reported by Sperduto et al., in 2018, and stated that KPS, the presence of extracranial metastases, the number of brain metastases, and hemoglobin at the time of diagnosis of brain metastases were significant prognostic factors [11]. In addition, among six drug types studied, only cytokine use was associated with improved survival [11]. Sperduto et al. also reported that patterns of care in the management of metastatic RCC to the brain have changed with fewer patients receiving whole-brain radiation therapy and more patients receiving SRS alone, potentially due to the accumulating evidence for SRS alone, as described above [11]. Also, importantly for prognostication, the authors of this study reported neurological causes of death were only half as common as non-neurologic causes of death in these patients [11].

23.3 Thyroid Cancers

A rare site of metastatic disease from a primary thyroid malignancy is the brain, and a comprehensive report by Chiu et al. in 1997 surveyed 47 cases of brain metastases from thyroid cancer, with 15% of these cases having brain metastases at the time of presentation [12]. In this cohort, 68% of the primary thyroid malignancies were differentiated, 23% were anaplastic, and 9% were medullary [12]. The median survival was just 3.8 months, underscoring the poor prognosis of patients with thyroid cancer metastatic to the brain. In this series, no survival benefit was obtained from the use of radioactive iodine, EBRT, or chemotherapy [12]. The only survival benefit shown arose from surgical resection of the metastatic lesions (median survival 16.7 months vs. 4.7 months with no treatment), although this study is limited by its retrospective design and potential for selection bias [12].

A second relatively large and more recent cohort reported by Choi et al. in 2016 included 37 patients diagnosed with brain metastases from differentiated thyroid cancer between 1995 and 2014 [13]. This study revealed that most patients with brain metastases from their thyroid cancers also had lung metastases, and in fact, this was the most common cause of death [13]. Despite this observation, those treated for their brain metastases had improved survival compared to those who did not receive treatment [13]. Among patients treated with surgery or radiosurgery for metastatic lesions, the median survival was 31 months, as compared to 5 months for those who did not receive either of these treatments [13].

Choi et al. also used the data from their cohort to define prognostic factors for this subset of patients with thyroid cancers and showed that age, KPS, number of brain metastases, and the absence of previous distant metastases prior to brain metastases were all independently associated with survival [13]. They suggest the use of these prognostic factors to define which patients should undergo more aggressive management involving surgery or radiosurgery for treatment of brain metastases [13].

23.4 Gastrointestinal Cancers

Among gastrointestinal cancers, CNS metastases are relatively rare; in esophageal and colorectal cancer, CNS metastases have an incidence of approximately 4%, and for pancreatic and gastric cancers, the reported incidence is 1% [14]. While standard recommendations for the management of brain metastases from primary gastrointestinal tumors have not been defined due to the paucity of clinical studies in these patients, here we summarize studies of large cohorts reporting how these patients have been treated and their outcomes.

23.4.1 Esophageal Cancers

The presence of brain metastases in esophageal cancers correlates with the presence of other metastatic sites [15]. In addition, in approximately half of these cases, there are multiple metastases, and the median survival of patients with brain metastases from esophageal tumors was 5 months [15]. Screening for metastatic disease of the brain in esophageal cancers is not advised due to the rarity and poor prognosis of esophageal cancer brain metastases and the lack of overall survival benefit [16].

Surgical resection of brain metastases for these patients is associated with increased survival, although no controls were provided to assess the validity of this association, and these patients may have initially had a more favorable prognosis [15]. In particular, these aggressively treated patients were more likely to have solitary brain metastases and typically did not have any additional metastatic burden at the time of treatment [15].

23.4.2 Gastric Cancers

In contrast to patients with esophageal cancers, patients with gastric cancers more often than not present with metastatic disease and have an incidence of just 1% for CNS metastases. Among patients found to have metastatic cancers to the CNS, most already had other extracranial metastases. Similar to esophageal

tumors, aggressive surgical resection or SRS (in conjunction with WBRT) for these brain metastases improves survival [17–20]. Multiple other reports have also supported this, with a recent cohort of 16 patients treated in Poland found to have an overall survival benefit with aggressive treatment [21]. More specifically, this study reported that patients who received WBRT after neurosurgery or WBRT and SRS had a survival benefit, with median overall survival 12.3 months [21]. A similar report from MD Anderson Cancer Center reported that in a cohort of 19 patients with an overall survival comparable to that of the Polish group, there was a statistically significant survival benefit with WBRT combined with surgery and steroids, as compared to those managed with steroids alone (54 vs. 7 weeks) [22].

23.4.3 Pancreatic Cancers

Pancreatic cancer is among the most aggressive gastrointestinal tumor types, with most primary tumors already metastasized to distant sites at diagnosis. Metastasis from pancreatic adenocarcinoma to the brain is extremely rare with an incidence of just 0.33% of patients [23]. Given the radioresistant nature of pancreatic adenocarcinoma and recent case reports suggesting that WBRT and SRS do not tend to provide significant benefit to patients with brain metastases from this primary, these are typically not recommended treatments [24]. Surgery for selected patients with brain metastases and controlled primary tumors may be associated with improved survival, but evidence arising from significant numbers of patients is lacking [24]. Overall, in pancreatic cancer, brain metastases are a relatively rare and poor prognostic sign, and there may be benefit with aggressive surgical treatment if the primary tumor is controlled [24].

23.4.4 Colorectal Cancers

Colorectal cancers are common among the general population, yet brain metastases from this primary tumor remain relatively rare. While the prognosis of colorectal cancer is generally better than other gastrointestinal malignancies, the presence of brain metastases reduces the 5-year survival to just 8% with a median survival of 3.2–8.3 months [14]. Aggressive neurosurgical intervention followed by whole-brain radiotherapy is associated with a survival benefit [25, 26]. Importantly, despite the presence of metastases outside the CNS, these benefits in survival were retained with aggressive treatment of CNS metastases, as reported by one study with 48 patients, showing improved survival with surgery and WBRT, as compared to surgery alone [27].

The role of chemotherapy in the management of brain metastases from colorectal cancer has not been definitively established. In one retrospective study involving 118 patients from South Korea, patients who had received surgery or radiation for CNS metastases and then received chemotherapy after brain metastasis exhibited improved survival versus those who did not (12.4 vs. 3.1 months) [28]. The authors state that on this basis, patients who are naïve to oxaliplatin or irinotecan may benefit if treated with this after the development of brain metastases to improve survival [28]. Another retrospective study of 49 patients, however, observed that patients with later development of brain metastases tend to do worse a priori, perhaps due to these patients having received more chemotherapy [29].

23.5 Germ Cell Tumors

Germ cell tumors may be divided into two histologic classes: seminoma and non-seminoma [30]. Management strategies for these two distinct subtypes differ significantly, and in this section, we focus our discussion on non-seminomatous germ cell tumors (NSGCT), as these represent the vast majority of all germ cell tumors metastatic to the CNS [30]. Current standard treatment for metastatic NSGCT consists of four cycles of etoposide and cisplatin or three cycles of bleomycin, etoposide, and cisplatin [31–33]. Early studies revealed that germ cell tumors metastatic to the brain occurred in approximately 10–15% of all patients

[34]. However, more recent data suggest the incidence is closer to 1–2%, since the era of modern chemotherapeutic regimens, including a platinum-based agent, has entered clinical use [35].

A recent study of 523 men with brain tumors from 46 centers in 13 countries showed that poor prognostic factors among patients with metastatic NSGCT to the brain included the presence of liver or bone metastases, elevations of alpha-fetoprotein, elevations of human chorionic gonadotropin, and primary mediastinal non-seminoma [36]. Patients with metastatic NSGCT can be separated into those with brain metastases present at initial diagnosis and those with brain metastases occurring later in their disease course [36]. Of the patients who had brain metastases at the time of initial presentation, 94% had concurrent pulmonary metastases, and 99% of these patients received chemotherapy [36]. Multimodality treatment and high-dose chemotherapy both were not associated with statistically improved survival, as determined by a multivariate analysis [36]. Interestingly, among patients with brain metastases present at initial diagnosis, neurosurgical resection and whole-brain radiotherapy were each not associated with improved survival either in multivariable analysis [36]. The authors concluded that chemotherapy should remain the standard of care in patients who present with brain metastases at the time of initial diagnosis and that combination or multimodal treatment should be reserved for particular clinical circumstances [36]. They concluded that combination treatments in this clinical scenario likely do not provide benefit and only provide additional toxicity to patients [36].

Conversely, in patients with brain metastases presenting later in the disease course, metachronous pulmonary metastases were identified in 62% of patients, and 54% of these patients received chemotherapy [36]. In this group of patients, chemotherapy, surgery, and radiation therapy were all associated with significantly increased overall survival in univariate analysis [36]. In a multivariate analysis, multimodality treatment and high-dose chemotherapy were the only treatment options that showed significance for overall survival, suggesting that in this case, these are the treatments of choice [36].

This study also reported that among patients with metastatic germ cell tumors, half of patients who passed away within 1 year due to their disease burden died as a result of systemic progression of their primary tumor, and not due to the neurologic manifestations of their disease [36]. Those patients who presented with poor clinical status in addition to metastatic disease of the brain tended to have worst outcomes [36].

23.6 Gynecologic Cancers

23.6.1 Neoplasms of the Uterus, Cervix, and Endometrium

Among gynecologic malignancies, the most common primary tumors that metastasize to brain arise from the uterine body, cervix, and endometrium [37, 38]. As treatment for these primary tumors improves, the incidence of brain metastases from these organs is increasing, especially after the advent of platinum-based chemotherapies. In a large study of 2848 Japanese patients with gynecological primary tumors, among whom 47 (1.7%) had brain malignancies, the median survival post-diagnosis was 20 weeks [38]. In this cohort, strong prognostic factors for poor survival included extracranial metastases, ECOG performance status 3–4, treatment-free interval <6 months, and no-anticancer treatment for brain metastases [38]. Likewise, an earlier retrospective study of 47 patients with gynecologic tumors and brain metastases, conducted by Growdon et al., showed that median survival was 7.5 months [37]. Multivariate analysis in this study population revealed again the poor prognostic significance of extracranial metastases and the good prognostic significance of papillary serious histology, as well as the use of any chemotherapy [37]. The authors concluded that multimodal therapy with WBRT, chemotherapy, and surgical resection of oligometastatic disease where feasible, in patients without extracranial metastases and few brain metastases, may increase survival [37].

23.6.2 Choriocarcinoma/Gestational Trophoblastic Neoplasia

Among the gynecologic malignancies, choriocarcinoma and gestational trophoblastic neoplasias (GTN) represent unique entities. Brain metastases are very common with an incidence of 67% of patients with choriocarcinoma at autopsy [39]. In this early study, published in 1982, across 24 patients, metastases to the brain were predominantly solitary lesions [39]. In another large study of 782 patients, approximately half of all patients with brain metastases and GTN presented with CNS metastasis [40]. Given the high rates of metastatic disease of CNS associated with GTN, routine screening of the CNS at the time of diagnosis and on follow-up is recommended for these tumor types [41].

Updated studies in patients with CNS metastases from GTN have shown that survival rates have increased significantly over the past few decades, with survival in a recent UK study reported at 85% [42]. Indeed, this is one of the few cases in which these uncommon metastatic lesions to the brain have been shown to respond to chemotherapy. More specifically, for the case of GTN, two chemotherapy regimens used in high-risk GTN (including cases with CNS metastases) are EMA-CO (etoposide, methotrexate, actinomycin, cyclophosphamide, and vincristine) or EMA-EP (etoposide, methotrexate, actinomycin, and cisplatin) [42, 43]. In most patients with GTN, radiation therapy was not necessary [42]. In a small minority of these patients studied, emergency neurosurgical interventions were required, but otherwise patients were managed with systemic and intrathecal chemotherapy alone [42].

23.7 Hematopoietic Cancers

Across hematopoietic cancers, metastasis to the central nervous system more commonly involves the leptomeninges, as opposed to the brain parenchyma itself [44]. Moreover, per an older report by Olson et al., approximately 24% of patients with leptomeningeal metastases had these as a result of non-Hodgkin's lymphoma (NHL) [45]. In addition, while most patients respond well to systemic chemotherapeutics, most agents do not have adequate penetration of the blood–brain barrier (BBB), resulting in isolated leptomeningeal or brain recurrence [46].

Patients with CNS metastases from hematopoietic cancers can present in a variety of ways and classically may present with epidural spinal cord compression [46]. Lower back pain and progressive neurologic dysfunction arising from spinal nerve roots in a patient with a history of hematopoietic malignancy is virtually pathognomonic [46]. Management of epidural spinal cord compression in this setting is the same emergent management as for other causes, involving early administration of dexamethasone, spinal MRI, and potentially radiotherapy or neurosurgical intervention as soon as possible [46]. Importantly, radiotherapy is typically first-line, as opposed to neurosurgical intervention in these cases, as lymphoma is a radiosensitive malignancy [46]. Neurosurgical intervention may be considered in those patients in whom radiotherapy cannot be done, for instance, in those who are not candidates for a second course or those who have had a limiting dose of radiation prior to presentation [46].

Leptomeningeal metastases occur in approximately 4–11% of patients with NHL and 10% of all patients with leukemia, most commonly in acute lymphoblastic leukemia (ALL) [44]. Clinically, these patients demonstrate multifocal involvement of the neuraxis, not localizable to a single location [44]. This should be suspected in patients with a history of hematopoietic malignancies presenting with cranial neuropathies, or findings indicative of spinal cord lesions, or hydrocephalus [46]. A definitive diagnosis of leptomeningeal metastasis in these patients is made by lumbar puncture followed by cytology and flow cytometry, although multiple studies have shown that the yield on the first cytology obtained is 50–84%, and increases on the third tap to 90–94%, underscoring the potential need for multiple lumbar punctures in the case of

high clinical suspicion, even if the first is negative [44, 46, 47]. In the event that three lumbar punctures remain nondiagnostic, further attempts are not recommended. For patients with leptomeningeal disease, symptomatic treatment can be achieved by corticosteroid administration, and bulky disease can be targeted with radiotherapy [44]. However, radiotherapy involving the entire craniospinal axis is associated with significant morbidity, due to the organs at risk involved in these treatment fields, such as the esophagus, GI tract, and bone marrow [44]. Intrathecal chemotherapy involves one of four agents at present: methotrexate, thiotepa, cytarabine, and liposomal cytarabine; between these, there have been no randomized studies comparing efficacy or tolerability, with the exception of lymphomatous meningitis [48]. In one study, cytarabine was compared to liposomal cytarabine (a depo slow-release formulation) in a randomized trial involving 28 patients with lymphoma and lymphomatous meningitis (response rate 71% for liposomal formulation vs. 15% for non-liposomal formulation, $p = 0.006$) [49]. Unfortunately, liposomal cytarabine has become unavailable due to manufacturing issues. Current intrathecal management options include methotrexate, thiotepa, or cytarabine.

More recent studies have also shown benefit with systemic chemotherapies in treating CNS involvement of lymphoma. A 2009 study by Fischer et al. reported that high-dose intravenous methotrexate and ifosfamide, in a cohort of 20 patients with CNS relapse of lymphoma, produced an objective response rate of 90%, with 12 complete remissions and 6 partial remissions [50]. Twelve patients received subsequent therapy, five of whom received high-dose chemotherapy and autologous stem cell rescue (ASCR) [50]. A review of 105 cases across German centers showed a 95% response rate in patients with a CNS relapse of systemic lymphoma using high-dose chemotherapy (methotrexate, ifosfamide, liposomal cytarabine) followed by ASCR, achieving a 2-year survival of 54–68% [51, 52]. In this study, transplant-related mortality was 2.8% [52].

23.8 Genitourinary Cancers

23.8.1 Prostate Cancer

Prostate cancer is among the most common cancers affecting men worldwide, and in the United States. Metastasis from prostate cancers to the central nervous system is relatively rare. In one study of over 16,280 patients treated at MD Anderson Cancer Center between 1944 and 1998, the incidence of prostate cancer metastatic to the craniospinal axis confirmed by neuroimaging was 0.8%, with an incidence of 0.63% for parenchymal metastases [53]. Small cell and cribriform histologic subtypes were approximately 20-fold more likely to metastasize to the brain. These metastases were primarily supratentorial (76%). For patients diagnosed with adenocarcinoma of the prostate, the median time from diagnosis to that of brain metastasis was 35 months, and for those with small-cell carcinoma of the prostate, the median time was 48 months, but it should be noted that the end date of this study precludes many of the modern treatments used at present for prostate cancers [53]. After brain metastases were identified, survival was 1 month in untreated patients and 3.5 months in those treated with radiotherapy, and notably just five patients in this study population underwent radiosurgery but did have a longer median survival at 9 months [53].

A more recent study of 13,547 prostate cancer patients from 2000 to 2010 at Memorial Sloan Kettering Cancer Center reported on 21 patients with CNS metastases [54]. In this more recent cohort, the incidence of brain metastases was lower at 0.16%, and 95% of patients with brain metastases had concurrent bone metastases [54]. The median time to detection of brain metastases from diagnosis was 46 months, slightly longer than in the MD Anderson cohort, potentially owing to improved local treatments [54]. Among these patients, median survival after diagnosis was 2.8 months [54].

Clinically, parenchymal brain metastases from prostate cancer behave similarly to those of other solid tumors. Given that the majority of prostate cancer metastases are osseas, however,

many CNS manifestations of prostate cancer arise from bone metastases. Although not strictly CNS metastases, skull base lesions can often manifest with cranial nerve palsies. Modern therapy for prostate cancer now involves agents such as abiraterone, which has been approved for use with metastatic castration-resistant prostate cancer, and has shown impressive benefit in this condition. However, the initial study supporting its use in prostate cancer had no patients with CNS metastases [55], although it is known that abiraterone can cross the BBB in animal models [56]. Given this exclusion criteria, and the relative rarity of CNS metastases from prostate cancer, no data on this therapy exist at present with respect to treatment of CNS metastases. Given the rarity of CNS metastases, management of these metastases would follow that of other solid tumor types. Systemic therapy in castrate naïve patients could consist of androgen deprivation perhaps combined with abiraterone since the latter agent crosses the BBB. For patients with CNS involvement of castration resistant disease abiraterone could still be part of therapy although multiple second line regimens exist.

23.8.2 Bladder Cancer

CNS metastases from bladder cancer are a relatively rare complication, and few reports of patient cohorts exist in the literature. An early study published in 1993 from the Memorial Sloan Kettering Cancer Center described 19 patients with brain metastases from transitional cell carcinoma of the bladder [57]. These patients received M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin) for neoadjuvant treatment of metastatic disease. Patients in this study who received radiation and surgery for their brain metastases survived a median of 19 months compared to 6 months for those receiving radiotherapy alone [57]. However, because only patients with solitary lesions received surgical intervention, it is not known whether this benefit of surgery holds for oligometastatic disease in the brain [57]. A more recent report with 16 patients from the Cleveland Clinic further substantiates the data that radiotherapy alone is likely inadequate treatment for metastatic bladder cancers to the brain. In this study, 11 of 16 patients received WBRT with or without surgery and had a median survival of 2 months, and of these 11 patients, the two that had surgery followed by radiation had survival of 2.75 and 12.75 months [58]. To summarize, bladder cancer metastasized to the brain confers a poor prognosis, and evidence from these studies supports aggressive combined modality therapy to maximize survival, in select patients, but due to the limited sample sizes of these studies, there are significant limitations in interpreting the results for a more generalized recommendation.

23.9 Concluding Remarks

In this chapter, we have focused on a number of less common metastatic tumors to the central nervous system. Among these, RCC metastatic to the brain is the most common, and we have also included discussions on the incidence and management of thyroid, gastrointestinal, germ cell, gynecologic, and hematologic malignancies that are metastatic to the brain. Given the rarity of these tumors, and the small number of patients studied with CNS metastases, treatment of disease in these settings is governed largely by retrospective studies, as well as case reports, and underlying knowledge of the biology of the primary tumor, as well as its response to surgery and radiation treatment. However, we caution the reader that this is not a general rule by any means, as in fact, while RCC is a radioresistant primary tumor, the metastases can respond well to SRS.

In general, the management of any patient with metastatic disease to the brain must incorporate their level of functional status and ability to tolerate treatment. The initial management consideration for patients with CNS metastasis should be a clinical trial if available. While patients with CNS metastasis not amenable to local therapy are often excluded from clinical trials of systemic therapy, this practice is not supported by several studies that demonstrate that toxicity is no worse in these patients than in those without CNS metastasis [59]. The design of early phase

clinical trials, therefore, should include patients with CNS metastasis. In addition, clinical trials for which eligibility is determined by molecular rather than histologic features should also allow patients with CNS metastasis. Patients with good performance status, with localized oligometastatic disease, symptomatic in the brain, generally benefit from SRS or surgical intervention.

Certain patient cohorts could be managed initially with systemic therapy. Such cohorts include patients with minimal or no symptoms and patients with chemosensitive histologies and CNS disseminated disease. Although not yet rigorously validated, select patients with good performance status and who desire further systemic therapy could be offered genomic sequencing of their tumor tissue through commercial vendors with the hope that actionable mutations would be uncovered. Looking forward, it is likely that the incidence of these less common brain metastases will increase, as treatment of primary tumors improves and as patients are living longer with their primary tumors. As a result, further research into earlier detection of CNS metastases, as well as targeting therapy using novel agents or immunotherapy approaches, is essential.

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Treatment of Leptomeningeal Metastases

24

Emilie Le Rhun and Michael Weller

24.1 Introduction

The incidence of leptomeningeal metastases (LM) in patients with metastatic cancer is difficult to estimate. A figure of 8% at autopsy from an almost historical study [1] is often cited. The contemporary incidence is probably higher. Breast cancer, lung cancer, and melanoma represent the main primary tumors in patients with LM. The prognosis for LM patients remains poor, limited to a few months for most affected patients. In recent cohorts of at least 30 patients, the median survival has been estimated at 2.6–7.3 months for LM from breast cancer [2–14], 3 to 9.7 months for LM from lung cancer [15–21], and 10 to 16.9 months for LM from melanoma [22, 23]. Only a few controlled clinical trials are available to guide the therapeutic strategy for LM patients. Treatment recommendations are therefore still mainly based on experts' opinion [24].

24.2 Therapeutic Options

Once they are present, neurological symptoms and signs are usually fixed and rarely improve. The aim of treatment is not only to prolong survival but also specifically to delay neurological deterioration and to maintain quality of life. The main treatment strategies include intra-CSF pharmacotherapy, systemic pharmacotherapy, and radiotherapy, and combinations thereof, but individual strategies vary widely across centers [25].

24.2.1 Intra-CSF Therapy

The decision for the use of intra-CSF pharmacotherapy alone or in combination with systemic pharmacotherapy should take into account the presentation of leptomeningeal disease as defined by cerebrospinal MRI and CSF findings. This is because the penetration of intrathecally administered drugs into leptomeningeal tumor nodules is limited and

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since its use in the presence of hydrocephalus, specifically CSF flow blocks, may lead to neurotoxicity.

Although intra-CSF therapy is widely used for the treatment of LM, only six randomized trials have tried to optimize its use. Four trials have compared different regimens of intra-CSF chemotherapy in LM patients from various primaries [26–29]. Only two trials have explored the role of the addition of intra-CSF chemotherapy to systemic treatment for the management of LM, and both focused on patients with breast cancer. In the first trial, intraventricular methotrexate added to systemic chemotherapy did not show superior survival in the combined modality arm, with 4.5 months in the experimental arm versus 7.5 months in the control arm [30]. However, in this trial, the enrollment was stopped after 35 patients instead of 50 because of poor accrual; moreover, a high rate of ventricular infections was noted, with 18% of revisions which may have negatively influenced outcome in the experimental arm. The neurological response was evaluated clinically only; imaging or CSF parameters were not used to determine success. In the contemporary Depo-Sein trial (NCT01645839), 73 patients were randomized between liposomal cytarabine plus systemic treatment and systemic treatment alone. The main objective was to demonstrate that adding local intra-CSF liposomal cytarabine to systemic treatment improves the LM-related progression-free survival [14]. The LM PFS was 3.8 months in the combined arm versus 2.2 months in the systemic treatment alone arm ($p = 0.04$). Quality of life was preserved in the combined arm. No significant difference was observed in terms of overall survival. No data are available on the value of intra-CSF therapy for LM from other primary tumors.

The three agents mainly used for intra-CSF treatment of LM are methotrexate, (liposomal) cytarabine, and thiotepa. Other compounds are also under evaluation for the treatment of LM. Intra-CSF trastuzumab, a drug that has a key role for the treatment of HER2-positive breast cancer, has been evaluated in combination with systemic pharmacotherapy in a phase I study (NCT01373710), with an overall good tolerance [31]. Data of a second phase I-II trial on intra-CSF trastuzumab in HER2-positive breast cancer with LM are pending (NCT01325207). An increased release of inflammatory cytokines without toxicity was observed after an intra-CSF injection of autologous tumor-infiltrating lymphocytes in a melanoma patient [32]. A survival of 7.8 months was observed in a cohort of 43 melanoma patients with LM after intra-CSF interleukin 2 treatment, and radiological responses were reported in 39% of patients [33].

Intra-CSF pharmacotherapy can be administered via repeated lumbar punctures or via repeated injections into ventricular devices. The ventricular route offers several advantages, such as avoiding the delivery of the drug into the epidural or subdural space, a uniform distribution of the drug within the CSF compartment, and better tolerability. The safety of ventricular devices has been reported in different cohorts of patients with a revision rate inferior to 7.4% using different surgical procedures [34–36]. A longer PFS with intra-reservoir as opposed to lumbar application was observed for methotrexate, but not for liposomal cytarabine in a sub-study of a randomized trial, presumably reflecting the different half-lives of both agents [37].

24.2.2 Systemic Pharmacotherapy

Systemic pharmacotherapy should in principle be as effective in the treatment of contrast-enhancing leptomeningeal lesions as for other systemic lesions because systemically administered therapy should reach the target as well as the contrast agent. Moreover, the blood-CSF barrier is commonly disrupted in LM patients, suggesting that the CSF compartment should also be at least partially covered. No randomized trials on systemic pharmacotherapy in LM are available. Systemic therapy should generally be

chosen according to the primary tumor and its molecular characteristics and according to the prior treatment of the tumor.

24.2.2.1 Systemic Treatment for Breast Cancer LM

Only few data are available for response to systemic treatment specifically in LM patients. Four partial responses and three stable diseases were observed among 13 patients treated with i.v. thiotepa (40 mg/m^2 × 21 days) [38]. Hundred-thirty breast cancer patients with recurrent brain metastases or LM or both were treated with ANG1005, a paclitaxel/Angiopep-2 drug conjugate, in a phase I/II trial. Twenty-two % partial responses were observed among the 23 patients with LM, and a survival of 8 months was noted in these patients [39]. A CNS-specific response was reported in 3 of 5 evaluable patients with LM after treatment with bevacizumab combined with etoposide and cisplatin in a pilot study (NCT 01281696) [40].

Anti-HER2 agents represent an option in breast cancer patients with Her2-positive tumors. However, only data on brain metastases are available. No trial has systematically evaluated the role of trastuzumab in patients with CNS metastases, but a potential benefit was noted in a few cohorts of patients with CNS metastases [41, 42]. The combination of lapatinib plus capecitabine has demonstrated a 65% rate of tumor reduction of at least 50% for brain metastases from HER2-positive breast cancer not previously treated by whole-brain radiotherapy (WBRT) [43]. Partial and complete responses between 24.5% and 44% have been reported under TDM-1, an antibody drug conjugate of trastuzumab and the antimitotic compound emtansine 1 in HER2-positive breast cancer brain metastases [44–46]. Forty-two % partial responses were noted in a phase 1b study on tucatinib with capecitabine and trastuzumab in patients with untreated or progressive brain metastases [47]. Other drugs such as mammalian target of rapamycin (mTOR) inhibitors, cyclin-dependent kinase (CDK) 4/6 inhibitors, or poly(ADP-ribose)-polymerase (PARP) inhibitors are under evaluation.

24.2.2.2 Systemic Treatment for Lung Cancer LM

No randomized trial for LM has been conducted in lung cancer patients. Chemotherapy with platinum based-combinations is commonly used in patients with metastatic lung cancer [48, 49]. The combination of chemotherapy with bevacizumab may be beneficial for NSCLC patients with brain metastases [50].

LM and brain metastases on the activity of anti-programmed cell death-1 or anti-programmed cell death-ligand 1 (PD-1/PD-L1) inhibitors in LM, but also in brain metastases from lung cancer. Intracranial response rates between 33% and 51% have been reported in patients with brain metastases [51–53].

EGFR mutations predict a response to EGFR tyrosine kinase inhibitors (TKI) with intracranial response rates between 43 and 88% for first-generation agents like erlotinib, gefitinib, or icotinib [54–57]; 21% for the second-generation TKI, afatinib [58]; and 54–83% for the third-generation TKI, osimertinib or AZD3759 [59–62], in patients with brain metastases. Limited data are available for lung cancer patients with LM. The prognosis is better in patients not previously with EGFR TKI at the time of LM diagnosis, with reported median survival of 10.2 months versus only 1.2 months in patients previously treated with EGFR TKI [21]. Other authors have reported survival of 5.9–6.2 months in LM patients after failure on EGFR TKI [63]. A role for high-dose EGFR TKI has been proposed, but not yet been clearly established [63, 64]. PFS was only 2 months and the median survival was 3.8 months in a small cohort of 11 LM patients with EGFR-mutant NSCLC under afatinib [65]. Among 32 LM patients with EGFR-mutant NSCLC treated with osimertinib in the phase 1 BLOOM study, 11 were EGFR^{Thr790Met} positive. Ten patients had a response on imaging [66]. New-generation EGFR TKI, such as AZD3759, are under evaluation.

Intracranial responses have been reported in the CNS with crizotinib [67, 68], ceritinib [69–72], alectinib [73–77], lorlatinib [78, 79], and brigatinib [80–82] in patients with brain metastases from anaplastic lymphoma kinase (ALK)-mutant lung cancer. However, only very few cohorts, with limited number of patients, are available on the efficacy of ALK inhibitors in LM patients with ALK-rearranged cancers. Up to 85.7% of CNS responses have been reported with alectinib in patients with asymptomatic brain metastases or LM or both [77]. The role of second-generation TKI such as ceritinib or brigatinib in patients with brain metastases or LM or both still has to be determined. No data are available in LM patients for ALK inhibitors such as entrectinib and ensartinib. LM from cancers with other targetable genetic alterations such as ROS1 fusion or BRAF mutations should be treated accordingly.

24.2.2.3 Systemic Treatment for Melanoma LM

Only very few data are available on melanoma LM patients. Systemic chemotherapy such as dacarbazine, temozolomide, or fotemustine has only a limited efficacy in general and in particular in patients with CNS metastases. In a cohort of 39 consecutive melanoma patients with LM, 14 were not treated due to a poor general status or rapidly progressive disease [23]. In this cohort, a median survival of 16.9 weeks was observed for the 25 treated patients, with a median of 21.7 weeks for the 21 patients treated with targeted therapy or immunotherapy. Brain metastases response rates with the immune checkpoint inhibitor ipilimumab, targeting cytotoxic lymphocyte antigen (CTLA) 4, vary between 5 and 16% in different cohorts of patients [83–85]. A response rate of 56% was noted in a single arm study evaluating the combination of nivolumab and ipilimumab in asymptomatic brain metastases with, however, 55% of grade 3–4 adverse events [86]. In a randomized study, comparing nivolumab plus ipilimumab to nivolumab alone in patients with asymptomatic brain metastases from melanoma without previous local brain-directed therapy, response rates were 75% in immunotherapy-naïve patients and 63% in the whole population in response to nivolumab plus ipilimumab and 32% in immunotherapy-naïve patients and 32% in the whole population with nivolumab alone [87]. In this cohort, 54% of grade 3–4 adverse events were observed with combined treatment and 16% after nivolumab alone.

Responses have also been reported under vemurafenib [88, 89] in retrospective series of melanoma patients with brain metastases. In a phase II trial, a response rate of 18% was observed under vemurafenib in patients with previously treated or untreated brain metastases from $BRAF^{V600}$-mutant melanoma [90]. Another phase II trial reported a 30.8% response rate after prior local treatment and 39.2% in the absence of prior local treatment in patients with Val600Glu or Val600Lys BRAF-mutant melanoma brain metastases treated by dabrafenib [91]. Limited data are available on the combination of BRAF and (*MAPK/ERK*) MEK inhibitors (dabrafenib plus trametinib or vemurafenib plus cobimetinib) in patients with CNS metastases from melanoma. A phase II trial evaluated the efficacy of the combination of dabrafenib and trametinib in BRAF-mutant melanoma patients with brain metastases. The response rate was 56% in patients with previous local brain treatment and 58% in patients without previous local therapy, with a good tolerance [92].

24.2.3 Radiotherapy

No randomized trial has assessed the efficacy and safety of radiotherapy in LM. Focal radiotherapy, using fractioned regimens or single fractions, can be used to treat leptomeningeal nodules. Prolonged responses have been described after stereotactic radiotherapy in patients with bulky or nodular disease previously treated with WBRT [93, 94]. Focal radiotherapy is also an option for the treatment of symptomatic cerebral or spinal sites, such as irradiation of skull base, interpeduncular cistern or the two first cervical vertebrae in the presence of cranial nerve impairment, or

irradiation of lumbosacral vertebrae in the presence of a cauda equina syndrome [24]. Focal radiotherapy is also sometimes used for the treatment of local CSF flow obstruction in order to restore CSF flow and permit the administration of intra-CSF pharmacotherapy [95]. The safety and efficacy of concomitant involved-field radiotherapy and intra-CSF methotrexate plus dexamethasone was reported in a phase II trial including 59 patients from various primaries (lung cancer, $n = 42$; breast cancer, $n = 11$; other, $n = 6$). The overall response rate was 86.7%, the median OS was 6.5 months whereas 20.3% grade 3–4 adverse events were noted [96].

WBRT has not been evaluated in any randomized trial, and most studies have reported no improvement of survival after WBRT in LM patients [16–18, 21, 97]. WBRT represents an option in patients with extensive nodular or symptomatic linear disease or in the presence of associated brain metastases. Yet, the phase III randomized QUARTZ trial showed only a small difference in quality-adjusted life years (QALY) and an absence of survival improvement after WBRT in NSCLC patients with brain metastases not eligible for surgical resection of stereotactic surgery [98]. Cerebrospinal radiotherapy is rarely an option for adult patients with LM from solid cancers because of the risk of bone marrow toxicity, enteritis, and mucositis in a context of concomitant systemic disease and commonly several lines of previous therapies.

24.3 Combination of Treatment

Therapeutic options are selected not only depending on the histological and molecular subtype of the primary cancer, the general and the neurological health status, the presence of concomitant systemic and brain metastases and their prior treatments but also depending on the clinical, cytological, and imaging presentation of LM [24].

Intra-CSF pharmacotherapy should be considered in selected patients with floating tumor cells in the CSF and for linear diffuse leptomeningeal or ependymal spread, potentially associated with nodular lesions that may require other therapeutic approaches. Intra-CSF pharmacotherapy may not be the preferred option in case of nodules only without linear disease and in the absence of tumor cells in the CSF. Intra-CSF therapy may also be inefficient and even toxic in case of CSF flow blocks.

Modification of systemic pharmacotherapy should always be considered in case of a new diagnosis of LM or in case of progression of LM.

Focal radiotherapy is usually performed in case of nodular disease especially for patients with negative CSF cytology, in case of symptomatic lesions involving cranial nerves and cauda equina, or in case of obstruction of CSF flow when intra-CSF pharmacotherapy is planned. For patients with rapid deterioration of their general or neurological status, best supportive care alone may be an option.

24.4 Follow-Up

LM patients should be regularly evaluated not only to guide the therapeutic strategy for the treatment of LM but also to adjust supportive care. The follow-up should include a clinical evaluation and a neuroimaging evaluation. The role of repeat CSF cytological assessment has remained controversial. A standardized scorecard should be used for follow-up [99].

Clinical symptoms and signs related to brain metastases, to neurotoxicity induced by treatments, to extra-cerebral disease progression, or to transient associated diseases should not be considered for the assessment of the clinical response to LM-directed treatment. A cerebrospinal MRI should be performed for the evaluation of response. MRI should be repeated on the same device or at least using an identical field strength. The RANO LM group has proposed criteria for the evaluation of response in LM patients [99]; however, these criteria have not been validated. Considering the prognosis of LM, evaluations should be performed every 2 months for the first 6 months and then every 3 months in case of stable disease [24].

24.5 Supportive Care

Supportive care may in general follow guidelines as outlined for other patients with CNS tumors [100]. Steroids should be given when clinically required only, at the lowest dose and for the shortest time. Their role has not been clearly defined for the management of LM outside of their use for the management of chemical meningitis or associated brain metastases. Drugs that do not interact with systemic treatments are usually recommended for the management of seizures, and primary seizure prophylaxis is not recommended [101]. One particular aspect in the context of LM is neurological symptoms related to hydrocephalus. They are usually relieved in 77–88% of the cases by ventriculoperitoneal shunting, with good results especially for headache and nausea [102–105]. The rate of complications of ventriculoperitoneal shunting is estimated at 9–15% [103]. They include infection, bleeding, malfunction, and obstruction. Peritoneal dissemination of tumor cells has been reported but appears to be rare [103, 104, 106]. Other options for the treatment of symptomatic hydrocephalus include repeated CSF depletion through lumbar puncture or through a ventricular device; lumboperitoneal shunting; or, in patients with obstructive hydrocephalus, external ventricular drainage. Intra-CSF pharmacotherapy should be avoided in patients with symptomatic hydrocephalus in the absence of a valve with an on/off option.

24.6 Conclusion

The management of LM should be individualized and consider the histological and molecular subtype of the primary cancer, the general and the neurological health status, the presence of concomitant systemic and brain metastases, and their prior treatments, as well as clinical, cytological, and imaging presentation of LM. Intra-CSF therapy can improve LM-related PFS but has not demonstrated a survival benefit. Modification of systemic pharmacotherapy should be considered in case of newly diagnosed LM. Advances in molecular diagnostics may help to identify new targeted treatments. Involved-field radiotherapy has a role for the treatment of meningeal nodules. Dedicated trials using validated tools for the response assessment are urgently needed.

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Part IV

Toxicity from Treatments

25 Neurocognitive Toxicity from Radiation Therapy for Brain Metastases

Karine A. Al Feghali, Caroline Chung, Jeffrey S. Wefel, and Mariana E. Bradshaw

25.1 Introduction

Brain metastases are the most common intracranial tumors and are most likely to arise from primary disease in the lung, breast, melanoma, renal, and colorectal [1–4], with incidences as high as 60% in patients with small-cell lung cancer (SCLC) [5] and EGFR-mutated or *ALK*-rearranged non-small-cell lung cancer [6, 7]. While the exact incidence of brain metastases is unknown, the estimated incidence is 7–14 per 100,000, with up to 25% of cancer patients developing metastatic disease in the brain [3, 8]. The incidence of brain metastases appears to be increasing [7, 9, 10] in the context of novel effective systemic therapies and the development of improved radiation therapy techniques that have resulted in improved overall survival and locoregional tumor control rates.

Unfortunately, efforts to prolong survival can sometimes come at the detriment of neurocognitive dysfunction and/or impairment of functional independence. Although not consistent across all studies, decline in neurocognitive function (NCF) following WBRT for brain metastases has been shown to precede deterioration in quality of life (QoL) by 9–153 days [11] . Neurocognitive decline is most often multifactorial and may result from systemic and central nervous system (CNS) disease and/or from the untoward effects of multidisciplinary treatment, including surgery, chemotherapy, and radiation therapy.

25.2 Radiation-Induced Neurotoxicity

Radiation-induced brain injury can be divided into acute (early, during radiation), subacute (up to 6 months post-radiation therapy), and late effects (chronic, more than 6 months post-radiation therapy) [9, 10]. Acute encephalopathy occurs almost exclusively if high dose per fraction is used, and not with the conventionally used dose of 3 Gray

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or less per fraction [12, 13]. Symptoms include headache, nausea, vomiting, and fever, which can be treated using corticosteroids.

Subacute complications include somnolence syndrome, whose symptoms are transient and include excessive sleepiness, drowsiness, and anorexia, and are mainly documented in children receiving PCI for ALL [14, 15], or in adults receiving definitive doses of radiation therapy (45–55 Gray) for primary brain tumors [16, 17]. Neurocognitive effects in the subacute period may include reduced information processing speed, problems in attention, word finding, memory retrieval, executive dysfunction, and decreased fine motor dexterity [18].

Late or chronic effects are of greatest clinical concern of all radiation-induced injuries, as they are usually irreversible and may include progressive dementia. Molecular mechanisms underlying the development of these chronic effects are inflammation [19, 20], hypoxia with vascular endothelial growth factor upregulation [21, 22], and inhibition of neurogenesis [23]. This cascade of events can lead to radiation-induced demyelination and leukoencephalopathy that can occur months to years after irradiation [10], as well as radiation necrosis [24]. In long-term SCLC survivors, PCI has been shown to result in progressive ventricular dilatation or cerebral atrophy up to 8 years after therapy completion, and slow decline in NCF [25, 26]. The risk of chronic irreversible neurotoxicity is greater for patients that are older, have other medical comorbidities [27], and have lower pre-treatment neurocognitive capacity, sometimes called "cognitive reserve" [28, 29].

Genetic predispositions may also contribute to the risk. For example, APOE e4 carrier status was shown to be a risk factor for worse memory function after treatment with WBRT (with or without memantine) [30].

The pathophysiology of radiation-induced neurotoxicity is not well understood. Acute effects have been linked to edema formation secondary to blood-brain barrier disruption, due to apoptosis of endothelial cells [31–34]. Animal studies have demonstrated that radiation blocks neurogenesis in the dentate gyrus of the hippocampus [35]. Preclinical studies in rodents have enhanced our understanding of some of the neurobiological mechanisms underlying chemotherapy and radiotherapy-induced adverse neurological effects. The main culprits are believed to be oxidative stress causing DNA single-strand or double-strand breaks, increased apoptosis, vascular injury, damage to white matter tracts, and neuroinflammation [28, 36–39]. Imaging biomarkers are being investigated as surrogates for early assessment of RT-induced neurotoxicity. In particular, dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) has shown promise in detecting early changes in vasculature and predict late neurocognitive dysfunction [40, 41]. Diffusion tensor imaging (DTI) has been used to detect white matter changes over time in patients receiving whole-brain irradiation, and to establish preliminary evidence of an association with NCF [42, 43].

25.3 The Impact of Radiation Therapy Targeting Brain Metastases on Neurocognitive Function

25.3.1 Whole-Brain Radiation Therapy

Whole-brain radiotherapy (WBRT) consists of two opposed-lateral treatment fields that encompass the entire brain (Fig. 25.1). It has been considered the standard of care for patients with brain metastases for many years, either postoperatively or as the sole treatment. However, it has been recognized that WBRT can have a notable impact on neurocognition, ranging from mild neurocognitive impairment to full-fledged dementia, and this has resulted in a re-evaluation of the appropriate role of WBRT.

Significant decline in NCF following WBRT has been detected using screening measures such as the Folstein Mini-Mental State Examination (MMSE). A secondary analysis of a trial of WBRT with or without thalidomide in patients with multiple brain metastases reported steady neurocognitive decline as assessed by the MMSE in both treatment arms [44]. Similarly, a decrease in MMSE scores was noted in a subset of 101

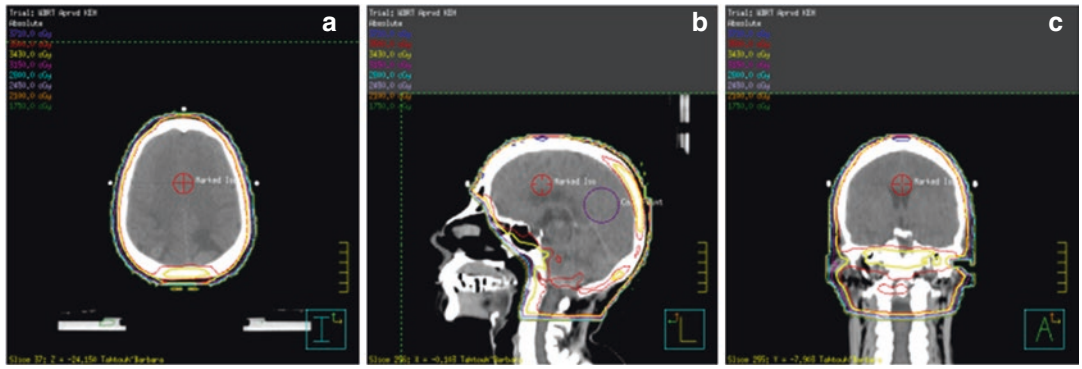

Fig. 25.1 Example of a whole-brain radiation therapy plan with a dose prescription of 30 Gray in 10 fractions. The three panels below represent cuts from the simulation computed tomography (CT) scans with isodose lines—transverse (**a**), sagittal (**b**), and coronal (**c**) views

patients treated with WBRT (40 Gy in 20 fractions) up to 15 months post-radiation. Brain atrophy was also observed in 30% of patients, but this was not correlated with MMSE decline [45]. Fractionation schedule did not appear to have a significant impact on MMSE score; comparison of accelerated fractionation (1.6 Gy twice a day to 54.4 Gy) versus standard WBRT fractionation (3 Gy daily to 30 Gy) revealed no significant difference in NCF between the two regimens as evaluated by MMSE [46].

Studies using more comprehensive neurocognitive assessment have reported neurocognitive dysfunction in 11–85% of patients treated with postoperative WBRT for brain metastases [47, 48], but these numbers vary depending on the assessment tool used and on the definition of neurocognitive deterioration in the different trials. In view of these alarming numbers and with the growing availability of more effective systemic therapies [49–52] and more conformal radiation treatment approaches such as stereotactic radiosurgery (SRS), there has been a growing interest in treatment approaches that can defer or avoid the use of WBRT.

25.3.2 Stereotactic Radiosurgery

According to the American Society for Radiation Oncology (ASTRO) definition, stereotactic radiosurgery (SRS) is a form of local radiotherapy that precisely delivers a high dose of radiation "in one to five fractions via stereotactic guidance, with approximately 1 mm targeting accuracy to intracranial targets and selected tumors around the base of the skull" [53]. It uses multiple beams of high-energy X-rays, gamma rays, or protons that converge on a discrete treatment volume, maximizing the ablative effect on the target while minimizing collateral damage to the adjacent normal brain parenchyma and other surrounding normal structures [54] (Fig. 25.2).

A number of studies have reported that in comparison to WBRT, SRS treatment of brain metastases is associated with less neurocognitive decline, and the number of metastases treated with SRS does not seem to correlate with the extent of decline in NCF. In a Japanese study comparing outcomes of patients with 1, 2 to 4, and 5 to 10 brain metastases treated with SRS, the MMSE score was maintained in 92%, 91%, and 89%, respectively [55]. In a large multicenter, randomized, controlled trial, 194 patients with a single brain metastasis received either SRS or WBRT. There was again no significant difference in overall survival between the treatment groups, but NCF-deterioration-free survival was significantly longer in patients who received SRS as compared to those who received WBRT. Additionally, incidence of cognitive deterioration at 6-month follow-up was less in patients randomized to receive SRS [47].

The mechanisms underlying this differential neurotoxicity of SRS versus WBRT have been investigated using MRI. It has been found that

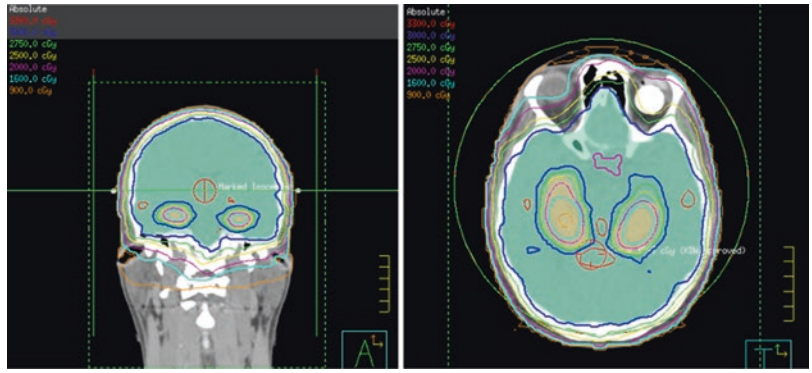

Fig. 25.2 Example of a hippocampal avoidance whole-brain radiation therapy plan using intensity-modulated radiation therapy

delayed white matter leukoencephalopathy is very common in patients treated with WBRT, reported in up to 97% of patients [56, 57], whereas its incidence is much lower (1–3%) in patients treated with SRS [55, 56].

25.3.3 Stereotactic Radiosurgery + Whole-Brain Radiation Therapy

The addition of WBRT to SRS is associated with better local control and distant intracranial control, but not with improved overall survival as compared to SRS alone and is associated with neurocognitive decline. This was demonstrated in a multicenter clinical trial of 213 patients with 1–3 brain metastases which was the first large-scale trial to incorporate formal and comprehensive measures of NCF. Patients were randomized to receive either SRS or SRS plus WBRT. WBRT offered no significant survival benefit; this was confirmed in a secondary analysis [58]. However, in long-term survivors, incidence of deterioration in NCF was less at the 3-month and 12-month time points in patients who received SRS alone [59]. Similarly,

Table 25.1 outlines the studies that compare neurocognitive side effects from SRS to those from WBRT with or without SRS. These randomized trials of patients with a limited number of brain metastases (1–4) clearly demonstrate that WBRT compromises NCF more than SRS, without yielding a survival benefit [60, 61, 64]. Ongoing studies are investigating SRS versus WBRT in patients with a larger number of metastases (clinicaltrials.org identifiers: NCT03075072 and NCT03775330) [65, 66].

It is thus reasonable to consider SRS monotherapy first when a patient presents with a limited number of brain metastases. While SRS controls gross disease, systemic therapy might also be needed to control microscopic disease in the brain. A strategy of close follow-up and regular high-quality neuroimaging to detect recurrences is preferred nowadays over more aggressive upfront treatment, and is consistent with the trend toward personalized treatment. It is, however, dependent on the patient and medical team's willingness to adhere to a strict follow-up schedule.

25.4 Neurotoxicity in the Setting of Prophylactic Cranial Irradiation

Studying the effect of prophylactic cranial irradiation (PCI) on NCF can help disentangle the CNS toxicity due to the effects of radiation therapy from the neurocognitive decline inherent to the presence of CNS disease itself.

PCI has been a long-standing standard of care in SCLC based on an individual patient data meta-analysis in limited-stage SCLC [67], and a seminal trial in extended-stage SCLC [68], showing an overall survival benefit with the use of PCI. The role of PCI in non-small-cell lung cancer (NSCLC) is not as straightforward; no overall survival benefit has been demonstrated

Table 25.1 Neurocognitive side effects of stereotactic radiosurgery (SRS) versus whole-brain radiotherapy alone or with SRS

	Study population	SRS dose	WBRT dose	Instrument for cognitive testing	Definition of the endpoint of cognitive deterioration	Results with SRS	Results with SRS + WBRT	Results with WBRT
Brown et al. [59]	213 patients with 1–3 brain metastases (no surgical resection)	18–22 Gy	30 Gy in 12 fx	– Learning and immediate memory (HVLT-R Total Recall) – Fine motor control (Grooved Pegboard Test) – Verbal fluency (COWA) – Processing speed (TMT Part A) – Executive function (TMT Part B) – Delayed memory (HVLT-R Delayed Recall) – Recognition (HVLT-R Recognition)	Decline >1 SD from baseline on at least 1 cognitive test at 3 months	63.5% at 3 months	91.7% at 3 months	–
Chang et al. [60]	58 patients with 1–3 brain metastases (no surgical resection)	15–20 Gy	30 Gy in 12 fx	HVLT–R Total Recall	Deterioration (5-point drop compared with baseline) in HVLT-R Total Recall at 4 months	24% at 4 months	52% at 4 months	–
Aoyama et al. [61]	28 patients with 1–3 brain metastases (no surgical resection)	18–25 Gy	30 Gy in 10 fx	MMSE	Median MMSE change between pre- and post-treatment	Pre-treatment MMSE: 27 Post-treatment MMSE: 28	Pre-treatment MMSE: 28 Post-treatment MMSE: 27	–
Soffietti et al. [62]	341 patients with 1–3 brain metastases (no surgical resection)	25 Gy	30 Gy in 10 fx	Cognitive functioning as part of the EORTC QLQ-C30 (used as a HRQOL measure)	Differences between the two treatment arms for all post-baseline time points	10.7-point difference in cognitive function scale at 12 months between the two treatment arms, in favor of SRS alone (statistically significant)		–

(continued)

Table 25.1 (continued)

	Study population	SRS dose	WBRT dose	Instrument for cognitive testing	Definition of the endpoint of cognitive deterioration	Results with SRS	Results with SRS + WBRT	Results with WBRT
Aoyama et al. [63]	92 patients with 1–4 brain metastases (no surgical resection)	18–25 Gy	30 Gy in 10 fx	MMSE	3-point drop in the MMSE	– 59.3% at 1 year, 51.9%, at 2 years and 51.9% at 3 years – The average duration until deterioration was 7.6 months	– 76.1%, at 1 year, 68.5%, at 2 years and 14.7% at 3 years – The average duration until deterioration was 16.5 months	–
Brown [47]	213 patients with total/subtotal resection of a single BM	12–20 Gy	30 Gy in 10 fx or 37·5 Gy in 15 fx	– Learning and immediate memory (HVLT-R Total Recall) – Verbal fluency (Controlled Oral Word Association) – Processing speed (TMT Part A) – Executive function (TMT Part B) – Delayed memory (HVLT-R Delayed Recall) – Recognition (HVLT-R Recognition)	Decline >1 SD from baseline on at least 1 cognitive test at 3 months	52% at 6 months		85% at 6 months
Kepka [48]	59 patients with total/subtotal resection of a single BM	15 Gy	30 Gy in 10 fx	MMSE	3-point drop in the MMSE	4.5% at 6 months		11% at 6 months

Abbreviations: SRS stereotactic radiosurgery, *WBRT* whole-brain radiotherapy, *Gy* Gray, *fx* fractions, *SD* standard deviation, *HVLT-R* Hopkins Verbal Learning Test-Revised, *COWA* Controlled Oral Word Association, *TMT* Trail Making Test, *MMSE* Mini-Mental State Examination, *EORTC QLQ-C30* EORTC Quality of Life Questionnaire C30, *HRQOL* health-related quality of life

in the different randomized controlled trials randomizing patients with NSCLC to PCI versus no PCI [69–74], although a meta-analysis indicated a disease-free survival benefit in a subset of patients [75].

Subacute effects of PCI have been demonstrated and are characterized by impairment in verbal memory function 6–8 weeks after PCI completion [76]. Late neurological complications from PCI have only been formally studied in three trials [74, 77, 78]. In RTOG 0214, a trial that randomized 340 patients with stage III NSCLC to PCI or no PCI, there was a trend toward greater decline in patient-reported cognitive functioning in the PCI arm. There was no significant difference in MMSE scores between the two arms, except at 3 months. There was a significant difference noted in the NCF analysis for the Hopkins Verbal Learning Test (HVLT), with patients who were treated with PCI exhibiting significantly greater deterioration in learning and memory at 1 year as compared to controls. There were no significant differences in QoL between the patients who received PCI and those who did not [77], unlike the sequential association between NCF decline and QoL deterioration noted earlier in this chapter in the setting of WBRT for brain metastases.

Dose effect of PCI on NCF was investigated in the RTOG 0212 trial. Patients (n = 265) with limited-stage SCLC who had a complete response after chemotherapy and thoracic RT were randomized to either standard-dose PCI (25 Gy in 10 fractions) or higher-dose PCI (36 Gy). The 36 Gy cohort was secondarily randomized to receive PCI in either18 fractions of 2 Gy or twice daily in 24 fractions. Chronic neurotoxicity in this study was defined as the deterioration in at least one of six cognitive domains without development of brain metastasis at 12 months. The incidence of chronic neurotoxicity was significantly higher in patients treated with 36 Gy compared with 25 Gy (85 and 89% versus 60%, respectively, p = 0.02) [78].

A study by Gondi et al. pooled QoL and NCF results from the two RTOG randomized studies mentioned above: RTOG 0214 and RTOG 0212 [79]. Findings revealed that patients who were treated with PCI had a significant threefold higher risk of decline in self-reported cognitive functioning at 6 months and 12 months as compared to patients followed on observation. PCI was also associated with a significant decline on HVLT Total Recall and HVLT Delayed Recall at 6 and 12 months [61].

25.5 Neurocognitive Assessment in Brain Metastases

Studies investigating neurocognitive effects of brain metastases and radiation have, to date, used different definitions of neurocognitive deterioration, and time to assessment, as well as different assessment methods, each with a different sensitivity. Some have relied exclusively on patient-reported outcomes, such as the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 [62]. Data from these studies should be interpreted with caution, as patients with neurocognitive impairment may not be fully aware of the extent of their neurocognitive problems [80]. In addition, self-reporting and actual formal neurocognitive testing are poorly correlated [81], as was documented in the Gondi et al. study described above; decline in HVLT and decline in self-reported cognitive functioning were not closely correlated [61]. Other studies have relied on screening measures, such as the MMSE, to compare cognitive outcomes between the different treatment modalities [40, 42]. However, the MMSE has been deemed not sensitive enough in a brain tumor population [82]. For this reason, the Food and Drug Administration (FDA) has recommended objective assessment over subjective self-report in neuro-oncology [83]. A battery of standardized neuropsychological tests is widely adopted in clinical trials measuring NCF [47, 59, 60, 84]. The International Cognition and Cancer Task Force was created and issued recommendations to harmonize studies of NCF in cancer patients [84]. The core clinical trial battery represented

in Table 25.2 and endorsed by the ICCTF was also endorsed by the RANO group [84, 88–92]. While this battery is not an exhaustive list of tests to acquire a fully comprehensive neurocognitive evaluation, this battery can be completed within a reasonable time frame that is tolerable for most patients and still includes the measures found to have appropriate psychometric properties and sensitive to the effects of the tumor and anticancer treatment on the domains of memory and learning, information processing speed, and executive function.

Although treatment-related neurocognitive deficits are being increasingly reported in clinical trials on cancer patients with brain metastases, their incidence and patterns are sometimes inconsistent between studies. This can be explained by various factors including heterogeneity of the patient population in each study, the particular treatment modalities used, the NCF tests employed, and the various statistical methods used to measure and report neuropsychological changes (some more sensitive than others) [93, 94].In order to evaluate the impact of anticancer therapies on NCF, testing at baseline is critical but may not always be available. Many studies have struggled with patient completion of follow-up neurocognitive testing [62], with reasons for loss to follow up often inadequately described; significant dropout in follow-up neurocognitive testing has resulted in low statistical power in at least some studies [94], though feasibility of repeated neurocognitive assessment in this patient population has been demonstrated [60].

Moving forward, the same battery of tests should be used consistently across studies, as a sensitive measure of brain functioning [82]. Improving the way the endpoint of NCF is reported can be critical, as a study has demonstrated that neurocognitive deterioration can precede radiological evidence of progression by around 6 weeks in patients with primary brain tumors [95]. Whether this finding can be extrapolated to patients with brain metastases remains to be studied.

Table 25.2 Clinical trial battery of neurocognitive tests recommended for cognitive function assessment in patients with brain metastases

Cognitive domain	Test
Learning and memory	Hopkins Verbal Learning Test-Revised (HVLT-R) [85]
Verbal fluency	Controlled Oral Word Association [86]
Information processing speed	Trail Making Test Part A [87]
Executive functioning	Trail Making Test Part B [87]

25.6 Strategies to Mitigate Neurotoxicity

Beyond limiting the dose of radiation to the whole brain by using SRS and/or newer systemic therapies, an alternative radiation strategy to avoid neurocognitive dysfunction, and more specifically short-term memory loss, is hippocampal avoidance whole-brain radiation therapy (HA-WBRT) (Fig. 25.3). It uses conformal radiation therapy to avoid neural stem cells in the hippocampal dentate gyrus, which are mitotically

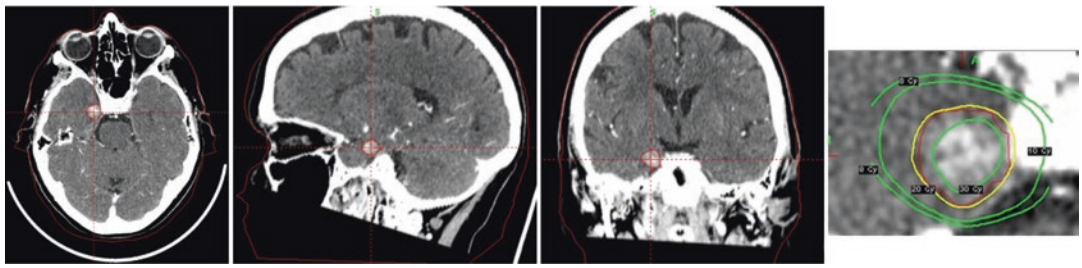

Fig. 25.3 Example of a stereotactic radiosurgery plan using Gamma Knife for a right temporal lesion, treated with a prescription dose of 20 Gy to the 50% isodose line

active and radiosensitive and are responsible for formation of new memories [23, 96, 97]. This technique was tested in the phase II cooperative trial RTOG 0933; results revealed that relative to historical controls treated without hippocampal avoidance, patients treated with HA-WBRT had significantly less relative decline in Hopkins Verbal Learning Test Delayed Recall at 4 months [98]. Two ongoing trials, NRG-CC003 and the Spanish PREMER Trial (NCT02397733), are currently examining the role of hippocampal avoidance in the setting of PCI for SCLC specifically [99–101].

In addition to adjustments to radiation, neuroprotective drugs, such as angiotensin-converting enzyme inhibitors [102], angiotensin type-1 receptor blockers [103], erythropoietin [104], and lithium [105, 106], have been investigated as a potential means of preventing neurocognitive toxicity. Phase III clinical trials have investigated the effectiveness of memantine and donepezil. As compared to placebo, patients treated with memantine, an N-Methyl-D-aspartate (NMDA) receptor antagonist, exhibited a trend toward less decline in the primary endpoint of HVLT-R Delayed Recall at 24 weeks. It is noted that this finding did not reach statistical significance (p-value = 0.059), likely due to the low statistical power due to unexpectedly high rates of death and loss to follow-up. Nonetheless, the patients receiving memantine had significantly longer time to neurocognitive decline and better performance in executive functioning and processing speed [107]. NRG-CC001 examined the combined use of HA-WBRT + memantine versus conventional WBRT + memantine in patients with brain metastases. Recently reported results demonstrated a delay in the time to neurocognitive decline in the HA-WBRT + memantine arm with no difference in OS or PFS [108]. In adult brain tumor survivors, donepezil, a reversible acetylcholine esterase inhibitor, did not show significant improvement in the overall composite cognitive score (primary endpoint). However, relative to placebo, patients treated with donepezil (10 mg/day) showed significant benefit in memory performance and fine motor dexterity [109]. It has been demonstrated that patients with moderate-to-severe Alzheimer's disease showed significantly greater neurocognitive benefits with higher doses of donepezil 23 mg/day than donepezil 10 mg/day [110]; it remains unknown whether a similar benefit would be seen in patients with brain metastases.

Finally, behavioral interventions have also been attempted to mitigate treatment-related neurocognitive impairment. Cognitive rehabilitation consists of clinic-based therapeutic programs designed to improve cognitive skills and functional capacity [111]. There is evidence to suggest benefit in cancer patients, including those with brain tumors [112–114], but further work is needed to determine whether these strategies are effective in the context of brain metastases. Specific strategies employed to date include the use of cognitive behavioral therapy and mindfulness exercises, which have reportedly yielded improvement in executive function, working memory, processing speed, and attention [115–119]. Neuroplasticity-based, computerized programs have also been investigated. In survivors of breast cancer, such programs have been associated with improved executive function, processing speed and verbal fluency [120]. However, a similar intervention was not successful with patients with primary brain tumors; participants failed to comply with the intervention and did not demonstrate improvements in NCF [121].

25.7 Conclusion

As new therapies are currently revolutionizing cancer treatment, and allowing patients with brain metastases to live longer, the concern for delayed neurotoxicity is all the more real, and strategies to delay or prevent this life-altering morbidity are all the more important. More efforts in the field of genetic characterization of brain metastasis should be deployed that could permit the identification of actionable mutations and allow treatment personalization. In the future, this approach should be favored over the "one-size-fits-all" strategy.

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Neurological Complications of Chemotherapy

26

Maria Diaz and David Schiff

26.1 Introduction

Neurotoxicity is a dose-limiting side effect of many antineoplastic drugs. Diagnosis can be challenging, as drug-induced neurotoxicity can mimic other cancer-related complications, such as direct infiltration of neoplasms, metastatic spread, paraneoplastic syndromes, metabolic disturbances, or opportunistic infections. Moreover, chemotherapeutic agents are frequently administered in combination with other agents and therapeutic modalities (radiotherapy, immunotherapy) that may also have deleterious neurologic effects. The ability to recognize the neurological complications of specific antineoplastic drugs can be critical to cancer management, as correct identification of the causative drug can prevent additional testing and needless discontinuation of non-culprit medications, as well as ensure appropriate modification of the offender. The mechanisms and site of injury vary, but most neurotoxic chemotherapy agents can be classified as predominantly affecting either the central nervous system (CNS) or the peripheral nervous system.

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26.2 Agents Associated with Predominantly Central Neurotoxicity

26.2.1 Ifosfamide

Ifosfamide, an alkylating agent, is an analog of cyclophosphamide. While cyclophosphamide rarely causes significant neurotoxicity, ifosfamide is associated with encephalopathy in 10–30% of patients [1–4]. The neurotoxic metabolite chloroacetaldehyde, produced in much higher quantities during ifosfamide metabolism than in cyclophosphamide's, seems to be responsible for this disparity in incidence [5]. Risk factors for ifosfamide-induced encephalopathy (IIE) include elevated creatinine, low albumin [1, 3], anemia [5, 6], and prior use of cisplatin [5]. The most common symptoms are lethargy, confusion, and mutism, typically developing hours to days into the treatment and spontaneously resolving within 48–72 h of discontinuation of the drug [7]. Seizures can also occur, and nonconvulsive status epilepticus (NCSE), which may be clinically indistinguishable from IIE itself, has been reported [8, 9]; electroencephalography (EEG) can help differentiate between these two entities and might be particularly useful in patients who fail to improve after discontinuation of ifosfamide. A variety of other neurological signs and symptoms have been described in association with ifosfamide, typically occurring in the context of encephalopathy,

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including hallucinations, myoclonus, asterixis, tremor [10], hemiballismus [11], cranial nerve dysfunction, and aphasia [3]. Although there is risk of recurrence with subsequent cycles, prior history of IIE is not considered a contraindication to repeat administration of ifosfamide [12]. While methylene blue and, to a lesser extent, thiamine have been used both for treatment and prophylaxis of IIE, retrospective studies have failed to demonstrate their efficacy [6, 13], and controlled trials are lacking. Serotoninergic syndrome has been reported with the use of methylene blue in this context [14].

26.2.2 Cytarabine

Cytarabine is a pyrimidine analog used in multidrug regimens for leukemias and lymphomas, and in intrathecal (IT) form for neoplastic meningitis. An acute or subacute cerebellar syndrome is well described in association with high intravenous (IV) doses (≥3 g/m^2 every 12 h) [15], typically manifesting as nystagmus, dysarthria, dysmetria, and gait or truncal ataxia starting hours to days after the completion of the infusion. This is particularly common in patients with impaired renal function, who may develop neurotoxicity even at lower doses [16], and for whom a dose reduction is generally recommended [17]. Signs of cerebral dysfunction including lethargy and seizures can also be present, and the full clinical picture of posterior reversible encephalopathy syndrome (PRES) consisting of headaches, altered consciousness, visual disturbances, and seizures has also been described in association with both intravenous and intrathecal cytarabine [18, 19]. In fact, there might be some overlap between the classic cerebellar toxicity and PRES, since cases presenting with clinical signs of cerebellar toxicity but radiographic findings of PRES (white matter edema with greater involvement of the posterior cerebral lobes) have been reported [20]. Other rare central neurotoxic effects include anosmia, optic neuropathy [21], and parkinsonism [22]. Peripheral neurotoxicity is uncommon, but an acute polyneuropathy mimicking Guillain-Barré syndrome has been described [23, 24].

Intrathecal administration of cytarabine is associated with a chemical meningitis, whose incidence can be reduced with concomitant use of steroids. More serious adverse effects include myelopathy [25], stroke secondary to cerebral vasospasm [26], and acute cerebellitis causing tonsillar herniation [27]. The liposomal formulation (DepoCyt), which maintains cytotoxic concentrations of the drug in cerebrospinal fluid (CSF) for up to 14 days, has been associated with a high risk of moderate to severe neurotoxicity when administered in conjunction with IV cytarabine and methotrexate, including cauda equina and conus medullaris involvement, pseudotumor-cerebri-like syndrome, encephalitis, and seizures [28, 29].

26.2.3 Fluorouracil

Fluorouracil is a pyrimidine analog that inhibits its DNA synthesis. Neurotoxicity is relatively uncommon but is notably more frequent and severe in patients with dihydropyrimidine dehydrogenase deficiency (DPD) [30]. Two different patterns of neurological toxicity have traditionally been described in association with this drug: an acute cerebellar syndrome, with manifestations similar to those seen with cytarabine, and an acute encephalopathy. They occur in 2–5% of patients, typically developing days to weeks after administration, and in rare cases can present together [31]. Both entities tend to be self-limited, although irreversible cerebellar toxicity has been reported [32]. Although the pathophysiology of these toxicities is not well understood, fluorouracil-induced encephalopathy has been associated with an increase in serum ammonia and other radiographic and pathologic features of hepatic encephalopathy in the absence of liver dysfunction [33].

More recently, an acute leukoencephalopathy presenting with a variety of focal neurological deficits (sometimes stroke-like) and characteristic radiographic changes has been described [34, 35]. Magnetic resonance imaging (MRI)

shows reversible symmetric restricted diffusion not following a vascular distribution. A delayed subacute leukoencephalopathy, with more progressive symptoms and white matter MRI T2 hyperintensities, is also possible [36]; it is unclear if these represent two separate entities or different stages of the same process. Capecitabine, an oral prodrug of fluorouracil, can also cause an acute leukoencephalopathy with similar MRI findings [37].

26.2.4 Fludarabine

Fludarabine is a purine analog that also acts by inhibiting DNA synthesis and is mainly used in the treatment of chronic lymphocytic leukemia (CLL) and as part of some conditioning regimens prior to stem cell transplantation (SCT). It can cause severe neurotoxicity in the form of a delayed leukoencephalopathy, typically irreversible [38]. Symptoms develop weeks to months after fludarabine administration and most commonly include progressive encephalopathy and retrogeniculate blindness [39, 40]. MRI demonstrates periventricular white matter hyperintensities in T2 and fluid attenuated inversion recovery (FLAIR) sequences with associated restricted diffusion and no enhancement [39]; clinical deficits are characteristically out of proportion to the mild radiographic findings. In contrast, progressive multifocal leukoencephalopathy (PML), a distinct pathology caused by opportunistic infection with JC virus also described after therapy with fludarabine [41, 42], is associated with white matter hyperintensities that do not show restricted diffusion and tend to correlate better with the severity of signs and symptoms. These differences in MRI might be very useful in distinguishing between the two entities, since they might overlap clinically, and, although PCR for JC virus in CSF is classically positive in PML, negative results are certainly possible [42]. Lastly, PRES has been reported, but only in the context of multidrug regimens prior to SCT, being potentially secondary to other agents such as cyclosporine [39].

26.2.5 Methotrexate

Methotrexate (MTX) prevents DNA synthesis by inhibiting the enzyme dihydrofolate reductase. It does not readily cross the blood-brain barrier (BBB), so neurotoxicity mostly occurs when the CNS is targeted through high IV doses or IT administration for the treatment of CNS lymphoma, neoplastic meningitis, or certain types of leukemia. Leukoencephalopathy is the most common of its neurotoxic effects, having acute/subacute and chronic variants.

The incidence of MTX-induced acute or subacute leukoencephalopathy is not well established in adults. In children, in whom this complication appears to be more frequent, it occurred in 3.8% of patients in one prospective study [43]. Symptoms typically develop a few days after MTX administration and most commonly include seizures or acute neurological deficits mimicking stroke, with or without mental status changes [43, 44]. MRI demonstrates T2/FLAIR white matter lesions without enhancement and, in most (but not all) patients, more extensive areas of restricted diffusion during the acute phase [43, 45]. Clinical findings tend to resolve in a few days and frequently do not recur with subsequent cycles of MTX [43]. EEG findings are often nonspecific, such as slowing, but NCSE has rarely been reported [46]. There is a less common variant of acute neurotoxicity known as disseminated necrotizing leukoencephalopathy, which presents with more fulminant neurological decline, frequently irreversible or even fatal, and contrast-enhancing lesions on imaging [47].

Chronic leukoencephalopathy is also better described in children, but can occur in adults as well. Cognition and memory are most affected, with severity ranging from mild cognitive impairment or learning disabilities to a progressive picture clinically resembling normal pressure hydrocephalus [48–50]. Deficits are more pronounced in patients who also receive brain irradiation [48]. Symptoms typically appear over 6 months after treatment, but earlier onset is possible [49]. MRI reveals white matter changes, cortical atrophy, ventricular dilatation, and, in

young children, subcortical calcifications [49, 51]. White matter damage can also be seen on imaging of asymptomatic patients with history of MTX exposure [43, 51].

The aforementioned toxicities can appear after IT or high-dose IV MTX, but there are a few complications specific to IT therapy. Similar to cytarabine, a benign chemical meningitis is common (10% of patients) and can be prevented with concomitant use of steroids. IT MTX can cause a transverse myelopathy, manifesting with bilateral lower extremity weakness, sensory loss, and sphincter dysfunction starting days to months after administration [52]. MRI shows T2 hyperintensities in the spinal cord that in some patients preferentially involve the dorsal columns, similar to the radiographic findings in subacute combined degeneration; a common biochemical mechanism with this disorder has been proposed, since both MTX and vitamin B12 deficiency interfere with the synthesis of S-adenosylmethionine [52–54]. Pathology shows necrosis and vacuolar degeneration [52, 55]. Recovery is variable, and further administration of MTX is contraindicated. PRES has also rarely been described in association with IT MTX [56]. Intraventricular administration through an Ommaya reservoir has been associated with disproportionate toxicity if there are any impediments to CSF circulation such as a spinal subarachnoid block [57], which could be of special importance in patients with neoplastic meningitis in whom malignant cells might obstruct normal CSF flow.

26.2.6 Asparaginase

Asparaginase converts the amino acid asparagine into aspartic acid and ammonia, depleting its supply to neoplastic cells. Indirectly, it also alters the levels of several hemostasis-related proteins, causing a prothrombotic state that is responsible for most of its side effects, including neurotoxicity. Twenty to fifty percent of all asparaginase-related thrombotic events involve the CNS [58, 59]. The main neurological complication is cerebral venous sinus thrombosis (CVST), which can present with signs of increased intracranial pressure (including headache, with or without vomiting, and papilledema), seizures, and/or focal neurological deficits. Intracranial hemorrhage and ischemic stroke are less common and can occur independently or as a consequence of a CVST [60, 61]. Additionally, several cases of PRES in the absence of thrombotic intracranial pathology have been reported [62]. Asparaginase can also cause encephalopathy, which is usually reversible and in many cases is accompanied by elevated plasma ammonia, although it is not clear if this relationship is causal or a mere association [63].

26.3 Agents Associated with Predominantly Peripheral Neurotoxicity

26.3.1 Cisplatin

Platinum analogs, such as cisplatin, are active against a variety of neoplasms by promoting the formation of DNA cross-links, which inhibit DNA synthesis. Cisplatin is the most neurotoxic of these agents, with the leading toxicity being peripheral neuropathy. This is dose- and duration-dependent, typically starting at cumulative doses of 300 mg/m^2 and becoming almost universal at doses greater than 600 mg/m^2 [64, 65]. Incidence seems to be further modulated by certain genetic polymorphisms in the enzymes involved in cisplatin metabolism [66]. Similar to other chemotherapy-induced neuropathies, it presents with sensory symptoms that progress symmetrically from distal to proximal. The first manifestations include loss of ankle jerks and impairment of vibratory sensation at the feet, which can then evolve into numbness, pain, paresthesias, more widespread reflex abolition, and sensory ataxia from loss of joint position sense [67]. Cisplatin causes apoptosis at the level of the dorsal root ganglion (DRG), where the neuronal bodies for large myelinated sensory fibers reside [68], which explains why strength and sensation to temperature and pinprick, mediated by different axons, are preserved. Accordingly, nerve conduction studies show evidence of decreased amplitude of sensory nerve potentials, indicative

of sensory axonal damage [69]. The neuropathy develops gradually during treatment, but symptoms can also begin or worsen after discontinuation, a phenomenon known as "coasting" [70]. Although there is eventual improvement, recovery is often incomplete. Currently no agents have been proven to prevent or improve cisplatin-induced neuropathy [71], and management is limited to symptomatic treatment.

Cisplatin can also cause ototoxicity, manifesting as tinnitus with or without high-frequency sensorineural hearing loss. Reported incidence is very variable, with some degree of hearing impairment detected in up to 100% of patients in some studies [72]. This inconsistency is in part determined by the different diagnostic criteria used to define ototoxicity, but, similarly to peripheral neuropathy, the risk is affected by other variables such as cumulative dose [73] or genetic polymorphisms [66]. Early detection through audiometry at baseline and periodically during and after treatment is recommended [72], since there are no effective treatments to reverse it.

Central neurotoxicity is significantly less frequent, presenting most commonly in the form of encephalopathy. Accompanying seizures and cortical blindness have classically been described [74, 75], and it is possible that many of these represent cases of what has more recently been identified as PRES [76]. Cisplatin has also been associated with acute ischemic stroke in young patients, in some cases with evidence of concomitant large vessel occlusion [77].

26.3.2 Oxaliplatin

Oxaliplatin is another platinum compound that has peripheral nerve toxicity among its major side effects, causing two distinct forms of neuropathy. The first one is an acute syndrome presenting during or shortly after infusion with cold-induced paresthesias, throat discomfort, intolerance to cold liquids, jaw stiffness, muscle cramps, and fasciculations [78, 79]. It affects over 85% of patients receiving standard doses and recurs in subsequent cycles, reaching peak severity in the second cycle and then maintaining intensity throughout the rest of the treatment [79]. Prolongation of the infusion time from two to six hours has been associated with lower rates of this complication [80]. The severity and complexity of this acute neuropathy seems to correlate with the incidence and intensity of the second form of peripheral neurotoxicity [78, 79]: a chronic neuropathy that is clinically and electrophysiologically comparable to that caused by cisplatin, with predominantly sensory symptoms. However, oxaliplatin-induced chronic neuropathy is slightly less common and less severe than its cisplatin-related counterpart, which has been attributed to milder toxic effects on DRG neurons [81].

26.3.3 Carboplatin

In contrast to other platinum analogs, carboplatin rarely causes neurotoxicity when used at conventional doses. On the other hand, high-dose therapy has been associated with a severe sensory-predominant neuropathy and ototoxicity [82]. Other uncommon neurotoxicities include PRES [83] and papilledema [84].

26.3.4 Paclitaxel

Several chemotherapeutic agents exert their antineoplastic effects by interfering with microtubule function, which leads to mitotic arrest of dividing cells and eventually apoptosis. This mechanism is shared by taxanes (including paclitaxel), epothilones, and vinca alkaloids, all of which also have in common a high potential for peripheral nerve toxicity, attributed to disruption of the microtubule-dependent process of axonal transport [85]. Reported incidence of paclitaxel-induced neuropathy is variable but surpasses 50%, with cumulative dose being the most important risk factor [86]. It predominantly affects sensory nerves, causing distal numbness and paresthesias with loss of reflexes, although a much less common motor neuropathy has also been described [87]. As with other chemotherapy-induced neuropathies, no effective treatment or prevention is

available, but prognosis is relatively good, with complete recovery in at least half of cases [86]. Additionally, an acute pain syndrome appears in over 80% of patients 1–2 days after each cycle, lasting for 4–5 days and typically manifesting as aching pain in varied distributions, more commonly involving the lower extremities. Although this condition was initially believed to be of musculoskeletal origin, its severity has been shown to correlate with the development of chronic sensory neuropathy, suggesting this phenomenon is also neuropathic in nature [88]. Very rarely, paclitaxel has been associated with seizures [89] and with a transient encephalopathy that manifests as confusion, behavioral changes, and word-finding difficulties starting a few days after treatment [90]. The nanoparticle albumin-bound formulation of paclitaxel, nab-paclitaxel, has a similar neurotoxicity profile; there are conflicting reports regarding whether either form of neuropathy is more or less frequent with this drug than with the standard formulation [86, 91].

26.3.5 Docetaxel and Cabazitaxel

Docetaxel, another taxane, can also cause a chronic sensory neuropathy and an acute pain syndrome, both with slightly lower incidence than paclitaxel [86, 91]. Rare side effects include Lhermitte's phenomenon (an electric shock-like sensation shooting down the back and limbs with neck flexion) [92] as well as an optic neuropathy [93]. Sensory neuropathy is seen even less frequently with cabazitaxel, a semisynthetic derivative of docetaxel [86].

26.3.6 Ixabepilone

Ixabepilone belongs to the epothilone class and is mostly used for the treatment of advanced breast cancer. Similar to taxanes, it causes a predominantly sensory peripheral neuropathy in over 60% of patients; motor and autonomic involvement has been rarely reported. The neuropathy is progressively more frequent at higher cumulative doses and typically develops after several cycles, resolving within a few weeks of drug discontinuation [94]. Even though it is reversible, management may require decreasing the dose in subsequent cycles or even stopping the medication [95].

26.3.7 Eribulin

Eribulin is another microtubule inhibitor whose main indication is also in the treatment of metastatic breast cancer. Compared to ixabepilone, the incidence of neuropathy is lower at 35%, and both the onset and resolution occur later; this more prolonged course might be influenced by a greater number of cycles and longer treatment duration with eribulin, in part due to better tolerability [96].

26.3.8 Vincristine and Other Vinca Alkaloids

Vincristine is the most neurotoxic of the vinca alkaloids, causing a peripheral neuropathy in virtually all patients exposed to standard doses. Loss of reflexes and sensory signs and symptoms such as numbness, tingling, and pain spreading from distal to proximal are most common, but motor involvement in the form of distal weakness also occurs in a smaller percentage of patients [97]. Effects are dose-dependent, and although eventual recovery is the norm, worsening of symptoms after drug discontinuation is possible [98]. In contrast to other chemotherapeutic agents, autonomic neuropathy is common in patients receiving vincristine; constipation is the most frequent presentation, but other signs such as orthostatic hypotension or urinary retention can be present as well [99]. Severe forms of peripheral neuropathy have been described in patients with Charcot-Marie-Tooth disease [100] and in those receiving concomitant antifungal treatment with azoles [101]; vincristine use is discouraged in these situations.

In addition to polyneuropathy, vincristine has been implicated in a variety of focal mononeuropathies, including multiple cranial neuropathies

causing ocular or facial weakness [102], vocal cord paralysis from recurrent laryngeal nerve involvement [103], diaphragmatic weakness due to phrenic neuropathy [104], or blindness arising from optic atrophy [105]. Central neurotoxicity has rarely been reported, in the form of inappropriate secretion of antidiuretic hormone (SIADH) [106] or PRES [107]. Vinca alkaloids are vesicants and can induce severe tissue injury when used in non-intravenous routes; there have been multiple case reports of inadvertent intrathecal administration of vincristine, causing an ascending myelopathy that is followed in a majority of cases by coma and death [108].

Vinorelbine is another vinca alkaloid associated with high incidence of sensorimotor peripheral neuropathy, which is reversible and milder than the one induced by vincristine [109]. Vinblastine can also cause a similar, mild peripheral neuropathy that is typically not clinically relevant, given that the dose-limiting side effects of this drug are hematological and manifest prior to neurotoxicity [67].

26.3.9 Bortezomib, Carfilzomib, and Ixazomib

Bortezomib is a proteasome inhibitor used in the treatment of multiple myeloma (MM). It produces a peripheral neuropathy in approximately 40% of patients [110]. The most common and incapacitating symptom is distal neuropathic pain in a stocking-and-glove distribution, accompanied by loss of proprioceptive sense and reflexes [67]. It typically appears after five cycles, which corresponds to a cumulative dose of 26 mg/m^2 in the standard dosing scheme, and plateaus after cycle 8. Depending on severity, dose reduction, withholding, or discontinuation of the drug is recommended, leading to improvement or resolution of symptoms in most patients [111]. The use of once-weekly as opposed to twice-weekly schedules and of subcutaneous instead of IV administration seems to reduce the incidence of neuropathy without compromising efficacy [112, 113]. Besides this sensory-predominant neuropathy, which—like most toxic neuropathies—is axonal in nature, a less common variant with sensorimotor involvement and evidence of demyelination in electrophysiological and pathological studies has been reported [114]. PRES has also been described, albeit very rarely [115]. A second generation of proteasome inhibitors has been developed in recent years; carfilzomib and ixazomib are the agents in this category currently approved for treatment of refractory or recurrent MM, and both of them have demonstrated a lower incidence of neuropathy relative to bortezomib [116, 117].

26.3.10 Thalidomide, Lenalidomide, and Pomalidomide

Thalidomide is a drug with antiangiogenic and immunomodulatory properties whose main antineoplastic use is in the treatment of MM. Peripheral neuropathy is a common side effect, characteristically presenting with distal paresthesias with or without sensory loss, and occasionally mild weakness [118]. Constipation attributed to autonomic dysfunction is also seen in more than half the patients [119]. In terms of central neurotoxicity, somnolence is the most common complaint, but dizziness and tremor have also been reported [120]. Parallel to the proteasome inhibitors, second generation agents related to thalidomide—including lenalidomide and pomalidomide—are significantly less neurotoxic, causing peripheral neuropathy in less than 5% of patients in clinical trials [121, 122].

26.4 Conclusion

Chemotherapy can produce both central and peripheral nervous system toxicity, which can dramatically affect the quality of life of cancer survivors, limit further treatments, or even be fatal. Although there is significant overlap between agents, particularly with chemotherapy-induced peripheral neuropathy, many drugs have distinct toxicities whose recognition is key to promptly establishing a diagnosis and determining the appropriate management.

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27 Neurological Complications of Targeted Therapies

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27.1 Introduction

Neurotoxicity secondary to cancer-directed therapies is a widely recognized phenomenon in the treatment of patients with solid and hematologic malignancies. As there has been more recent use of targeted agents, early and timely recognition of rare but potential severe adverse neurologic effect will be critical, as this may limit the treatment course [1]. Toxicity may be the result of direct effects upon the nervous system, such as with chemotherapy-induced peripheral neuropathy, while there are also indirect effects to consider, which may occur due to metabolic or toxic factors produced by therapy. Early recognition is essential, particularly as the development of novel therapies has led to rapid adoption of these therapies as standard of care. As many of the agents and modalities discussed in this section have been established as treatments in systemic cancers, many are currently in use for central nervous system metastases or are under investigation, thus requiring more attention in distinguishing the effect of treatment from progressive intracranial disease.

27.1.1 EGFR

Epidermal growth factor receptor (EGFR) is part of the erbB family, encoded by erbB-1 (HER1), erbB-2 (HER2), erbB-3 (HER3), and erbB-4 (HER4), and is frequently overexpressed in non-small cell lung cancer (NSCLC) [2–4]. EGFR overexpression is found most commonly in adenocarcinoma histology and has been associated most frequently with women, those of East Asian descent, and non-smokers [5]. Over the past decade, collective understanding of the prognostic significance of EGFR in NSCLC has evolved, with advances in molecular profiling and characterization leading to the development of agents targeting EGFR. Use of EGFR tyrosine kinase inhibitors (TKI) now represents the standard of care for treatment of patients with NSCLC and activations mutations in EGFR [6]. In EGFR-mutated patients, initiation of EGFR TKIs in the newly diagnosed setting has led to prolonged progression-free (PFS) when compared to chemotherapy [7–10]. The later-generation EGFR TKIs have continued to demonstrate survival benefit in comparison to chemotherapy, both in local and metastatic NSCLC, notably osimertinib, given its demonstrated CNS activity [11].

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27.1.2 Gefitinib

Gefitinib was the first EGFR TKI to be approved as a monotherapy for patients with previously treated NSCLC. In the phase III IPASS trial, patients with EGFR-mutated NSCLC were randomized to either gefitinib or carboplatin/paclitaxel in the frontline setting [8]. While neurotoxicity was observed in the gefitinib-treated cohort in 66 patients (10.9%), 69.9% of patients randomized to the carboplatin-paclitaxel arm noted neurotoxic adverse effects [12]. Although prospective trials have shown activity of gefitinib in brain metastases from NSCLC, osimertinib remains the preferred agent in this setting [13].

Ocular side effects, specifically visual disturbances, were observed in two phase II trials in which patients with advanced NSCLC were treated with gefitinib. These were primarily described as blurred vision, photophobia, and bilateral hemianopia; however, it was not felt that gefitinib was associated with these adverse effects [14].

27.1.3 Erlotinib

Erlotinib is a first-generation EGFR TKI first approved in 2004 for second-line monotherapy in treatment of patients with locally advanced or metastatic NSCLC, following initial treatment with chemotherapy [15]. In patients with EGFR-mutated NSCLC brain metastases, erlotinib was shown to delay time to intracranial disease progression as well as overall survival in comparison to EGFR wild-type disease [16]. Regarding associated toxicity, in the phase III EURTAC trial which led to the approval of erlotinib as a first-line agent, the predominant drug-related adverse effects were non-neurologic, namely, fatigue, rash, and diarrhea. Among the 84 patients who were randomized to erlotinib, 8 (9%) reported neuropathy, as compared to 12 of 82 patients receiving standard chemotherapy [7].

27.1.4 Afatinib

Afatinib is a second-generation, irreversible pan-EGFR TKI approved for initial therapy of patients with advanced EGFR-mutant NSCLC. In the combined analysis of the phase III trials LUX-LUNG 3 and LUX-LUNG 6, in which afatinib was compared to chemotherapy in first-line treatment, in patients with asymptomatic brain metastases, afatinib was associated with longer PFS [9, 17–19]. In comparison to the other EGFR TKIs, neurotoxicity is uncommon with afatinib in the LUX-LUNG trials [20].

27.1.5 Osimertinib

Osimertinib is a third-generation irreversible EGFR TKI which inhibits both EGFR TKI-sensitizing and EGFR T790 M resistance mutations [6]. It is favored as initial management for patients with synchronous presentation of systemic and CNS disease [6]. Similar to other EGFR TKIs, it is not active in EGFR wild-type disease. It has been used increasingly in the first-line setting for treatment of advanced EGFR-mutant NSCLC, having shown efficacy superior to other TKIs for first-line treatment of EFGR-mutated NSCLC [6]. In initial and salvage therapy, osimertinib has also demonstrated improvement in central nervous system (CNS) penetration as well as durable response rates [11, 21]. Neurologic adverse effects in the osimertinib arm included headache, back pain, and asthenia [11].

27.1.6 Cetuximab

Cetuximab is a chimeric mouse/human monoclonal antibody against EGFR frequently used in management of head and neck, as well as colorectal cancers [22]. In the study of cetuximab monotherapy for salvage treatment of advanced colorectal cancer, among the most frequently reported adverse effects included headaches [23]. Additionally, there have been case reports of cetuximab-associated chronic inflammatory demyelinating polyneuropathy (CIDP), though causality was not established [24]. Nonconvulsive status epilepticus in the setting of posterior reversible encephalopathy syndrome (PRES) secondary to cetuximab has also been reported [25].

27.2 ALK

Approximately 5% of NSCLCs harbor alterations in the anaplastic lymphoma kinase (ALK) gene [27]. An inversion in chromosome 2 resulting in the 5′ end of the echinoderm microtubule-associated protein-like 4 (EML4) gene with the 3′ end of the ALK gene results in the fusion oncogene EML4-ALK [28]. Like EGFR-mutated NSCLC, ALK-rearranged tumors are associated with specific clinical phenotypes including young age and never smokers, as well as adenocarcinoma histology [3]. ALK rearrangements are mutually exclusive of EGFR and KRAS mutations. Screening for ALK following histologic confirmation of NSCLC is essential, as ALK-rearranged tumors are sensitive to ALK TKIs, which have been established as first-line therapy for newly diagnosed ALK-rearranged NSCLC [29]. Alectinib and ceritinib, specifically, have gained FDA approval for treatment of brain metastases in both the newly diagnosed and pretreated settings [26, 27].

27.2.1 Crizotinib

Crizotinib is a first-generation ALK TKI and one of the earliest used in clinical settings. In patients with ALK-rearranged brain metastases, its use has declined secondary to improved outcomes noted with alectinib and ceritinib as well as to higher rates of CNS relapse which have been observed [28]. In a large phase III trial, PROFILE 1014, among the most common neurologic adverse effects identified in this trial include vision changes (73.1%), neuropathy (50%), headache (48%), and dizziness (44%) [29].

27.2.2 Alectinib

Alectinib is FDA approved for first-line therapy for patients with ALK-rearranged NSCLC and for patients who had progressed while previously on crizotinib. In at least three phase III studies, ALEX, J-ALEX, and ALESIA, alectinib was compared to crizotinib in untreated, ALK-rearranged NSCLC. In all three trials, alectinib was associated with either prolonged PFS or reduction in the risk of disease progression or death [30–32]. Alectinib has additionally been found to have improved CNS penetration, achieving high brain-to-plasma ratios, intracranial response rates, and delayed risk of CNS progression in patients with baseline brain metastases [32]. In the J-ALEX trial, neurologic toxicity including dysgeusia, headache, and dizziness was observed and, however, was either grade 1 or grade 2. Additionally, the frequency of these events was lower in the alectinib-treated arm in comparison to crizotinib [32].

27.2.3 Ceritinib

Ceritinib is a second-generation selective ALK TKI with established potency 20 times greater than crizotinib and FDA approved in the first-line setting for patients with advanced, ALK-rearranged NSCLC [33]. In ASCEND-4, a randomized phase III trial in which ceritinib was compared to standard chemotherapy (pemetrexed-platinum therapy), in patients with measurable brain metastases, ceritinib was associated with prolonged PFS and higher intracranial response rates [33]. Headache (16%) was the most commonly reported neurologic adverse effect [33].

27.2.4 Brigatinib

Brigatinib is a second-generation ALK inhibitor which has activity against both ALK and ROS1 mutations and which has been associated with prolonged PFS in patients with untreated, advanced ALK-rearranged NSCLC, when compared to crizotinib [34]. Additionally, brigatinib has also been shown to result in higher intracranial response rates in patients with baseline brain metastases, notably in patients who received prior treatment with crizotinib [35]. There has not been any reported significant neurologic toxicity associated with brigatinib [34].

27.2.5 Lorlatinib

In the setting of suspected ALK resistance, there may still be therapeutic benefit in use of additional ALK inhibitor therapy. Lorlatinib has activity against all known ALK inhibitor resistance mechanisms and was granted FDA approval for treatment of ALK-rearranged NSCLC following progression on crizotinib and an additional ALK inhibitor [35]. Although the optimal timing of lorlatinib in treatment of brain metastases remains under investigation, it has demonstrated activity within the CNS. Lorlatinib-related neurologic adverse effects reported included sensory peripheral neuropathy (30%), cognitive changes (18%), and dizziness (9%) of patients [35].

27.3 NTRK

The neurotrophin receptor kinase genes, NTRK1, NTRK2, or NTRK3, encode the TRKA, TRKB, and TRKC proteins (collectively known as the TRK family proteins) and have been under investigation for cancer therapy [36]. In cancer, TRK proteins can be activated by several mechanisms: somatic NTRK mutations (colorectal cancer, NSCLC, melanoma, and AML), activating splice variants of NTRK1 gene (neuroblastoma, AML), and through TRK overexpression (breast, cutaneous, and lung cancers) [37–42]. NTRK fusions have also been identified in rare cancers and are found at varying frequencies in adult and pediatric populations [43]. Among the NTRK TKIs, larotrectinib and entrectinib are in clinical development; entrectinib specifically has shown activity in brain metastases in preclinical and early-phase trials [44, 45].

27.3.1 Larotrectinib

Larotrectinib is a potent and selective inhibitor of all three TRK proteins, which has gained FDA approval for adult and pediatric patients with advanced solid tumors harboring an NTRK gene fusion. In a phase I study in adults and phase II study in pediatric patients with TRK fusion-positive cancers receiving larotrectinib, of 55 patients, dizziness (25%) and headache (2%) of all grades were reported to be related to treatment [43]. In the pooled analysis of 176 adult and pediatric patients, neurologic events of any grade occurred in 53% of patients including dizziness, gait disturbance, and paresthesias. There was one grade 4 encephalopathy occurring in one patient (0.6%) [43].

27.3.2 Entrectinib

Entrectinib is an oral, pan-TRK TKI which has additional activity against ROS1 and ALK [46]. To date, it has been tested in four clinical trials in patients harboring NTRK, ROS1, or ALK fusions [47]. In a combined safety analysis of two phase I trials of entrectinib in patients with advanced solid tumors, neurologic side effects included paresthesias (29%), myalgias (23%), and dizziness (19%) which were all grade 1 or 2; there was one grade 3 cognitive disturbance which improved with dose interruption [48].

27.4 Her2

Human epidermal growth factor receptor 2 (HER2), a member of the EGFR family of receptors, is an oncogene, also referred to as HER2/neu or ERBB-2. It is a predictive factor in breast cancer as its overexpression is associated with disease recurrence and overall worse prognosis [49]. There is a 12% 10-year risk of development of brain metastases in the setting of HER2-positive breast cancer. HER2 overexpression is found in 20% of breast cancers, and confirming status is essential in the care of patients with breast cancer as HER2 overexpressing tumors are likely to benefit from HER2-targeting agents. Furthermore, tumors which lack HER2 overexpression are less likely to benefit from such therapies [50]. In addition to clinical use in HER2-expressing breast cancers, the HER2-directed agents have also been used in management of HER2 overexpressing or amplified gastroesophageal adenocarcinoma [51].

27.4.1 Trastuzumab

Trastuzumab is a monoclonal antibody directed against HER2 and the only HER2-directed agent which has been associated with a survival benefit when combined with chemotherapy for adjuvant treatment of HER2-positive breast cancer [52]. There has been concern that while there is prolonged survival in Her2-positive breast cancer brain metastases with trastuzumab, this is owing to extracranial control of disease—as in the setting of an intact blood-brain barrier (BBB), the CNS penetration of trastuzumab is thought to be minimal [53, 54]. Additionally, following trastuzumab, the brain is frequently the first site of relapse in patients with HER2-positive disease. Headaches are among the most frequently reported treatment-related symptoms, noted in 10% of patients [52]. There have also been case reports of trastuzumab-induced migraine [55].

27.4.2 Ado-trastuzumab Emtansine

Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate, composed of trastuzumab, a derivative of maytansine 1 (DM1), which is a microtubule inhibitor, and a thioether linker [56]. It is used as alternative first-line treatment for HER2-positive breast cancer or may also be used as second-line therapy with potential use in the setting of brain metastases. The phase III MARIANNE trial compared T-DM1 with placebo, T-DM1 and pertuzumab, trastuzumab, and taxane chemotherapy for advanced HER2-positive breast cancer. Peripheral sensory neuropathy was reported more frequently in the taxane with trastuzumab (20.1%) compared to the T-DM1 with pertuzumab (13%) and T-DM1 only arms (12%) [57]. The presence of microtubule inhibitor in T-DM1 has been proposed as a mechanism for development of neuropathy [58].

27.4.3 Lapatinib

Lapatinib is an EGFR1- and HER2-directed TKI which has been used in combination in various clinical scenarios for management of HER2-positive breast cancer and refractory brain metastases, specifically in combination with capecitabine. Neurotoxicity has not been observed with lapatinib [59].

27.4.4 Pertuzumab

Pertuzumab is a monoclonal antibody against HER2 which is combined with trastuzumab and taxane chemotherapy for treatment of previously untreated metastatic HER2-positive breast cancer. The role of pertuzumab in management of brain metastases remains under investigation. in the post hoc analysis of the phase III trial in which pertuzumab, trastuzumab, and taxane chemotherapy were compared with placebo, trastuzumab, and docetaxel, the median time to development of brain metastases was prolonged in comparison to the placebo group [60, 61]. In this phase III trial, across all grades, headaches (17%) and peripheral neuropathy (2.7%) were more frequent in the pertuzumab-treated group [60].

27.4.5 Neratinib

Neratinib is a dual-kinase inhibitor approved for adjuvant treatment following trastuzumab for early HER2-positive breast cancer [62]. It has not yet shown improvement in PFS or intracranial response rates in the setting of brain metastases [62]. In the randomized phase III trial ExteNET, the neurologic adverse effects reported including headaches (19%), muscle spasms (11%), and dizziness (10%) [63].

27.5 PARP Inhibitors

Poly (adenosine diphosphate [ADP]—ribose) polymerase (PARP) is essential to the repair of single-stranded DNA breaks through the base-excision repair (BER) pathway. Through synthetic lethality, PARP inhibition leads to formation of double-stranded DNA breaks which are unable to be accurately repaired in

tumors with homologous recombination deficiency [64, 65]. 15% of epithelial ovarian cancers are deficient in homologous recombination repair, likely owing to germline mutations in BRCA 1 and 2 [66, 67]. PARP inhibition is thus an attractive therapeutic option for treatment of ovarian cancer in women with BRCA 1 or 2 germline mutations as well as in breast cancer brain metastases, which demonstrate higher levels of homologous recombination deficiency [68].

27.5.1 Olaparib

Olaparib is a first-in-class oral PARP inhibitor which induces synthetic lethality in BRCA 1- and 2-deficient tumor cells. In a phase II study, olaparib monotherapy versus placebo, in patients with platinum-sensitive, relapsed high-grade serous ovarian carcinoma was associated with prolonged PFS and a lower rate of grade 3 and 4 toxicity [69]. In the olaparib-treated arm, the most common neurologic adverse effects were headache (18.4%) and asthenia (11.8%) [69]. In a separate phase I study, olaparib was combined with paclitaxel and/or carboplatin and then subsequently continued on olaparib monotherapy [70]. Three of 21 patients stopped combination therapy due to development of peripheral neuropathy [70].

27.5.2 Veliparib

In the phase II trial I-SPY 2, veliparib, an oral PARP-1 and PARP-2 inhibitor, showed improved pathological complete responses in patients with early breast cancer treated with veliparib in combination with neoadjuvant chemotherapy [71]. A subsequent phase III study, BrighTNess, showed that while there was an increase in the pathological complete response with the addition of veliparib and carboplatin to paclitaxel followed by cyclophosphamide and doxorubicin, the addition of veliparib to carboplatin and paclitaxel did not [71]. In the veliparib-treated group, peripheral sensory neuropathy (38%), dysgeusia (19%), and dizziness (14%) were more frequent than in the veliparib placebo groups [71].

27.6 Cyclin-Dependent Kinase (CDK) Inhibition

The cyclin-dependent kinases (CDK), specifically CDK 4/6 in combination with cyclin D, are critical drivers of cell proliferation and thus provide a therapeutic opportunity for cancer treatments due to disordered cell cycle regulation [72, 73]. Development of inhibitors of CDK 4/6 has been an exciting area of exploration of potential cancer therapies, specifically in treatment of breast cancer brain metastases.

27.6.1 Palbociclib

Palbociclib is an oral CDK inhibitor currently FDA approved for metastatic, hormone receptor (HR)-positive, HER2-negative metastatic breast cancer, in combination with the aromatase inhibitor (AI) letrozole [74]. In a phase III study, patients with untreated, HER-negative, HR-positive breast cancer were randomized to either palbociclib and letrozole or placebo and letrozole. No neurologic adverse effects were reported [74]. In an earlier phase II study, the most common neurologic adverse effects were headaches (14%), dizziness, and peripheral neuropathy (10%) [75].

27.6.2 Abemaciclib

Abemaciclib is an oral CDK inhibitor FDA approved for initial treatment of postmenopausal women with HR-positive, HER2-negative breast cancer, as shown in the phase III study MONARCH 3 [73]. Only headaches (15.6%) were reported in the abemaciclib treatment arm [73]. Abemaciclib has also been used in management of HR-positive, HER2-negative breast cancer brain metastases and metastatic KRAS-mutated NSCLC [73, 76].

27.6.3 Ribociclib

Ribociclib is approved in combination with letrozole in postmenopausal women with metastatic or advanced HER2-negative, HR-positive breast cancer [77]. In a comparison of letrozole monotherapy and ribociclib plus, headaches occurred in 26.9% of patients who received ribociclib [77]. This combination is currently under investigation in a phase I trial in treatment of breast cancer brain metastases (NCT03096847).

27.7 Phosphoinositide-3-Kinase (PI3K) Inhibitors

Phosphoinositide-3-kinase (PI3K) pathway is a signal transduction pathway and one of the most active cell signaling pathways in human cancer [78]. PI3K isoforms (gamma and delta) are major effectors of receptor tyrosine kinases, transducing signal into intracellular messages [78]. PI3K delta is constitutively active in hematologic malignancies, and its inhibition targets proliferation and survival of leukemia and lymphoma cells. PI3K gamma reduces differentiation and migration of cells within the tumor microenvironment, which support and protect malignant cells [79]. For these reasons, the PI3K pathway is a rationale target for therapeutic interventions in treatment of hematologic malignancies and in combination with hormonal therapy for breast cancer brain metastases [80].

27.7.1 Idelalisib

Idelalisib is an oral, selective PI3K delta inhibitor which promotes apoptosis, approved currently for treatment of recurrent chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL) in combination with rituximab. Early-phase clinical trials established antitumor activity as well as safety in CLL patients and in the context of indolent non-Hodgkin's lymphoma (NHL) [81]. A large, phase III randomized trial of idelalisib and rituximab versus placebo and rituximab in relapsed/refractory CLL demonstrated improved ORR on the idelalisib arm as well as prolonged OS [82]. In this trial, no significant neurologic adverse effects were reported.

27.7.2 Duvelisib

Duvelisib is a dual inhibitor of PI3K delta and gamma, which has shown antitumor activity also in management of relapsed/refractory CLL/SLL. It gained recent FDA approval as monotherapy for relapsed/refractory CLL/SLL following failure of two prior lines of therapy. In two phase I trials, duvelisib was associated with significant clinical responses across multiple disease types including indolent NHL, relapsed/refractory CLL, and peripheral and cutaneous T-cell lymphoma (TCL) [82, 83]. Headache was reported in 18% of patients who received duvelisib [83].

27.8 Bruton's Tyrosine Kinase (BTK) Inhibitors

Bruton's tyrosine kinase (BTK) is a Tec kinase which is critical to B-cell receptor (BCR) signaling, which is activated in CLL. When activated, BTK leads to downstream activation of cell survival pathways including MAPK and NF-kappa B [84]. BTK inhibition is a promising therapeutic target for treatment of hematologic malignancies, with investigations underway for its role in CNS relapse of disease [84, 85].

27.8.1 Ibrutinib

Ibrutinib is a first-in-class, oral, selective BTK inhibitor which is FDA approved for untreated and previously treated CLL. Its use has also been explored in CNS relapse of mantle cell lymphoma, which occurs in 4.1% of cases [85]. Ibrutinib binds to its target (cysteine-481 residue of BTK) and thus interrupts BCR signaling leading to B-cell apoptosis [84]. The most devastating complication associated with ibrutinib is hemorrhage from any site; however, there have been few cases of reported intracranial hemor-

rhage [86]. Other neurologic adverse effects noted include headache, which was reported in 13.8% of patients receiving ibrutinib [87].

Ibrutinib can cause hypogammaglobulinemia, thus predisposing patients with CLL to infections, namely, of the upper respiratory tract and other bacterial and fungal infections which occur in the setting of immunosuppression, specifically pneumocystis carinii and aspergillus [88–90]. Progressive multifocal leukoencephalopathy (PML) is a rare but devastating neurologic disease which is triggered by the polyoma John Cunningham (JC) virus, which has been reported in a patient with CLL following treatment with ibrutinib [91].

27.8.2 Acalabrutinib

Acalabrutinib is an irreversible BTK inhibitor which has properties designed to be more selective and specific in comparison to ibrutinib, with less off-target effects [92]. Phase I/II studies in patients with relapsed CLL have shown ORR which have been consistent across all high-risk subgroups with 95% of patients showing some response to therapy [92]. The most common adverse effect was headache in 43% of patients [92]. As with ibrutinib, cases of PML have also occurred during treatment with acalabrutinib [93].

27.9 BRAF and MEK Inhibitors

BRAF is a serine threonine kinase and a member of the RAF kinase family, as part of the RAF/MEK/ERK serine threonine kinase cascade which regulates cell growth and differentiation and has been associated with human cancers [93]. Activating mutations in BRAF are present in up to 60% of advanced melanoma, with 80–90% of the mutations consisting of the substitution of glutamic acid for valine at position 600 (V600E); the remaining mutations involve substitution of glutamic acid for lysine (V600K) [93]. A phase I study with an oral BRAF inhibitor in patients with BRAF-mutated metastatic melanoma showed complete or partial tumor regression in 11 of 16 patients in the dose-escalation cohort and in 26 of 32 patients in the extension cohort [94]. BRAF inhibitors have demonstrated impact as monotherapy, but now combination regimen with MEK inhibitors has supplanted monotherapy. MEK or MAPK kinase is downstream of BRAF and has been associated with improved PFS and OS in BRAF-mutated melanoma [95–97]. These agents have established activity in the CNS, with combination BRAF/MEK inhibition being preferred therapy in certain settings. In addition to the combination regimens discussed here, investigation of encorafenib and binimetinib is ongoing [98].

27.9.1 Dabrafenib and Trametinib

Dabrafenib is an oral reversible BRAF inhibitor which has demonstrated activity in treatment of advanced melanoma, both as monotherapy and in combination with MEK inhibition. In a phase III trial, comparing dabrafenib to dacarbazine in patients with unresectable stage III or IV melanoma harboring BRAF mutations, headaches were reported in 5% of patients receiving dabrafenib [95].

Dabrafenib has been combined with MEK inhibition (trametinib) to delay development of resistance and to mitigate non-neurologic toxicity of BRAF inhibition. Trametinib is a highly selective inhibitor of MEK1/MEK2 and was initially approved as monotherapy for BRAF-mutated melanoma. In evaluation of combination therapy, two phase III trials of dabrafenib/trametinib have been conducted: in one, the combination of dabrafenib and trametinib was compared to dabrafenib and placebo. Neurologic adverse effects were uncommon with combination treatment. Ocular symptoms have been reported with trametinib but are also quite rare [99].

27.10 Bcr-Abl

The driver event in chronic myelogenous leukemia (CML) is the translocation between the long arms of chromosomes 9 and 22, resulting in a shortened chromosome 22 also known as the Philadelphia chromosome (Ph) [100]. The manifestation of which is the formation of the fusion gene *BCR-ABL1* on chromosome 22, which is found in over 90% of CML patients [100, 101]. There are three common variants of the BCR-ABL1 proteins which result from the translocation, which is determined by the site of the break point. Oral TKIs are the standard of care in treatment of CML for initial management. A newer second-generation TKI, radotinib, has gained approval outside of the US for initial treatment of CML or TKI-refractory CML [102]. Arterial ischemic events have been described as a class-wide effect of TKIs, including cerebrovascular involvement [103]. To date, these drugs have not been studied in brain metastases or are reported to have minimal activity in the CNS [104].

27.10.1 Imatinib

Imatinib is a first-generation TKI and the first TKI available for use in patients with CML in chronic phase (CP CML) [105]. Prospective trials have compared imatinib to interferon in combination with cytarabine in initial treatment for CP CML [105]. In the imatinib-treated group, headache was the most common neurologic adverse effect, reported in 31.2% of patients [105].

27.10.2 Dasatinib

Dasatinib is a second-generation BCR-ABL TKI which gained initial approval for second-line treatment of CML in the setting of imatinib failure [106]. The DASISION trial was a randomized phase III study in which dasatinib was compared to imatinib in treatment-naive CML [107]. Among ten cardiovascular ischemic events which occurred within 1 year of dasatinib, there were two transient ischemic attacks [107]. Also noted was one death secondary to Klebsiella meningoencephalitis [107].

27.10.3 Bosutinib

Bosutinib is an oral TKI and inhibitor of ABL and SRC kinase FDA approved also for initial treatment of CP CML. In a phase II study of bosutinib in recurrent glioblastoma, in which nine patients were enrolled, seizure and cerebral edema were reported; however, these were not attributed to bosutinib [108].

27.10.4 Ponatinib

Ponatinib is approved in the US for adult patients with refractory CML or Philadelphia-positive (Ph+) acute lymphocytic leukemia (ALL), as well in those with BCR-ABL threonine to isoleucine (T315I) mutation [109]. In a phase II trial of ponatinib in patients with CML or Ph+ ALL, headaches were reported in 23% of patients with chronic-phase CML [109]. As with other TKIs, peripheral neuropathies are uncommon but may occur [110]. Ponatinib has been associated with peripheral arterial occlusive disease. As such, there may also be risk of cerebrovascular disease given this toxicity profile. Case reports of ocular arterial thrombosis have been reported with ponatinib [111].

27.11 JAK Inhibitors

27.11.1 Ruxolitinib

Ruxolitinib is an FDA-approved, selective Janus kinase 1 and 2 (JAK) inhibitor used for treatment of myelofibrosis [112]. In 2005, the JAK2 V617F mutation was identified and is the most common molecular abnormality in myeloproliferative neoplasms [113, 114]. JAK2 mutations are pres-

ent in 50% of patients with primary myelofibrosis [115]. There were no neurologic adverse effects noted in a trial of ruxolitinib [112]. Other JAK inhibitors have yet to be approved due to significant off-target effects including with neurologic toxicity [116].

27.12 Antibody-Drug Conjugate

27.12.1 Brentuximab

Brentuximab vedotin is an anti-CD30 antibody-drug conjugate approved for relapsed and refractory Hodgkin's lymphoma. In a randomized, phase III trial, brentuximab, doxorubicin, vinblastine, and dacarbazine (A+AVD) was compared to doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). Peripheral neuropathy occurred in 67% of patients in the A+AVD group with trial drug being discontinued in 10% of patients [117]. Peripheral neuropathy by brentuximab is caused by disruption of axonal transported and is predominantly sensory with 11% of patients experiencing motor symptoms [118].

27.13 Radiolabeled Antibodies

27.13.1 Ibritumomab

Radioimmunotherapy links monoclonal antibodies to radiolabeled isotopes. 90Y-Ibritumomab tiuxetan is an anti-CD20, murine monoclonal antibody, combined with a chelator tiuxetan that is conjugated to the radioisotope yttrium-90, subsequently combined with radiation as treatment for patients with relapsed or treatment-refractory follicular lymphoma. Its use has been limited by severe toxicity, specifically cytopenias and reports of treatment-related myelodysplastic syndrome and acute myeloid leukemia [119]. In a randomized trial of ibritumomab, headaches were most frequently reported in patients receiving ibritumomab; however, all were grade 1 and 2 adverse effects [120].

27.14 SMO

The smoothened (SMO) receptor is one of the main upstream transducers of the sonic hedgehog (SHH) signaling pathway, which is activated aberrantly in disease and thought to be an essential component of tumorigenesis [121]. SMO is a validated target for use in anticancer therapy with FDA approval for SMO antagonists vismodegib and sonidegib, both approved for advanced basal cell carcinomas with investigations underway for other indications including SHH-dependent medulloblastoma and progressive meningioma (NCT02523014) [121, 122]. SMO mutations have been identified infrequently in NSCLC brain metastases [123, 124].

27.14.1 Vismodegib

Vismodegib is a first-in-class SMO inhibitor FDA approved for treatment of adults with metastatic or locally advanced basal cell carcinoma which is not appropriate for surgery or radiation. In the STEVIE trial, safety of vismodegib was assessed in patients with advanced or metastatic basal cell carcinoma [125]. Muscle spasms were the most frequently reported treatment-emergent adverse effect reports, occurring in 98% of patients; headaches were reported in 10.8% of patients [125]. When also studied in the pediatric population, vismodegib is also not associated with any significant neurotoxicity [126].

27.14.2 Sonidegib

Sonidegib is a selective inhibitor of SMO which has demonstrated high tissue penetration (including blood-brain barrier) and oral bioavailability. In a phase I study of sonidegib in adult patients with advanced solid tumors, similar to vismodegib, muscle spasms were the most frequently reported in 32% of patients [127].

27.15 HDAC Inhibitors

Histone deacetylases (HDAC) are involved in chromatin remodeling and epigenetic regulation of gene expression, which is important in cancer growth. Altered histone deacetylation has been found in several solid tumors and is the target of HDAC inhibitors. The addition of HDAC inhibitors to radiation has been investigated in the treatment of breast cancer brain metastases [128].

27.15.1 Vorinostat

Vorinostat is an orally active, potent inhibitor of HDAC, which functions by binding to a zinc ion in the catalytic domain of the enzyme [129]. It is FDA approved for treatment of cutaneous manifestations of cutaneous T-cell lymphoma, with investigations ongoing for other solid tumors [130, 131]. In a prior trial of patients with AML, there was one case of grade 4 intracranial hemorrhage and grade dizziness [132]. No other neurotoxicity has been reported.

27.15.2 Panobinostat

Panobinostat is a pan-HDAC inhibitor which has potent inhibitory activity at low concentrations against all classes of HDAC enzymes [133]. It is FDA approved in combination with bortezomib and dexamethasone for patients with multiple myeloma (MM), who failed at last two previously lines of therapy. In a large phase III study of panobinostat, bortezomib, and dexamethasone, peripheral neuropathy was the most common neurologic adverse effect noted in the panobinostat cohort at 61% with 17% of patients experiencing grade 3 or 4 peripheral neuropathy [134]. Sixty-seven percent of patients randomized to placebo reported peripheral neuropathy, although with fewer grade 3 or 4 toxicity [134].

27.15.3 Belinostat

Belinostat is a pan-HDAC inhibitor which has been studied in patients with solid and hematologic malignancies, now currently FDA approved for relapsed or refractory T-cell lymphoma [135]. It carries both antitumor and antiangiogenic properties [135]. In a phase II study assessing the safety and efficacy of belinostat in patients with relapsed or recurrent primary TCL or cutaneous TCL, dizziness and headaches were reported in 5 and 1 patient, respectively, among treatment-emergent adverse effects [135].

27.15.4 Valproic Acid

Valproic acid (VPA) is a class I HDAC inhibitor whose best-known indication has been for treatment of seizure disorders but has gained attention for its potential role as a cancer therapy [136]. In a small phase I study of eight patients with metastatic neuroendocrine carcinoma on VPA monotherapy, partial response was noted in one patient with five patients achieving stable disease. VPA was also studied in combination with 5-fluorouracil (5-FU), epirubicin, and cyclophosphamide in 15 patients with metastatic breast cancer, producing objective responses in 64% of patients [137]. In a trial of eight patients with advanced NSCLC, neurotoxicity was dose-limiting as somnolence, ataxia, and memory loss were observed [138].

27.16 Proteasome Inhibitor

Proteasomes are present in all cells and carry the responsibility of degrading proteins which regulate cell cycle progression, specifically an endogenous inhibitor of NF-kappa B, I kappa B. The result of degradation of I kappa B is activation of NF-kappa B, which upregulates proteins which promote cell survival, thus reducing likelihood of apoptosis [139]. This activation of NF-kappa

B has been implicated in the growth, survival, and migration of myeloma cells [139]. As such proteasome inhibitors form the backbone for treatment of multiple myeloma. Peripheral neuropathy is commonly reported with proteasome inhibitor therapy.

27.16.1 Bortezomib

Bortezomib is a first-in-class proteasome inhibitor approved for treatment of multiple myeloma and mantle cell lymphoma. Peripheral nerve injury is the most frequent and significant non-hematologic toxicity associated with bortezomib given impact of quality of life and impact upon treatment regimen [140]. Peripheral neuropathy was assessed in two phase II studies of 256 patients with relapsed/refractory multiple myeloma. Prior to start of therapy, 81% of evaluable patients were found on exam to have baseline peripheral neuropathy. Treatment-emergent neuropathy was reported in 35% of patients receiving higher doses of bortezomib (1.3 mg/m^2) versus 21% receiving 1 mg/m^2 [140]. Grade 3 and higher toxicity were more frequent in patients with baseline peripheral neuropathy. Bortezomib typically causes a painful, sensory neuropathy thought to be secondary to direct toxicity on the dorsal root ganglion [141]. Other patterns including motor and autonomic neuropathy have been reported [141, 142]. Guidelines for management for bortezomib-induced peripheral neuropathy have also been established by the International Myeloma Working Group [143]. Bortezomib has been linked to central nervous toxicity including PRES and cerebellar toxicity [144–146].

27.16.2 Carfilzomib

Carfilzomib is a second-generation proteasome inhibitor approved for treatment of progressive multiple myeloma in patients previously treated with bortezomib and immunomodulatory therapy as well as in combination with dexamethasone and lenalidomide for heavily pretreated multiple myeloma. In comparison to bortezomib, carfilzomib causes a milder peripheral neuropathy, likely the result of less off-target effects [147]. Combined safety data from four phase II trials of single-agent carfilzomib was evaluated. Of 526 evaluable patients, 378 patients (71.8%) had active peripheral neuropathy at the time of trial enrollment [147]. During the course of trial, only 13.9% of patients reported peripheral neuropathy with only 1.3% being grade 3 or higher [147].

27.16.3 Ixazomib

Ixazomib is an oral proteasome inhibitor currently under investigation for treatment of multiple myeloma. In a phase III study of ixazomib, peripheral neuropathy of any grade was reported in 27% of patients versus 22% in the placebo group [153]. Similar to carfilzomib, ixazomib is associated with less severe peripheral neuropathy when compared to bortezomib.

27.17 mTOR Inhibitors

The mammalian target of rapamycin (mTOR) signaling pathway is a central regulator cell metabolism, growth, proliferation, and survival [148]. The mTOR pathway plays a critical role in normal and disease states, specifically tumor formation and angiogenesis, and as such is the target of inhibition by several antitumor therapeutic agents [150]. mTOR inhibitors function by binding to the FK-binding protein and modulate mTOR. In addition to its use as antirejection therapy in the setting of renal transplantation, mTOR inhibitors have gained approval for use in tuberous sclerosis and renal cell carcinoma and have been investigated in combination with PI3K inhibitors in breast cancer brain metastases [151, 152]. Calcineurin inhibitors, which include mTOR inhibitors, as a class, have been associated with neurotoxicity [153].

27.17.1 Everolimus

Everolimus is an mTOR inhibitor which has been used in combination therapy with aromatase inhibitor (AI) in postmenopausal women with AI-resistant, advanced ER-positive breast cancer. As activating mutations in mTOR pathway are common in breast cancer, this makes for a logical therapeutic option in managing disease [154]. In a phase III study comparing everolimus and exemestane to exemestane and placebo, headaches were reported in 19 patients in the everolimus treatment arm in comparison to 13 in the placebo arm [155].

27.17.2 Sirolimus

Similar to everolimus, sirolimus acts by blocking the response of T- and B-cell activation by cytokines, thus preventing cell cycle progression and proliferation [156]. Sirolimus has been increasingly used for treatment of angiomyolipomas in tuberous sclerosis and has shown some antimalignancy effects in the setting of posttransplant squamous cell carcinoma [157, 158]. Sirolimus has not been associated with significant neurotoxicity except when used in combination with cyclosporine A [159].

27.17.3 Temsirolimus

Temsirolimus is a highly specific inhibitor of mTOR which acts by binding the intracellular protein FKBP-12, forming an inhibitory complex of mTOR, causing cell cycle arrest and tumor suppression [160]. Along with everolimus, temsirolimus is approved for advanced renal cell carcinoma and has been used off-label for locally advanced, recurrent or metastatic endometrial cancers. In a report of temsirolimus-related adverse effects from the phase III Global Advanced Renal Cell Carcinoma (ARCC) trial, there were no grade 3 or 4 neurologic side effects [160]. In a study of 35 patients with mantle cell lymphoma receiving weekly temsirolimus 250 mg, there was one case each of grade 3 muscle weakness, motor neuropathy, cranial neuropathy, blurred vision, and headache, with one case of grade 4 decrease consciousness [161].

27.17.4 VEGF

The vascular endothelial growth factor (VEGF) family was first identified and isolated in 1989 with its main effector, the VEGF ligand, known to be a key mediator of angiogenesis in cancer [162–164]. VEGF acts by binding to either of its receptors, VEGF receptor 1 or 2 (VEGFR-1/VEGFR-2), which, under physiologic states, promotes angiogenesis for essential functions such as embryonic development and wound healing [164]. In cancer, VEGF is upregulated, allowing for tumor cell growth to occur by formation of new tumor vasculature. Several antitumor agents have been developed to target either VEGF or its receptors [164].

As a class, nearly all of the VEGF and VEGF receptor inhibitors have been implicated in the development of hypertension as well as increased risk of arterial thromboembolic events [165, 166]. The mechanism for increased risk of thromboembolism remains under investigation; however, it is thought to be related to disruption of tumor-associated endothelial cells, "switching" the endothelium from an anticoagulant to a prothrombotic state [167]. Reversible posterior leukoencephalopathy (RPLS) has also been reported as a class-wide phenomenon in the setting of VEGF inhibition and is thought to be secondary to disordered cerebral autoregulation and capillary dysfunction [168].

27.17.5 Cabozantinib

Cabozantinib is a small-molecule TKI currently used for treatment of advanced renal cell carcinoma (mRCC) and progressive, metastatic thyroid cancer. In addition to its effects on the

VEGF receptor, as well as on the MET and AXL genes, both of which portend poor prognosis when present as they may predict resistance to VEGF receptor inhibition [169]. In a randomized phase II comparing cabozantinib to sunitinib as first-line therapy for mRCC, dysgeusia was the most common neurologic toxicity: noted in 41% of patients receiving cabozantinib [169]. In METEOR, a phase III trial of patients with advanced clear cell RCC who had been previously treated with VEGFR therapy, patients were randomized to either cabozantinib or everolimus. In patients receiving cabozantinib, 7.3% of patients had venous thromboembolic events and 0.9% had arterial events [170]. A rare but serious complication of cabozantinib is RPLS, though this was not observed in METEOR.

27.17.6 Lenvatinib

Lenvatinib is an oral multitargeted TKI with activity against VEGF receptors 1–3, FGFR, PDGFR-alpha, RET, and KIT proto-oncogenes, currently used for radioiodine-refractory differentiated thyroid cancer and for combination therapy with everolimus for advanced RCC following prior anti-VEGF treatment [171]. There have been case reports of lenvatinib-associated PRES [172, 173].

27.17.7 Sorafenib

Sorafenib is an oral multitargeted TKI which acts on several factors including VEGF receptor 2, FLT3, PDGF receptor, FGFR1, C-raf, and B-raf. It is used for treatment of previously untreated and previously treated advanced RCC. In a phase II trial, patients with metastatic clear cell RCC were randomized to either bevacizumab monotherapy, bevacizumab and temsirolimus, bevacizumab and sorafenib, or sorafenib and temsirolimus [174]. Grade 3 headaches were noted in all treatment groups [174]. In a phase II of first-line sorafenib versus interferon alfa 2a, confusion was the only adverse effect attributed to sorafenib, reported in 1 patient. A phase III study of sorafenib in advanced RCC, sensory neuropathy was reported in 13% of patients receiving sorafenib [175]. Brain metastases secondary to mRCC have propensity to hemorrhage; however, in a review of the incidence of CNS bleeding, anti-VEGF TKIs, including sorafenib and sunitinib, and anti-VEGF monoclonal antibody, bevacizumab, were not associated with increased risk of CNS hemorrhage [176].

27.17.8 Sunitinib

Sunitinib is a VEGF receptor TKI with effects also on PDGF receptor and the c-kit oncogene. In a phase III comparing sunitinib to interferon alfa in mRCC, headaches were reported in 11 of 375 patients in the sunitinib arm in comparison to 14 of 360 treated with interferon [177]. Sunitinib-associated AIDP and cognitive impairment have also been reported [178, 179].

27.17.9 Pazopanib

Pazopanib is an oral TKI which acts on VEGF, PDGR, and kit receptors and used for locally advanced or mRCC. In a phase III trial of pazopanib, headaches were reported in 30% of patients [180]. Other trials have shown pazopanib to be reasonably tolerated with side effect profile similar to other VEGF/VEGFR inhibitors [181]. Myalgias and muscle spasms have been described in association with pazopanib [182].

27.17.10 Axitinib

Axitinib is an oral TKI with activity against VEGF receptors 1, 2, and 3 currently used for advanced renal cell carcinoma. In a phase II study of axitinib in refractory mRCC, headaches were reported in 29% of patients treated with axitinib [183]. Two patients treated with axitinib were found to have cerebral hemorrhage, one of whom had an underlying brain metastasis [183]. In a phase II study with and without dose titration of axitinib in mRCC, headaches and dizziness were

reported at higher frequency in the axitinib titration arms [184]. No other specific neurotoxicity has been reported with axitinib.

27.17.11 Regorafenib

Regorafenib is an oral small-molecule multikinase inhibitor which is active against VEGF receptors, stromal and oncogenic receptor tyrosine kinases, currently FDA approved for treatment of heavily pretreated metastatic colorectal cancer (mCRC) [185]. In a phase III trial of regorafenib monotherapy in mCRC, sensory neuropathy (7%) and headaches (5%) were reported in the regorafenib-treated arm [185]. There have been isolated case reports of hyperammonemic encephalopathy and transverse myelitis in patients on regorafenib [186].

27.17.12 Vandetanib

Vandetanib is an oral inhibitor of VEGFR, RET, and EGFR used for treatment of patients with metastatic or unresectable hereditary MTC or multiple endocrine neoplasia type 2a [187]. In a phase II of vandetanib, headaches (47%) and dysgeusia (33%) were among the neurologic adverse effects noted [187]. In a phase I/II trial of vandetanib in 64 patients with recurrent malignant glioma, among the ≥ grade 3 adverse effects included seizure (ten patients) and intracranial hemorrhage (one patient) [188]. There were also two other patients who experienced symptomatic intracranial hemorrhage [188].

27.17.13 Bevacizumab

Bevacizumab is a monoclonal antibody against VEGF, which inhibits binding of the VEGF ligand to its receptor. It has been used widely for treatment of multiple diseases, gaining FDA approval for macular degeneration, metastatic CRC, metastatic NSCLC, RCC, ovarian cancer, cervical cancer, and recurrent/progressive glioblastoma. In the phase III AVAGLIO trial in which bevacizumab was added to standard therapy of temozolomide and radiotherapy for newly diagnosed glioblastoma, patients were randomized to either bevacizumab or placebo [189]. In the bevacizumab-treated arm, cerebral hemorrhage of all grades was reported in 3.3% of patients, with 2% of hemorrhages being grade 3 or higher, more frequent than in the placebo group [189]. There has been ongoing debate around whether bevacizumab, in the setting of known intracranial metastases, increases risk of hemorrhage. In an evidence-based review of the incidence of hemorrhage in NSCLC-associated metastases, bevacizumab was not associated with an increased risk of bleed [176]. Similarly, in a phase II of bevacizumab in recurrent glioblastoma, patients received bevacizumab monotherapy followed by irinotecan and bevacizumab combination therapy, and there were no intracranial hemorrhage among the adverse effects [190]. Consistent with the larger class of antiangiogenic TKIs, bevacizumab has also been implicated in the development of RPLS and associated conditions [191, 192].

27.17.14 Ramucirumab

Ramucirumab is a recombinant monoclonal antibody of immunoglobulin G1 (IgG1) class which binds and blocks activation of VEGFR-2. It is currently used for advanced gastric cancer, NSCLC, and mCRC. In a meta-analysis of safety data from six completed phase III trials of ramucirumab, of six bleeding events reported during treatment of ramucirumab, two were intracranial hemorrhage [193]. There were seven grade 5 arterial thromboembolic events (ATE), including one cerebrovascular on ramucirumab, in comparison to 10 total ATEs on the control arm and three cerebrovascular events [193].

27.17.15 Ziv-aflibercept

Aflibercept is an inhibitor of the VEGF ligand by blocking its binding to all class of VEGFRs, and placenta growth factor (PIGF) binds to

VEGFR-1. It is approved for use in combination with chemotherapy for mCRC. In a phase I study of aflibercept administered subcutaneously to patients with advanced solid tumors, cerebral ischemia of any grade was reported in 3% of all patients [194]. A retrospective review of pooled safety data of 1562 patients who received intravitreal aflibercept, among intraocular adverse effects, central retinal artery occlusion (CRAO) was found in two patients [194]. There was one patient with stroke which was nonfatal [195].

27.18 Summary

Novel cancer therapies have been adopted into treatment regimens and, in some diseases, represent the new standard of care. As these therapies have resulted in improvement in response rates and survival, newer toxicities have emerged involving the central and peripheral nervous systems. Although the majority of neurological adverse effects are rare, they may be severe, and with increasing familiarity of the tumor-directed qualities of these drugs, recognition of patterns will be important in order to avoid loss of neurologic function. Furthermore, increasing knowledge of treatment-related neurologic toxicities will hopefully reduce misdiagnosis and the time to intervention.

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28 Neurological Complications of Immune-Based Therapies

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28.1 Introduction

Immune-based therapies represent an exciting and promising approach to treatment of solid and hematologic malignancies. For several cancers, specifically melanoma and non-small cell lung cancers (NSCLC) lacking driver mutations, immunotherapies, namely, checkpoint inhibitors, are embedded into standard of care management. As it is only expected that immune-based approaches will continue to rise, recognition and understanding of its potential pitfalls are necessary. Though infrequent, neurotoxicity associated with immune-based therapies has been identified, involving both central and nervous systems. As when a neurologic toxicity is suspected with chemo- or targeted therapy, it is critical that nervous system effects in the setting of immune-based therapies are understood, as it may be confused with direct invasion of cancer into the nervous system or other disease-related complication. This will be critical in reducing the risk of delayed diagnoses and permanent neurologic deficits.

28.2 Immune Checkpoint Inhibitors

Immune checkpoint blockade represents one of the most promising and attractive options for treatment of human cancers. To date, use of immune checkpoint inhibitors has revolutionized the management paradigms of many solid tumors, namely, melanoma and lung cancers [1, 2]. In normal physiologic states, immune checkpoints prevent autoimmunity, thus protecting viscera from damage in the setting of immune responses to infection [2]. The dysregulation or disruption of these normal mechanisms has been exploited for antitumor activity and therapeutic use. In the setting of tumor cells, the immune response is mediated by both adaptive and innate components of immunity: adaptive through the activation of cellular and humoral factors and innate by way of natural killer (NK) cells [3, 4].

Cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed death 1 and 2 (PD-1/PD-2), and programmed death ligand 1 and 2 (PD-L1/PD-L2) are immune checkpoints which have been targeted with monoclonal antibodies and have been integrated into treatment protocols in cancer. While the clinical benefits and durability of these agents are important and have

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changed the landscape of management, immune checkpoint inhibition has been associated with a broad spectrum of adverse effects, including effects upon the central and peripheral nervous system, which, although rare, may be severe and lead to neurologic morbidity [5–8]. The National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) have developed guidelines for management of immune-related adverse effects (irAEs) which affect the nervous system [9].

28.2.1 Anti-PD-1 Inhibitors: Pembrolizumab and Nivolumab

Pembrolizumab is an anti-PD-1 monoclonal antibody currently FDA approved for several cancers among which includes unresectable or metastatic melanoma, EGFR/ALK wild-type NSCLC, and mismatch repair-deficient colorectal cancers [10–12]. In advanced melanoma, the efficacy of pembrolizumab was first established in phase III trials, in which it was compared to chemotherapy in patients who were ipilimumab refractory. In KEYNOTE-002, patients were randomized to either pembrolizumab or chemotherapy; patients randomized to pembrolizumab showed prolonged PFS, higher ORR, and longer OS [13]. In KEYNOTE-006, pembrolizumab was compared to ipilimumab in immunotherapy-naive advanced melanoma patients. In the pembrolizumab cohort, PFS and OS were significantly prolonged and the ORR was higher in comparison to ipilimumab [12, 14–16]. More recently, pembrolizumab has gained approval for metastatic nonsquamous NSCLC without sensitizing mutations to EGFR or ALK. In comparison to standard chemotherapy, with the addition of pembrolizumab to pemetrexed/platinum therapy, there was prolonged OS and PFS [11].

Nivolumab is also an anti-PD-1 monoclonal antibody which has been used as monotherapy, as well as in combination with ipilimumab. In comparison to chemotherapy in BRAF wild-type patients, nivolumab was associated with increased OS, PFS, and ORR [14]. In patients who were previously treated with anti-CTLA-4 therapy, there was no difference in OS when nivolumab was compared to chemotherapy, though objective responses were more common [17].

The neurotoxicity profile of anti-PD-1 and anti-PD-L1 is similar. Although immune-related neurological adverse effects are rare (1–3%), they can be severe [18]. Peripheral nervous system complications, namely, involving the neuromuscular axis, have occurred frequently with myasthenia gravis, necrotizing myopathy, vascular neuropathy, and polyradiculopathy being reported [19–25]. Although the peripheral nervous systemic syndromes have been predominant in the literature, immune checkpoint blockade may also involve the central nervous system including transverse myelitis, limbic encephalitis, posterior reversible encephalopathy syndrome, and meningitis being reported [26].

28.2.2 Anti-PD-L1 Inhibitors: Atezolizumab, Avelumab, and Durvalumab

Atezolizumab is an engineered humanized anti-PD-L1 monoclonal antibody, which is currently approved for use in metastatic NSCLC, locally advanced or metastatic urothelial carcinoma, and most recently, triple-negative breast cancer [27–30]. The PD-L1 pathway is broadly expressed in urothelial cancers, thus providing a rationale for its use in this disease. The approval of atezolizumab for treatment of urothelial cancers led to the subsequent accelerated approvals of avelumab and durvalumab, also anti-PD-L1 inhibitors [28].

Avelumab is a PD-L1 blocking antibody which gained approval in the US for treatment of metastatic Merkel cell carcinoma (mMCC) [31]. The JAVELIN Merkel 200 trial was a phase II in which patients with chemotherapy-refractory mMCC were treated with avelumab with a primary endpoint of best overall response. At median follow-up of 10.4 months, 32% had an objective response with 79% of these patients having achieved OR by the first baseline visit [32]. Avelumab has been investigated in other solid tumors including advanced NSCLC, GEJ adenocarcinoma, and renal cell carcinoma [34].

Durvalumab is a selective, high-affinity anti-PD-L1 blocking monoclonal antibody which has been studied in multiple solid tumors, including stage IIIB and stage IV NSCLC, where its anti-tumor activity was noted. It has current approvals in the locally advanced or metastatic urothelial cancer [30]. In a phase III randomized study, durvalumab was compared to placebo in patients with locally advanced unresectable NSCLC [33]. PFS in the durvalumab-treated group was longer in comparison to placebo [33].

The neurotoxicity profile associated with anti-PD-L1 inhibitors is similar to anti-PD-1 and was discussed in the earlier section.

28.2.3 Anti-CTLA-4 Inhibitors: Ipilimumab and Tremelimumab

Ipilimumab is a monoclonal antibody directed against CTLA-4, which acts to upregulate antitumor immunity. In a phase III study with patients with metastatic melanoma, it was associated with longer overall survival and higher ORR [34–38]. In a subsequent phase III study, the addition of ipilimumab to nivolumab was compared to ipilimumab monotherapy and nivolumab monotherapy in patients with untreated, metastatic melanoma [38]. The results of which showed improved outcomes in the nivolumab-treated arms (either monotherapy or in combination with ipilimumab) [38]. Headaches were the most common neurologic adverse effect reported in this study; however, the frequency was similar in both the nivolumab and ipilimumab monotherapy groups [38].

Various other neurologic toxicities have been linked to ipilimumab including autonomic neuropathy, chronic inflammatory demyelinating neuropathy, transverse myelitis, and myasthenia gravis (**207, 241**). In this case series, the median time to onset of immune-related adverse effects (iRAEs) was 1–2 weeks, resulting in discontinuation of ipilimumab [39]. Other syndromes which have been reported include PRES, aseptic meningitis, and ocular manifestations including Tolosa-Hunt syndrome, uveitis, optic neuropathy, and orbital inflammation [40–42].

Tremelimumab is another anti-CTLA-4 monoclonal antibody. Survival benefit with its use has yet to be demonstrated and investigations are ongoing.

28.3 CAR T-Cell Therapy

Chimeric antigen receptor (CAR) T-cell therapy is a promising and innovative approach to exploiting the antitumor potential of the immune system. CAR T cells are genetically modified autologous T cells which are manipulated to express the antigen-binding domain from a B-cell receptor that is then fused to the intracellular domain of a CD3 T-cell receptor [43]. So far, the therapeutic target of CAR T cell has been CD19, which is expressed on normal B cells and in most B-cell malignancies [44, 45]. T cells which express anti-CD19 CARs can recognize and kill CD19-positive target cells [44]. In the first report of successful treatment with CAR T-cell therapy of 15 patients with advanced B-cell malignancies who received CAR T-cell therapy, eight achieved complete remissions (CR) and four achieved partial remission (PR) [45]. In an earlier study of CAR T-cell therapy, five patients with relapsed B-cell ALL were treated with CD19-expressing CARs. Patients with persistent morphological disease or minimal residual disease (MRD) at the time of CAR infusion achieved complete remission [46]. Use of anti-CD19 CAR T cells is under investigation for treatment of CLL and NHL [44].

One of the challenges to CAR T-cell treatment is reducing neurologic toxicity without interfering with clinical benefit and antitumor efficacy. In earlier studies where CD19 CAR T cells were administered concurrently with high-dose interleukin-2, confusion and obtundation were observed [47]. In the study of 15 patients with advanced B-cell malignancies, neurologic adverse effects observed included aphasia and myoclonus [44]. Two patients with severe neurologic toxicity required treatment with tocilizumab, the IL-6 receptor-blocking antibody. Ultimately, all patients had neurologic recovery. The mechanism underlying the developing of neurotoxicity has been considered to be secondary to complement release syndrome (CRS);

however, there is now growing understanding that neurotoxicity may occur separately from CRS [48]. Tocilizumab is approved for treatment of CRS; however, there is no consensus for therapeutic interventions for the neurotoxicity associated with CAR T-cell therapy [48]. In a study of 53 patients with ALL treated with CAR T cells, eleven developed mild neurotoxicity, mostly mild encephalopathy, headache, or tremor [48]. Severe neurotoxicity was noted in 22 patients, heralded by mild somnolence and disorientation, ultimately progressing to global aphasia, seizure, myoclonus, and encephalopathy [48]. There was a strong correlation of neurotoxicity with CRS, and predictive factors of severe neurotoxicity included high pretreatment disease burden, high peak CAR T-cell expansion, and higher elevations of serum proinflammatory cytokines [48].

28.4 Immunomodulatory Drugs

Immunomodulatory drugs or IMiDs are a class of agents which have been used primarily in treatment of hematologic malignancies [49]. The molecular mechanisms of action remain largely unknown [50]. There are three IMiDs currently in use: thalidomide, lenalidomide, and pomalidomide, each consisting of two portions, phthalimide and glutarimide [51].

28.4.1 Thalidomide

Thalidomide was the first IMiD to receive approval for use, initially for treatment of morning sickness in 1954. Due to discovery of teratogenic effects, thalidomide was withdrawn from the market in 1961 [50]. Currently, thalidomide is approved for multiple myeloma given both its immunomodulatory and antiangiogenic effects [52]. It has additionally been investigated as both monotherapy and in combination with temozolomide in melanoma brain metastases [53, 54]. The most frequent neurological adverse effect associated with thalidomide is peripheral neuropathy. In a systematic review of published phase II clinical trials of thalidomide monotherapy, the incidence of peripheral neurotoxicity was 29% in patients across 15 trials at the target and median dose of thalidomide [55]. The pattern of peripheral neuropathy typically follows a sensory, length-dependent pattern. Autonomic neuropathy is rarer but can occur and may present with bradycardia and impotence [56]. Thalidomide can also cause an acute encephalopathy manifesting as somnolence [57].

28.4.2 Lenalidomide

Lenalidomide is a second-generation IMiD which gained FDA approval in 2006 as combination therapy with dexamethasone for relapsed/refractory multiple myeloma [49]. It is more potent as an antiangiogenic agent with less associated neurotoxicity [58]. In pooled analysis of two large phase III trials of patients with relapsed/refractory multiple myeloma receiving lenalidomide and dexamethasone or dexamethasone and placebo, 1.4% of patients experience grade 2 and grade 3 peripheral neuropathy [59]. There were no grade 4 neurologic adverse effects.

28.4.3 Pomalidomide

Pomalidomide is a second-generation IMiD approved for multiple myeloma following failure of two prior lines of therapy. In a tolerability study of pomalidomide and low-dose dexamethasone, nine patients (26%) experienced neuropathy during treatment, of which six patients had peripheral neuropathy at baseline [60]. Other neurologic toxicity seems to be uncommon.

28.5 Other Monoclonal Antibodies

28.5.1 Rituximab

Rituximab is a human monoclonal antibody directed against CD20-positive B cells, used for treatment of several disease states including the hematologic malignancies (NHL, CLL)

and nonmalignant diseases (rheumatoid arthritis, thrombotic thrombocytopenic purpura). Rituximab is relatively well tolerated neurologically with few adverse effects reported, among which include headaches, myalgias, and dizziness [61]. Progressive multifocal leukoencephalopathy (PML), although uncommon, has been reported in patients with hematologic malignancies receiving rituximab in combination with chemotherapy or with hematopoietic stem cell transplant [62, 63]. In scenarios where rituximab is administered intrathecally, as with most biologic agents administered, this route may cause encephalopathy.

28.5.2 Ofatumumab

Ofatumumab is also a human monoclonal antibody against CD20, also targeting B cells, currently used for treatment of treatment-refractory CLL. In comparison to rituximab, it binds a separate extracellular loop of CD20 and does not induce apoptosis as its mechanism for cell death [64]. In a phase II trial, patients with previously treated CLL received ofatumumab, followed by combination of ofatumumab and bendamustine for up to six cycles [65]. After cycle 1, two patients developed profound weakness, confusion, and failure to thrive which was ultimately attributed to bendamustine, leading to early closure of the study [65]. Muscle weakness and ataxia were among the other neurological adverse effects reported [65].

28.5.3 Obinutuzumab

Obinutuzumab is a glycoengineered, type II antI-CD20 monoclonal antibody which is approved in combination with chlorambucil for initial treatment of CLL. In a trial of first-line treatment of follicular lymphoma, patients were randomized to induction therapy with either obinutuzumab-based or rituximab-based chemotherapy, and there were no significant neurologic adverse effects [66].

28.5.4 Alemtuzumab

Alemtuzumab is an anti-CD52 antibody which has been used in initial treatment for patients with T-cell prolymphocytic leukemia (T-PLL) and is FDA approved for relapsing remitting multiple sclerosis. It has also been used in combination with other agents as part of induction regimens including fludarabine, mitoxantrone, and cyclophosphamide [67]. In a retrospective analysis to evaluate safety and efficacy of alemtuzumab in patients with recurrent T-PLL, among six grade 5 adverse effects, there were two cases of cerebral hemorrhage in the setting of thrombocytopenia and one case of cerebral infarction; the authors note that these events were not obviously related to alemtuzumab [68]. Rare cases of PML have been reported associated with alemtuzumab [69].

28.5.5 Blinatumomab

Blinatumomab is a bispecific T-cell receptor-engaging (BiTE) antibody which engages normal CD3+ T cells and CD19+ B ALL cells, leading to lysis of tumor cells [70]. It is used in the treatment of Ph-relapsed or refractory B-cell precursor ALL. Blinatumomab has been associated with neurological toxicity, including symptoms at the time of infusion secondary to cytokine release syndrome, manifesting with neuropsychiatric signs including encephalopathy, dizziness, aphasia, and seizure [71]. CNS events have been reported in up to 20% of patients on blinatumomab with 16 reported events in a total of 95 patients [70]. In a cohort of relapsed ALL, six patients with CNS events, including seizure and encephalopathy, were retreated with blinatumomab at lower doses; four of six patients did not have reemergence of neurologic symptoms [72].

28.6 Summary

Similar to novel-targeted agents, immune-based cancer therapies have been incorporated into treatment regimens across various diseases.

Although overall response and survival outcomes have increased with the advent of this approach to care, immune-related neurologic adverse effects are emerging and deserve prompt attention. Albeit rare, ongoing investigation and understanding of specific drug or treatment-related neurotoxicities are warranted to reduce late recognition and delayed intervention.

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29 Health-Related Quality of Life Related to Toxicity Treatments in Central Nervous System Metastases

Tobias Walbert and Erika S. Horta

29.1 Introduction

As doctors, we are always aiming to cure, or at least to prolong, the lives of our patients. Also, we pledge to "do no harm." Those concepts collide at times, especially in cancer when an already fragile patient might face detrimental side effects of therapy. The traditional outcome measures in medical oncology focus on prolonging patient survival and time to disease progression. While these measures are objective and therefore relatively easy to assess, it has been recognized in the neuro-oncology community that increasing survival becomes less relevant if the patient has limiting neurologic and cognitive dysfunction [1].

Therefore, patients and families as well as the regulatory community are increasingly interested in therapies that not only prolong survival but also improve patient function and health-related quality of life.

It is estimated that 6–50% of all cancers metastasize to the central nervous system (CNS) [2–5], resulting in 150,000 to 200,000 cases per year in the US [5, 6]. CNS symptoms may vary from headaches, memory impairment, and focal weakness to spasticity depending on where the brain or spinal cord is affected. Treating brain metastasis is important as patients with untreated CNS metastasis will die within 1 year, but if the CNS burden is not overwhelming, patients live longer and they are more likely to die of systemic cancer progression [6]. The spectrum of therapies to treat CNS metastasis is broad, and treatments unfortunately can cause symptoms and side effects in addition to those of the underlying disease.

As the net effect of brain metastasis and its treatment affects more than semiology can reveal in a doctor's appointment, a new concept was developed to better assess patients and the impact of the disease on their daily lives. Health-related quality of life (HRQoL) is a way to measure how the treatment and the disease impact a patient's life. This multidimensional concept encompasses not only the physical aspects (i.e., symptomatology) but also the psychological, emotional, spiritual, and social aspects (Fig. 29.1), which become increasingly relevant as survival rates for cancer patients improve. Differences in toxicity and patient status during survival have become critical variables in making treatment choices, and that is why treatment-related HRQoL, although subjective, is an outcome to consider in cancer therapy. The Food and Drug Administration has therefore established new pathways for drug approval beyond the traditional survival endpoints and progression-free survival. Approval of a therapy

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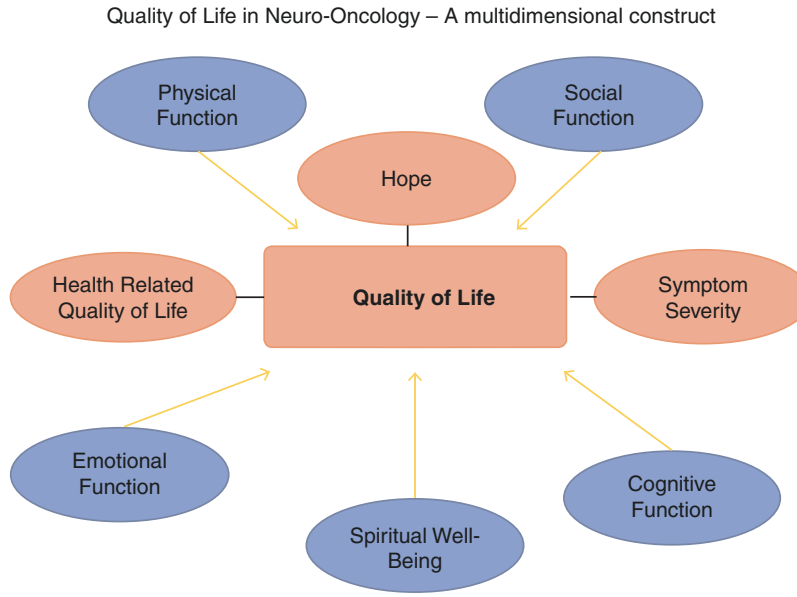

Fig. 29.1 Quality of life and the multiplicity of factors that can affect it

requires substantial evidence of clinical benefit, defined as improvement in how a patient "feels, functions, or survives." Clinical outcomes assessment (COA) is an umbrella term to further define tools to assess clinical benefit. COAs encompass different measures to assess the impact of anticancer therapy on patient benefit. This benefit can be measured by focusing on patient symptoms, overall mental state, and function. The FDA determined that COAs can be used to assess whether a drug provides treatment and safety benefits compared with other treatments. Overall COAs fall into the categories of patient-reported outcomes (PROs), clinician-reported outcomes, observer-reported outcomes, and performance outcomes [7].

29.2 Factors Impacting Health-Related Quality of Life in CNS Metastasis

Patients with CNS metastasis experience symptoms that can be defined as general cancer symptoms and CNS-specific symptoms. General cancer symptoms might include fatigue as well as anxiety and depression and are associated with the underlying systemic disease, while CNS-specific symptoms are directly due to the CNS disease and include cognitive deficits, seizures, and focal weakness or symptoms caused by elevated intracranial pressure such as headaches, nausea, and vomiting.

There is a lack of research assessing the overall impact of CNS metastasis on HRQoL; however, a study with ependymoma patients revealed that patients with spinal tumors reported significantly worse pain, numbness, fatigue, changes in bowel patterns, and weakness than patients whose brain was affected. In addition, many spine patients perceived a higher symptom burden and intensity than patients with brain disease [8]. It is important to note that neurological adverse effects do not just add morbidity but might also have severe socioeconomic impact, affecting patients and their families financially. It has been shown that the diagnosis of CNS metastasis might increase health-care expenditures three to four times, driven mainly by pharmacology costs [4]. Furthermore, neurological adverse effects add approximately $1136 per month in patient care [9]. Due to neurological dysfunction, only half of patients with brain tumors return to work.

29.3 Methods of HRQoL Assessment

Clinical outcome assessments are tools to appraise the impact, beneficial or not, of a treatment and/or disease (Table 29.1). Although centered on the patient, these assessments can be reported by the patient, clinician, or a third party such as a caregiver. These measures may assist patients and caregivers when discussing treatment options with their physicians. Treatment decisions in metastatic CNS disease can be highly personal, and there are many variables to consider. The best possible treatment approach is not only based on the patient's underlying systemic disease and CNS metastasis but also encompasses the patient's overall clinical condition and treatment preferences.

One way to measure the overall disease impact and patient preferences is to focus on HRQoL, symptom burden, and (instrumental) activities of daily living. These patient-reported outcomes (PROs) mirror the patient's perspective and are therefore subjective by definition. Assessment of patients' HRQoL has evolved over time. Historically, assessment of a patients' functional status determined by health-care providers was used as a surrogate of HRQoL. An example is the Karnofsky Performance Scale (KPS) [10] that has been used extensively to screen for clinical trials and medical decision-making [11]. Unfortunately, the underlying reliability is limited with an inter-physician agreement of only 29% [12]. Physicians usually overestimate the HRQoL of patients with CNS metastasis, especially when physical and/or cognitive symptoms are prevalent [13]. An ideal HRQoL measurement tool is not time-consuming and should be written with vocabulary that is understandable to the patient, especially when dealing with individuals that might have cognitive impairment. An HRQoL assessment tool should also have high reliability and validity and measure the impact of the disease/treatment in the patient in multiple modalities [1]. In an attempt to fulfill this difficult task, several PRO measures have been developed to measure HRQoL and symptom burden specifically in patients with CNS disease.

The most commonly used PRO measures for patients with cancer affecting the CNS include (1) the European Organization for Research and Treatment of Cancer's (EORTC) Health-Related Quality of Life (HRQoL) instruments (the 30-item Quality of Life Questionnaire (QLQ-C30) and its 20-item Brain Neoplasm version (QLQ-BN20), (2) the MD Anderson Symptom Inventory–Brain Tumor (MDASI-BT), (3) the Functional Assessment of Cancer Therapy–Brain (FACT-Br), and (4) the EuroQol Group's 5-dimension health questionnaire (EQ-5D). Collectively, these PRO measures assess multiple domains of HRQoL, symptoms, and functional limitations. Table 29.2 summarizes the PRO measures.

Table 29.1 Types of clinical outcome assessments and their differences

COA	Reported by	Measurement	Qualifiers	Examples
PRO	Patient	Health condition or perspective	– Can be self-administered or not – Response from patient, not an interpretation of it	10-point pain scale
PerfO	Health-care professional	– Patient's performance in task or test – Performed by patient – Administered by a professional	– Standard instructions required – Health-care provider needs to be trained in how to assess the patient.	PASAT test
ClinRO	Health-care professional	Patient's health condition	Clinical judgment	KPS
ObsRO	Third party (not the patient nor a health-care provider)	Patient behavior or condition	Self-administered or not No standards or training	ESAS-r

Table 29.2 Commonly used Patient-Reported Outcomes (PROs) Measures of Symptoms and Quality of Life (QOL) in Brain Tumors

PRO	Number of questions	Type of questions (number)
MDASI-BT	28	General (13), brain-tumor specific (9), interference scores (6)
EORTC QLQ-C30	30	Individual (6), quality of life (2), physical (5), social (2), emotional (4), cognitive (2), role (2), fatigue (3), nausea (2), pain (2)
EORTC QLQ-BN20	20	Individual (7), future uncertainty (4), visual disorder (3), motor functions (3), communication (3)
FACT-BR	50	General (27), brain-tumor specific (23)

29.3.1 The EORTC QLQ-C30 and QLQ-BN20

The QLQ-C30 includes five functional scales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, nausea/vomiting, and pain), a global health status scale, and six single-item scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The QLQ-BN20 subscale was specifically developed for brain cancer patients and produces 11 scores focused on CNS symptoms. It includes four symptom scales (visual disorders, motor dysfunction, communication deficit, and future uncertainty) and seven single-item scales (headaches, seizures, drowsiness, hair loss, itchy skin, weakness of legs, and bladder control). All scales and single-item measures are linearly transformed and scored from 0 to 100. A higher score for a functional scale represents a higher/healthier level of functioning. For the global health status, a higher score represents a higher quality of life (QOL). For symptom scales and items, a higher score represents a higher level of symptomatology/problems, that is, a poorer QOL. The psychometric properties of the QLQ-BN20 were assessed using data from primary brain tumor trial EORTC protocols 26,951 and 26,891 and since then has been used in CNS metastases trials as well [14, 15]. The QLQ-BN20 showed high internal consistency, with Cronbach's coefficient alpha ranging from 0.71 to 0.90 [16]. However, both the QLQ-C30 and the QLQ-BN20 were not highly sensitive to change from baseline in some primary brain tumor trials, and several of the QLQ-BN20 single items (e.g., headaches, hair loss, itchy skin, leg weakness) have shown poor test-retest reliability [17, 18].

29.3.2 The MD Anderson Symptom Inventory–Brain Tumor (MDASI-BT)

The MDASI-BT is a more symptom-based assessment survey. Similar to the EORTC tools, it has a general cancer-focused segment as well as a more CNS disease-specific module. The overall goal is to assess symptom severity and degree of disease interference across different domains pertinent to people with brain tumors and CNS metastatic disease. It provides a single composite score for symptom severity and a second composite score for symptom interference as well as 21 symptom items and 7 interference items assessing the interference with general activity, mood, work including housework, relationships, walking, and enjoyment of life. The MDASI-BT has been extensively used in primary brain tumor trials and has been validated for CNS metastasis [19]. The MDASI-BT has a short completion time (about 4 min) and can be administered on paper or tablet or via a phone interview [20]. It has been validated for the "past 24-hour" and "past week" recall periods [21].

29.3.3 Functional Assessment of Cancer Therapy–Brain and National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy–Brain Symptom Index (FACT-BR)

The FACT-BR consists of 27 items measuring general (FACT-G) cancer-related physical, social, emotional, and functional well-being factors and

an additional 23 items focusing on CNS-specific issues such as seizures, cognition, aphasia, vision changes, hearing, weakness, numbness, ataxia, aphasia, and headaches. The outcomes can be scored in different ways including subscale and total scores. A FACT-BR-derived and abbreviated scale, the 24-item National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy–Brain Symptom Index (NFBrSI-24), focuses on patients with advanced brain cancer. This short form was developed to measure those symptoms in advanced brain tumors perceived as most important by both patients and clinicians. The FACT-BR and the NFBrSI-24 have shown good reliability and validity [22].

29.3.4 The EuroQol 5-Dimension Health Questionnaire (EQ-5D)

The EQ-5D is a PRO HRQoL questionnaire that has been used extensively in general cancer and brain tumor trials [23–25]. This 6-item measure is a generic preference-weighted measure of health status that combines responses on five items (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) into a single, preference-weighted, interval-level score. Each dimension is scored according to the degree of impairment in daily function, ranging from 1 to 3. An EQ-5D index is then calculated from these five outcomes dimensions. This index represents a patient's overall health state, ranging from 0 (death) to 1 (perfect health). Given its shortness, the EQ-5D has been commonly used in economic models to evaluate the cost-effectiveness of treatments (e.g., cost per quality-adjusted life year).

29.4 Treatments and HRQoL

HRQoL is influenced by metastatic CNS lesions as well as by treatment. While it is difficult to separate contributing factors, it is generally accepted that CNS metastasis affects HRQoL negatively, while anticancer treatment may have a negative as well as positive impact on the HRQoL. Different treatment modalities target metastatic cancer in multiple ways causing side effects that can be either treatment specific or cumulative in nature. Especially in a disease with limited survival, it is important to consider the benefits of any treatment and to compare them with any short- and long-term sequelae and how they might impact the patient's HRQoL. Anticancer treatment includes surgery, radiotherapy, and systemic medical therapies such as chemotherapy and immunomodulatory agents. Providing patients and families with treatment-related QOL information will empower them to make informed treatment decisions rather than relying on survival data alone.

29.4.1 Surgery and HRQoL

Objectives of surgery might be not only to secure a tissue diagnosis but also to remove a solitary brain lesion with the goal to prepare a patient for further therapy such as radiation and to ultimately improve survival. Surgical removal can be lifesaving in acute emergencies such as herniation or increased intracranial pressure. In addition, it can have a positive impact on a patient's HRQoL by decompressing neural structures in the spinal cord to preserve or restore physical function or by minimizing symptoms such as pain or aphasia caused by a lesion in an eloquent area [26]. It might also be the preferred choice if increase in size caused by disease progression or radiation-induced injury results in neurological decline. In the case of solitary brain lesions, it has been shown that resection results in better control of the CNS disease, being associated with improved survival and HRQoL when compared to whole brain radiation therapy (WBRT) [26].

Prognostic factors associated with improved HRQoL and outcomes are high KPS or a good modified Rankin scale prior to surgery. Risk factors for a low postsurgical HRQoL are low KPS or modified Rankin scale, recurrent disease, left hemispheric lesions, and hemorrhagic complications [27]. Subtotal resections are favored next to eloquent brain regions such as motor pathways and speech and vision cortex in an effort to preserve function and HRQoL.

29.4.2 Radiation Treatment

Radiation is the most commonly used tool in the setting of spinal cord and brain metastasis with the goal of reducing and controlling disease burden. Clinicians aim to decrease symptoms and by doing so to stabilize or even to improve HRQoL.

For patients with a single or a limited number of metastatic lesions and good performance status, surgical resection and radiosurgery offer treatment options that have been shown to improve survival [28]. Patients with multiple brain metastases are routinely treated with WBRT, but survival remains limited with 3–6 months following treatment [29]. Therefore, symptom management and the maintenance of HRQoL are of high importance [11]. Clinicians aim to decrease symptoms and by doing so to stabilize or even to improve HRQoL. In addition, it has been shown that baseline HRQoL is associated with overall survival: patients with better baseline HRQoL having longer survival [30–32]. Patients with low baseline HRQoL are more likely to have shorter survival. This was shown in a study of 269 patients undergoing WBRT: While the baseline HRQoL was of prognostic significance, changes over time were not [11]. Factors that correlate with better HRQoL are small CNS metastasis volume, better KPS, asymptomatic brain metastasis, and controlled systemic cancer [2, 30, 31].

Most studies assessing HRQoL in the setting of radiation therapy have focused on the role of WBRT and stereotactic radiosurgery (SRS). It is challenging to compare the HRQoL outcomes of the two radiation modalities as patient populations are not comparable. Studies have shown that WBRT did not result in significant improvements [4, 11] while SRS has been associated with improved HRQoL [4, 25].

A prospective study with 97 patients undergoing SRS, looking at neurocognitive outcomes as well as HRQoL, showed that a baseline KPS <90 and tumor volume >12.6 cm^3 were both associated with slower information-processing speed and lower HRQoL scores over 6 months' time [2]. Intracranial tumor progression was linked to worsening of executive functioning and motor function. Over time, SRS did not result in declining neurocognitive functioning or HRQoL.

The most common side effects of radiation therapy that affect HRQoL are cognitive impairment and fatigue. Cognitive impairment is a known side effect of WBRT that has acute as well as long-term implications for patients and their caregivers. In the first months, patients are affected by alterations in alertness, attention, and memory; however, most of these symptoms are of transient nature [33]. Severe dementia, while rare and only affecting approximately 2–5% of patients undergoing WBRT, has severe consequences for a patient's HRQoL [3], and the neuro-oncology community is trying to find strategies to reduce its use or to delay it, like sparing the hippocampal-avoidance fields [34]. Moderate cognitive impairment is also seen in SRS, but it appears to not deteriorate over time, becoming stable [2]. The addition of SRS to WBRT has been shown to improve local CNS tumor control [6, 29], but patients' cognition and HRQoL are more affected than with SRS alone. The difference between SRS and WBRT in HRQoL seems related to the fact that WBRT has a greater impact on cognition than SRS [32].

Up to 80% of patients during radiation therapy complain about fatigue [35], and it can be a long-term complaint that persists for years after therapy has been finished [36, 37]. Lessening of fatigue over time is associated with prolonged survival [31]. Strategies on how to approach and treat fatigue include education, increased physical activity, and nutritional and mental health counseling as well as mind-body interventions [38]. Prior to starting any intervention, patients must undergo a detailed review of any medications that might increase fatigue and have blood work done to rule out metabolic reasons for fatigue [39].

29.4.3 Chemotherapy and Immunotherapy

When a patient is found to have brain metastases, chemotherapy should be tailored to include drugs that can cross the blood-brain barrier. Some

examples of these drugs include temozolomide, etoposide, methotrexate, cisplatin, fotemustine, and irinotecan. Unfortunately, chemotherapy is related to many neurological and non-neurological side effects that affect HRQoL.

Neuropathy contributes to complications such as falls, but also to impaired HRQoL due to pain and physical limitations. It can affect 60–70% of patients acutely, and 30–40% of patients can have long-lasting deterioration of HRQoL due to neuropathy, even after discontinuing therapy [40]. Although duloxetine is the only drug to demonstrate reduced symptoms of sensory neuropathy and improved HRQoL in a randomized trial [41], there is no Federal Drug Association-approved therapy for chemotherapy-induced peripheral neuropathy. Cancer societies like the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) have developed guidelines to treat neuropathic pain [42].

Monoclonal antibodies, immunotherapy, and targeted therapies like small molecule inhibitors are new treatment modalities in CNS metastasis and cancers. Utilizing the immune system to treat CNS metastasis is a novel approach that shows great promise. However, it is already known that these treatments have a wide range of side effects that can affect the central and peripheral central nervous system. Few studies compare HRQoL in patients treated with immunotherapy to HRQoL in patients treated with chemotherapy. In lung cancer patients, those treated with anti-PDL1 therapies (atezolizumab and pembrolizumab) had better HRQoL scores than patients treated with platinum-based chemotherapy or docetaxel [43, 44]. Patients treated with PDL1 inhibitors reported less fatigue, pain, nausea /vomiting, insomnia, and improved measures for physical, role, and social function. However, improvement in HRQoL can be delayed for months after starting therapy [44]. Targeted agents also seem to improve HRQoL for patients with advanced colorectal cancer [45], but consistent improvement was not seen in patients undergoing combination therapy of WBRT and targeted agents [4]. While immunotherapy has shown success in CNS metastasis as well, it remains unclear how it affects CNS function, symptom scores, and HRQoL in this subpopulation.

29.5 Conclusion

In a complex disease such as cancer with brain metastasis, disease and treatment can synergistically impact the patient in a variety of ways that go beyond the signs and symptoms diagnosed in a doctor's office. When determining the true benefits of a treatment strategy, the quantity but also the *quality* of life must be considered. As every treatment may have positive and detrimental effects on patients' lives, it is crucial to assess HRQoL and to discuss these trade-offs with patients and their families.

ClinRO, clinician-reported outcome; *COA*, clinical outcome assessment; *ESAS-r*, Edmonton Symptom Assessment System–Revised; *KPS*, Karnofsky Performance Score, *ObsRO*, observer-reported outcome; *PASAT*, paced auditory serial addition test; *PerfO*, performance outcome; *PRO*, patient-reported outcomes

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Part V

Prognostic Classifications and Future Trial Design

Prognostic Indices for Patients with Brain Metastases

30

Paul W. Sperduto

30.1 Introduction

Brain metastases are a common and complex conundrum for cancer care. An estimated 300,000 patients are diagnosed each year with brain metastases in the United States [1] and that incidence is growing due to advances in treatment that result in patients living longer and thus at prolonged risk for development of brain metastases [2]. It is a complex problem because of the marked heterogeneity of this patient population: brain metastases may arise from a wide variety of tumor types and subtypes. Furthermore, these patients may have already received a plethora of different treatments for their cancer or may present with brain metastases at the time of initial diagnosis. This heterogeneity has long plagued interpretation of clinical trials involving this patient population because it was essentially impossible to sufficiently stratify studies to verify similar groups of patients were being compared [3]. Interpretation of clinical trials and efforts to estimate prognosis are further complicated by the plethora of possible combinations of currently available treatment options [surgery, stereotactic radiosurgery (SRS), whole brain radiation therapy (WBRT), chemotherapy, targeted drug therapies, and immunotherapies]. Furthermore, four prospective randomized trials have shown WBRT adds no survival benefit over SRS alone in SRS-eligible patients [4–7] and, on the other end of the prognostic spectrum, there is evidence that supportive care may be as effective as WBRT [8]. Accordingly, WBRT is used less commonly than in the past.

30.2 Classification Systems

These concerns led to efforts to better understand prognosis. The purpose of a prognostic index is to predict outcome before, not after, treatment. It is important to distinguish prognostic from predictive factors. A prognostic factor identifies good vs. bad outcome irrespective of treatment used, whereas a predictive factor identifies good versus bad outcome for a specific treatment. Gaspar et al. published the Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis for brain metastases (Table 30.1) in 1997 [9]. This prognostic index consisted of three classes: I (age < 65, Karnofsky Performance Score (KPS) ≥ 70, controlled primary tumor, no extracranial metastases), II (all patients not in class I or III), and III (KPS < 70) which correlated with median survival of 7.7, 4.5, and 2.3 months, respectively, at that time. Weltman et al. published the Score Index for Radiosurgery (SIR) (Table 30.2) in

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Table 30.1 Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis (RPA) for patients with brain metastases

Class	Criteria	Median survival
Class I:	Age <65 yrs and KPS ≥ 70 and controlled primary tumor and no extracranial metastases	7.1 mo
Class II:	All patients not in Class I or III	4.2 mo
Class III:	KPS < 70	2.1 mo

KPS Karnofsky Performance Status (Ref. [9])

Table 30.2 Score Index for Radiosurgery (SIR)

	Score		
	0	1	2
Age (years)	≥60	51–59	≤50
KPS	≤50	60–70	80–100
Systemic disease	Progressive	Stable	CR or NED
Number of lesions	≥3	2	1
Vol. largest lesion (ml)	>13	5–13	<5

KPS Karnofsky Performance Status, *CR* complete response, *NED* no evidence of disease
Median Survival (MS) by SIR Score: SIR 1–3 (MS 2.91 mo), SIR 4–7 (MS 7.00 mo), SIR 8–10 (MS 31.38 mo). (Ref. [10])

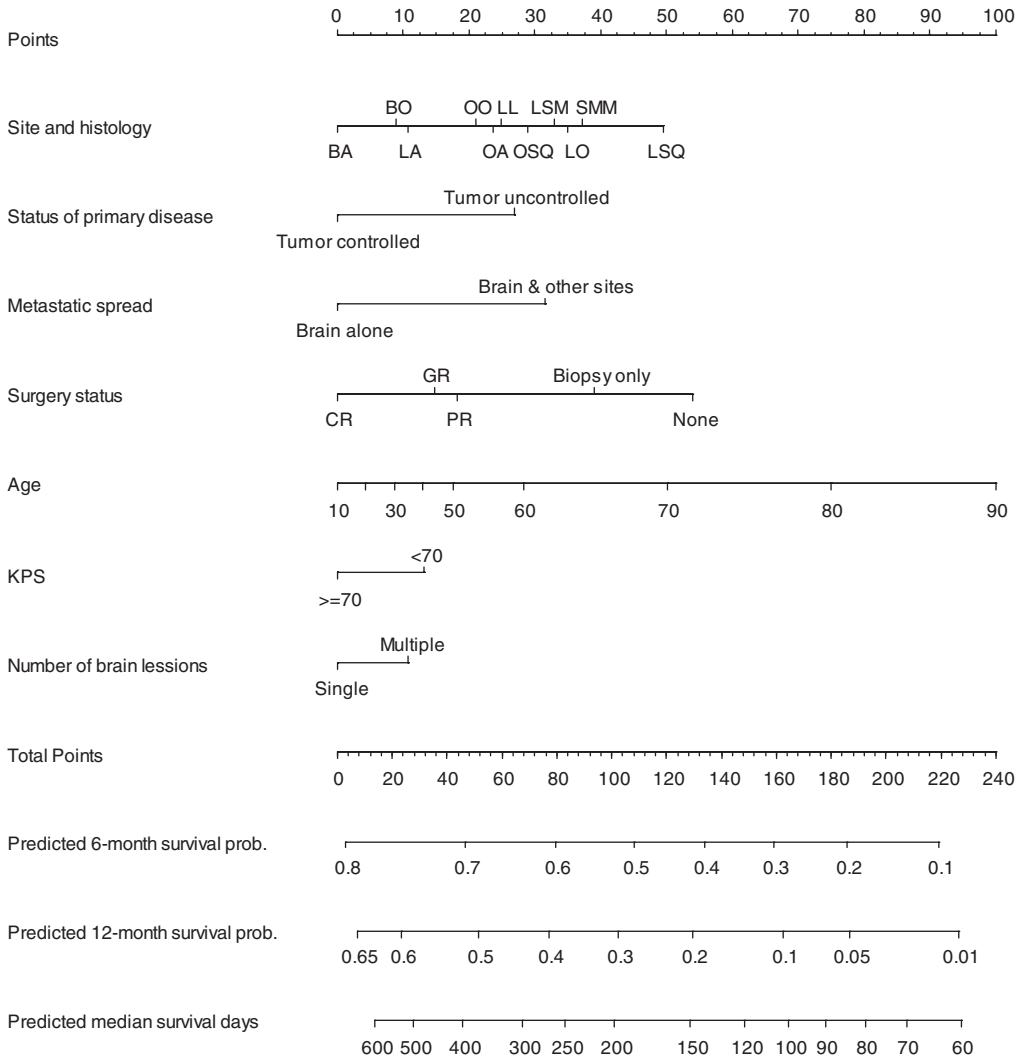
Table 30.3 Basic Score for Brain Metastases (BSBM)

	Score	
	0	1
KPS	50–70	80–100
Control of primary tumor	No	Yes
Extracranial metastases	Yes	No

KPS Karnofsky Performance Status
Median Survival (MS) by BSBM: BSBM 3 (MS >32 mo), BSBM 2 (MS 13.1 mo), BSBM 1 (MS 3.3mo), BSBM 0 (MS1.9 mo). (Ref. [11])

2000 [10]. This index used the sum of scores (0-2) for each of five prognostic factors (age, KPS, status of systemic disease, number of brain metastases, and the volume of the largest metastasis). Lorenzoni et al. published the Basic Score for Brain Metastases (BSBM) (Table 30.3) in 2004 [11]. This index is based on the sum of scores (0-1) for three prognostic factors (KPS, control of primary tumor, and extracranial metastases). In 2012, Sloan-Barnholtz published a nomogram (Fig. 30.1) in an effort to further individualize prognosis [12]. In 2014, Kondziolka published an interesting survey study in which experts in the field were asked to estimate survival for a series of patients given all relevant clinical parameters. This study showed even experts cannot predict outcomes with certainty for all patients [13]. All prognostic indices have limitations but can provide guidance for clinical decision-making and are essential for stratification of clinical trials so that those trials are comparing comparable patients, thus making the results of those trials worthwhile, relevant, and interpretable.

Our group has published a series of articles developing and refining a diagnosis-specific prognostic index, the Graded Prognostic Assessment (GPA), for patients with brain metastases. The GPA was first published in 2008 [14] based on 1960 patients from five randomized Radiation Therapy Oncology Group (RTOG) trials (7916, 8528, 8905, 9104, and 9508). Analysis showed four prognostic factors (age, KPS, extracranial metastases, and number of brain metastases) were significant for survival. Those prognostic factors were weighted in proportion to their regression coefficients and scaled such that patients with the best/worst prognosis would have a GPA of 4.0/0.0, respectively. In 2010, we refined the GPA based on an analysis of a retrospective multi-institutional database of 4259 patients. That study found survival varies by diagnosis and diagnosis-specific prognostic factors [15]. The Breast-GPA was then further refined using tumor subtype [16] and a summary report was published [17]. More recently, the GPA indices for lung cancer, melanoma, and renal cell carcinoma have been updated using molecular and other clinical factors with new data from patients (2186 lung cancer and 823 melanoma patients) diagnosed since 2005 including molecular factors. The Lung-molGPA incorporates EGFR and ALK gene status [18, 19] and similarly the Melanoma-molGPA incorporates *BRAF* status [20, 21]. The



*Abbreviations for site and histology: BA – Breast and Adenocarcinoma, BO – Breast and Other, LA – Lung and Adenocarcinoma, LL – Lung and Large cell, LO – Lung and Other, LSM – Lung and Small cell, LSQ – Lung and Squamous cell, OA – Other and Adenocarcinoma, OSQ – Other and Squamous cell, SMM = Skin-Melanoma, OO – Other and Other. Surgery: PR – Partial Resection, CR – Complete resection, GR – Gross Resection. (Reference 12)

Fig. 30.1 Nomogram for 6 month and 12 month survival probability and median survival prediction for RTOG brain metastases patients∗. ∗Abbreviations for site and histology: *BA* Breast and Adenocarcinoma, *BO* Breast and Other, *LA* Lung and Adenocarcinoma, *LL* Lung and Large cell, *LO* Lung and Other, *LSM* Lung and Small cell, *LSQ* Lung and Squamous cell, *OA* Other and Adenocarcinoma, *OSQ* Other and Squamous cell, *SMM* Skin-Melanoma, *OO* Other and Other. Surgery: *PR* Partial Resection, *CR* Complete resection, *GR* Gross Resection. [Reprinted from Sloan-Barnholtz-Sloan JS, Yu C, Sloan AE, et al. A nomogram for individualized estimation of survival among patients with brain metastasis. Neuro Oncol 2012;14:910–918. With permission from Oxford University Press]

original Melanoma-GPA found only two factors were significant (KPS and the number of brain metastases) whereas in the updated Melanoma-molGPA, five factors (BRAF status, KPS, age, extracranial metastases, and number of brain metastases) were found to be significant. The Renal GPA has also been updated. Data from 711 renal cell carcinoma patients with brain metastases, diagnosed between 2006 and 2016 showed four prognostic factors significant for survival: KPS, Hemoglobin, extracranial metastases, and the number of brain metastases [22]. The Renal GPA was updated accordingly [23].

Table 30.4 shows the median survival time for patients with brain metastases by diagnosis-specific GPA. Table 30.5 shows the diagnosis-specific definition of the updated GPA indices and a user-friendly worksheet to facilitate calculation of the Graded Prognostic Assessment by diagnosis and estimate survival for patients with brain metastases. A free on-line/smart phone application is available at brainmetgpa.com which further simplifies calculation of the GPA.

Table 30.6 shows a multivariate analysis of risk of death and median survival by treatment (excluding drug therapies) and diagnosis. It is important to understand these data are retrospective in nature with the selection bias inherent in all retrospective studies so one should not conclude that one treatment is better than another based on these data. Figure 30.2 shows Kaplan-Meier curves for survival for six diagnoses by GPA, demonstrating excellent separation between groups.

The diagnosis-specific GPA indices presented here defines how survival has improved for brain metastasis patients has improved over the past four decades. This progress mirrors the progress seen in survival for patients with the same diagnoses who do not have brain metastases. These data hold several implications for clinical management and research involving patients with brain metastases: (1) There is marked heterogeneity in outcomes for patients with brain metastases and these outcomes vary not only by diagnosis but also by diagnosis-specific prognostic factors, as detailed herein. Because of this heterogeneity, we should not treat all patients with brain metastases the same way; treatment should be individualized and the past philosophy of fatalistic futility should be abandoned. (2) On the other hand, as shown in Table 30.4, if a patient

Table 30.4 Median survival time for patients with brain metastases by diagnosis specific—graded prognostic assessment score

Diagnosis	Overall MST (95% CI) *N*	DS-GPA 0–1.0 MST (95% CI) *n* (%)	1.5–2.0 MST (95% CI) *n* (%)	2.5–3.0 MST (95% CI) *n* (%)	3.5–4.0 MST (95% CI) *n* (%)	*p* (log-rank)
NSCLC	15 (14–17) 1521	7 (6–9) 337 (22%)	14 (12–15) 664 (44%)	26 (23–31) 455 (30%)	47 (37–NE) 65 (4%)	<.001
SCLC	5 (4–6) 281	3 (2–3) 65 (23%)	5 (4–7) 119 (42%)	8 (6–9) 84 (30%)	17 (5–27) 13 (5%)	<.001
Melanoma	10 (9–11) 823	5 (4–7) 136 (17%)	8 (7–9) 386 (47%)	16 (13–19) 256 (31%)	34 (24–50) 45 (5%)	<.001
RCC	12 (11–13) 669	4 (3–5) 170 (25%)	12 (9–14) 178 (27%)	17 (13–21) 204 (30%)	35 (20–41) 117 (17%)	<.001
Breast cancer	14 (12–16) 400	3 (3–4) 23 (6%)	8 (6–9) 104 (26%)	15 (13–16) 140 (35%)	25 (23–27) 133 (33%)	<.001
GI cancer	5 (4–6) 209	3 (2–5) 76 (36%)	4 (3–7) 65 (31%)	7 (5–12) 50 (24%)	14 (10–27) 18 (9%)	<.001
Other	6 (5–7) 450	–	–	–	–	–

The top row in each cell is the median survival time (MST) in months and its associated 95% CI. The bottom row is the frequency and percentage of patients with the corresponding DS-GPA category for a given diagnosis. Abbreviations: *DS-GPA*, Diagnosis Specific-Graded Prognostic Assessment; *NSCLC*, non-small cell lung cancer (adenocarcinoma); *SCLC*, small cell lung cancer; *RCC*, renal cell carcinoma; *GI*, gastrointestinal; *NE*, not estimable

Table 30.5 GPA worksheet to estimate survival from brain metastases by diagnosis

Non-small cell/small cell lung cancer	GPA	Scoring criteria			Patient score
		0	0.5	1.0	
	Age	≥70	<70	n/a	____
	KPS	<70	80	90–100	____
	ECM	Present		Absent	____
	#BM	>4	1–4	n/a	____
	Gene Status	EGFR neg/unk and ALK neg/unk	n/a	EGFR pos or ALK pos	____
				Sum Total=	____
Adenocarcinoma MS by GPA: GPA 0–1.0 = 6.9; 1.5–2.0 = 13.7; 2.5–3.0 = 26.5; 3.5–4.0 = 46.8					
Non-adenocarcinoma MS by GPA: GPA 0–1.0 = 5.3; 1.5–2.0 = 9.8; 2.5–3.0 = 12.8					

Melanoma		0	0.5	1.0	Score
	Age	>70	<70	n/a	____
	KPS	<70	80	90-100	____
	ECM	present	n/a	absent	____
	#BM	>4	2–4	1	____
	Gene Status	BRAF neg/unk	BRAF pos	n/a	____
				Sum total =	____
MS (mo) by GPA: 0–1.0 = 4.9, 1.5–2.0 = 8.3, 2.5–3.0 = 15.8, 3.5–4.0 = 34.1_____					

Breast cancer		0	0.5	1.0	1.5	2.0	Score
	KPS	< 50	60	70-80	90-100	n/a	____
	Subtype	basal	n/a	LumA	HER2	LumB	____
	Age	>60	<60	n/a	n/a	n/a	____
						Sum Total =	____
	Subtype:	Basal = Triple Negative (ER/PR/HER2-neg), LumA = Luminal A (ER/PR-pos, HER2-neg) LumB = Luminal B (Triple Positive, ER/PR/HER2-pos) HER2 = HER2-pos, ER/PR-neg					
MS (mo) by GPA: 0–1.0 = 3.4, 1.5–2.0 = 7.7, 2.5–3.0 = 15.1, 3.5–4.0 = 25.3_____							

Renal Cell Carcinoma		0	0.5	1.0	2.0	Score
	KPS	<80		80	90-100	____
	ECM	Present	Absent			____
	Hgb	<11	11.1–12.5	> 12.5		____
	#BM	>4	1–4			____
					Sum Total =	____
MS (mo) by GPA: 0–1.0 = 3.3, 1.5–2.0 = 7.3, 2.5–3.0 = 11.3, 3.5–4.0 = 14.8_____						

GI cancers		0	1	2	3	4	Score
	KPS	<70	70	80	90	100	____
MS (mo) by GPA: 0–1.0 = 3.1, 2.0 = 4.4, 3.0 = 6.9, 4.0 = 13.5_____							

Abbreviations: *GPA* Graded Prognostic Assessment, *KPS* Karnofsky Performance Score, *ECM* extra-cranial metastases, *#BM* number of brain metastases, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *MS* median survival in months, *neg/unk* negative or unknown. (Refs. [17, 19, 21])

has a GPA of 0-1.0, regardless of diagnosis, their expected survival is poor. For these patients, supportive care, as suggested by the QUARTZ Trial [8], may be the best option. (3) For patients with GPA scores above 1.0, the median survival time (Table 30.4) varies more by diagnosis and more aggressive treatment strategies may be appropriate, but these retrospective data do not provide a basis for assuming that longer survival is a consequence of more aggressive treatment. Indeed, the survival by treatment data shown in Table 30.6 is certainly fraught with selection bias and should

Table 30.6 Multivariable analysis of risk of death and median survival[b] by treatment and diagnosis

Diagnosis	Statistics	Treatment					
		WBRT	SRS	WBRT + SRS	S + SRS	S + WBRT	S + WBRT+SRS
NSCLC *n* = 1521	Risk of death (HR)	1.0	1.08	1.20	0.66[a]	0.78	0.79
	95% CI		0.92 to 1.27	0.94 to 1.54	0.50 to 0.88	0.58 to 1.06	0.40 to 1.58
	p-value		0.35	0.15	< 0.01	0.11	0.51
	Median survival[b]	13	14	10	32	20	20
	n (%)	342 (22%)	767 (50%)	139 (9%)	114 (7%)	76 (5%)	13 (1%)
SCLC *n* = 281	Risk of death (HR)	1.0	0.97	0.24[a]	0.00	0.42[a]	0.00
	95% CI		0.41 to 2.26	0.10 to 0.59	NA	0.25 to 0.73	NA
	p-value		0.94	0.002	0.99	0.002	0.98
	Median survival[b]	4	7	15	12	15	15
	n (%)	229 (81%)	13 (5%)	21 (7%)	1 (0.4%)	16 (6%)	1 (0.4%)
Melanoma *n* = 823	Risk of death (HR)	1.0	0.69[a]	0.62[a]	0.50[a]	0.54[a]	0.70
	95% CI		0.54 to 0.89	0.45 to 0.86	0.36 to 0.69	0.35 to 0.84	0.36 to 1.36
	p-value		< 0.01	< 0.01	< 0.01	< 0.01	0.29
	Median survival[b]	6	10	9	13	11	11
	n (%)	91 (11%)	464 (56%)	73 (9%)	95 (12%)	34 (4%)	12 (1%)
Renal cell *n* = 711	Risk of death (HR)	1.00	0.84	0.78	0.38	0.64	1.29
	95% CI		0.62 to 1.12	0.51 to 1.19	0.25 to 0.59	0.38 to 1.08	0.45 to 3.68
	p-value		0.23	0.25	<0.01	0.09	0.64
	Median survival[b]	5	11	11	24	16	11
	n (%)	90 (12%)	410 (58%)	41 (6%)	70 (10%)	23 (3%)	4 (1%)
Breast cancer *n* = 400	Risk of death (HR)	1.0	1.07	0.74	0.59	0.72	0.47[a]
	95% CI		0.66 to 1.73	0.47 to 1.16	0.28 to 1.23	0.43 to 1.21	0.23 to 0.96
	p-value		0.80	0.18	0.16	0.72	0.04
	Median survival[b]	7	13	15	24	18	30
	n (%)	131 (33%)	115 (29%)	86 (22%)	19 (5%)	28 (7%)	20 (5%)
GI Cancer *n* = 209	Risk of death (HR)	1.0	0.72	0.69	2.30	0.33[a]	0.39[a]
	95% CI		0.40 to 1.28	0.39 to 1.22	0.43 to 12.4	0.19 to 0.56	0.17 to 0.90
	p-value		0.26	0.21	0.33	< 0.001	0.03
	Median survival[b]	3	7	7	9	10	8
	n (%)	95 (45%)	35 (17%)	35 (17%)	2 (1%)	34 (16%)	8 (4%)

Diagnoses: *NSCLC* non-small cell lung cancer (adenocarcinoma), *SCLC* small cell lung cancer, *GI* gastrointestinal
Treatments: *S* surgery, *WBRT* whole brain radiation therapy, *SRS* stereotactic radiosurgery
Statistics: Risk of death: hazard ratio (HR) normalized to patients treated with whole brain radiation therapy alone (HR = 1.0) and calculated by multivariable Cox regression, adjusted for DS-GPA and stratified by institution
[a]Statistically significantly better than WBRT alone; 95% confidence interval
[b]Median survival in months based on one-sample Kaplan-Meier method. (Refs. [17, 19, 21])

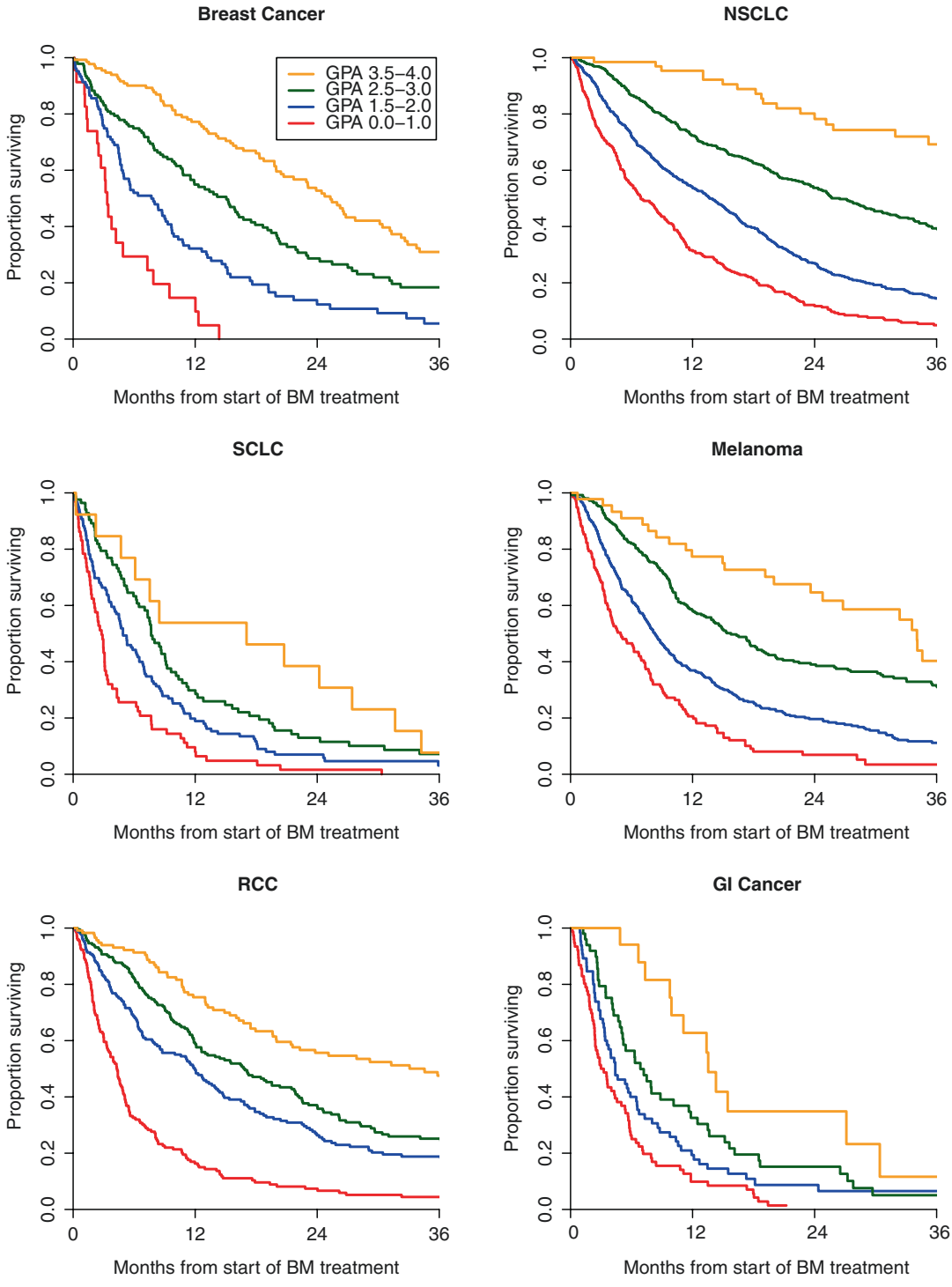


Fig. 30.2 Kaplan-Meier Curves for Survival by GPA for Six Diagnoses: Breast Cancer, Non-Small Cell Lung Cancer, Small Cell Lung Cancer, Melanoma, Renal Cell Carcinoma, Gastrointestinal Cancers

not be blindly applied or expected. Nonetheless, these data reflect patterns of care for patients with brain metastases. (4) Performance status is prognostic in every diagnosis. Clinicians should take the time to accurately assess and document their patients' performance status. (5) Table 30.5 shows the number of brain metastases is a significant prognostic factor for lung cancer, melanoma, and renal cell carcinoma, but not for breast or gastrointestinal cancers. Patients should not be denied treatment because of the number of brain metastases. (6) Extracranial metastases are only prognostic in lung cancer and melanoma but not in breast cancer, renal cell carcinoma, or gastrointestinal cancers. The implication here is that those patients with non-lung, non-melanoma malignancies should not be denied aggressive treatment for their brain metastases because they have extracranial metastases. (7) Age is strongly prognostic in lung cancer and weakly prognostic in breast cancer and melanoma but not prognostic in renal cell carcinoma or gastrointestinal cancers. Thus, age should not be used as a rationale to withhold aggressive treatment for non-lung malignancies. (8) Because lung cancer and brain metastases from lung cancer are so common, those patients have masked our understanding of the distinct course for patients with non-lung malignancies and brain metastases, as demonstrated by points 5, 6, and 7 above. (9) Tumor subtype in breast cancer is of paramount importance and prognostic significance but it is not as prognostic as the Breast-GPA index. (10) A disproportionate number of patients with gastrointestinal cancers present with GPA of 0-1.0. Whether this is due to lack of screening MRI in these patients versus other biological reasons remains unclear but the finding should serve as a reminder that brain metastases are not uncommon in GI cancer patients. Ongoing research will better elucidate prognosis for these patients and the GI-GPA will be updated accordingly. (11) Clinicians may use the worksheet in Table 30.5 or go to brainmet-gpa.com, a free user-friendly smart-phone application to calculate their patient's GPA score and estimate survival [12]. The GPA may be used for purposes of stratification in clinical trials dealing with patients with brain metastases.

All prognostic indices are imperfect and cannot always predict the outcome for an individual patient. The following case study is remarkable for the patient's outcome but also because it demonstrates the application of the GPA in a clinical setting but also the potential pitfalls of prognostic indices for such a heterogeneous patient population.

30.3 Case Study

A 36-year-old white female marathon runner presented in August 2005 with a right neck mass [24]. Fine needle aspiration initially confirmed a malignancy, later confirmed as a malignant melanoma by excisional biopsy of a posterior scalp lesion on 9-15-05. This malignant melanoma was histopathologically staged as Clark's Level IV, Breslow depth at least 6 mm, with angiolymphatic invasion and positive deep and peripheral margins. Brain MRI for initial radiologic staging on 9-27-05 showed multiple scalp lesions but no evidence of parenchymal brain metastases. PET scan 9-27-05 showed hypermetabolic activity only in the left neck. On 10-11-05, she underwent a left modified radical neck dissection and wide local excision of the scalp lesion. Pathology confirmed metastatic melanoma in 3 of 28 lymph nodes with extension into the adjacent soft tissues in two areas. Pathology from the scalp excision showed a maximum tumor depth of 1.9 cm and the deep margin remained positive. She underwent two additional scalp excisions and the deep margin remained positive. Her stage was T4bN2bM0, stage IIIC. She received 64 Gy radiation therapy to the left neck and scalp, completed 1-20-06. She then received 3 cycles of cisplatinum, interferon, and vinblastine followed by interleukin-2, completed in March 2006. She did well without evidence of recurrence until November 2006 when she underwent a debridement of necrotic tissue in the scalp lesion. PET scan 12-5-06 showed a 0.7 cm hypermetabolic nodule in the retroperitoneum consistent with metastatic recurrence. Brain MRI 12-6-06 showed three brain metastases (2.5 cm right caudate, 1.1 cm left pari-

eto-occipital, and 0.7 cm left posterior frontal) (Fig. 30.3a), which were not present on the prior scan of 6/22/06.

Whole brain radiation therapy was not given (and has not been given) due to the prior scalp radiation. She underwent SRS (Gamma Knife) on 12-13-06 to all three lesions: right caudate, 20 Gy to a volume 8.4 cc (Fig. 30.3b); left posterior frontal 24 Gy to a volume of 0.47 cc (Fig. 30.3c); and left parieto-occipital, 24 Gy to a volume of 1.6 cc (Fig. 30.3d). She underwent SABR to the pelvic soft tissue metastasis (25 Gy x 5 over 2 weeks, completed 2/23/07). Between March and June 2007, she received four cycles of carboplatin, paclitaxel, and temozolomide treatment. In September 2007, she developed headaches, nausea, vomiting, and confusion. MRI 9-26-07 showed a marked increase in enhancement and edema in the right frontal lobe consistent with radiation necrosis (Fig. 30.3e). Due to increased headaches and possible radiation necrosis, the temozolomide was discontinued. She has received no treatment since September 2007. The edema was treated with steroids, which were gradually tapered off over 4 months. Brain MRI 5-23-08 showed improvement with central necrosis of the previously solid-appearing lesion (Fig. 30.3f). Brain MRI 10-23-08 showed

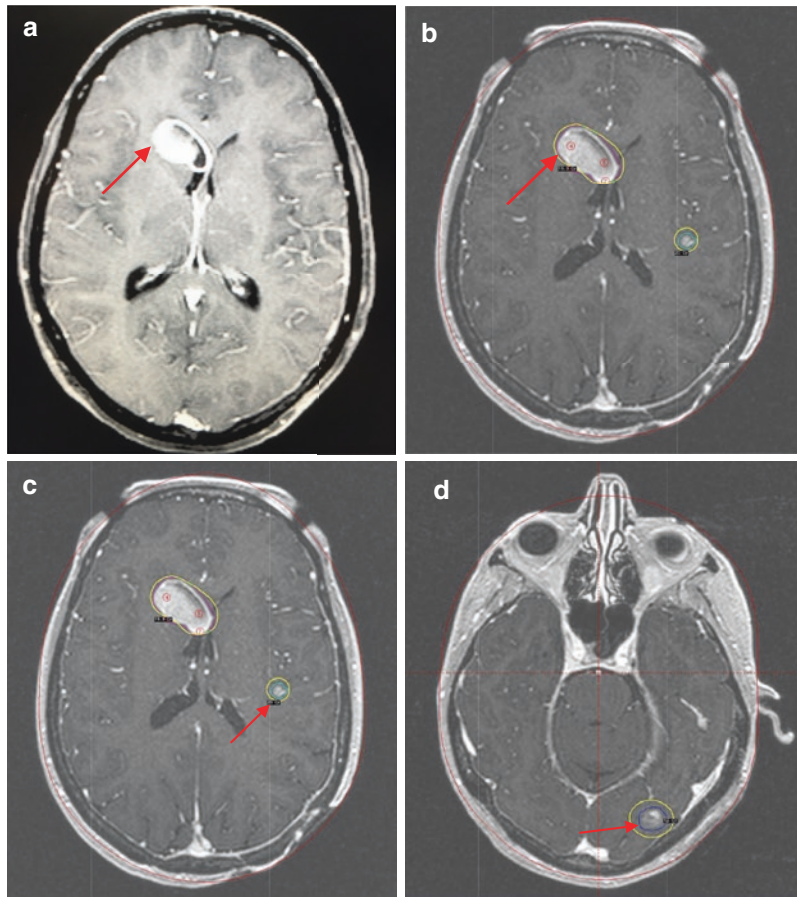


Fig. 30.3 Serial Brain MRI images for Case Report: (**a**) Initial MRI shows largest of 3 brain metastases, 12-06-2006; (**b**) Gamma Knife plan for right frontal brain metastasis, 12-13-2006; (**c**) Gamma Knife plan for left frontal brain metastasis, 12-13-2006; (**d**) Gamma Knife plan for left occipital brain metastasis, 12-13-2006; (**e**) MRI 9 months after GK shows marked radiation necrosis and edema, 9-26-07; (**f**) MRI 18 months after GK shows resolving radiation necrosis, 5-23-2008; (**g**) MRI 21 months after GK shows minimal residual enhancement, 10-23-2008. (**h**) MRI 10.7 years after GK shows no evidence of disease, 8-02-2017

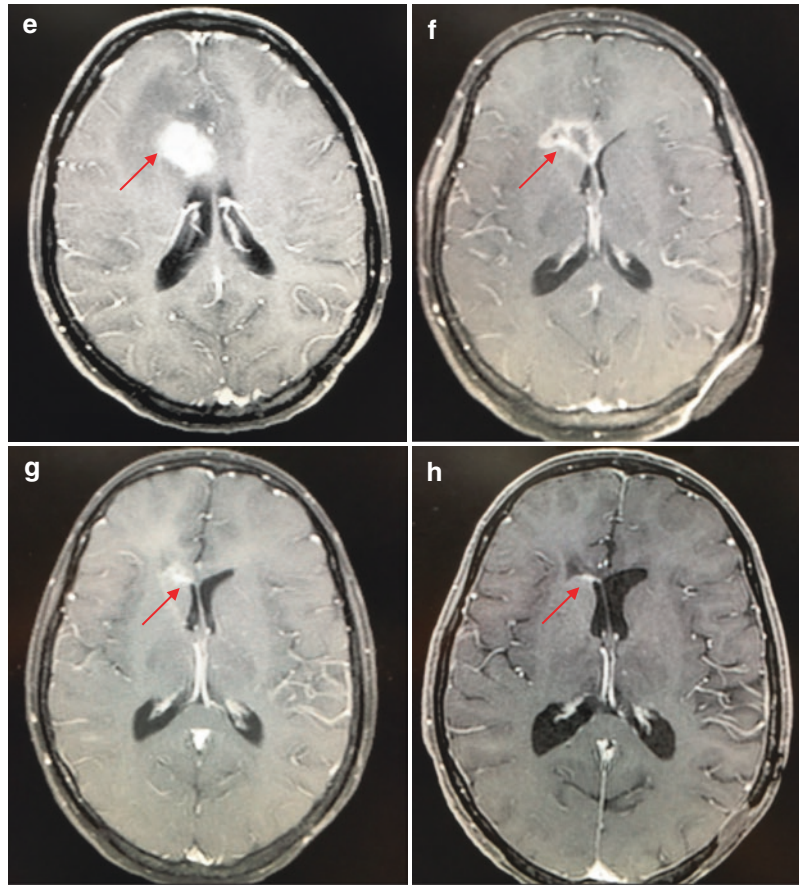


Fig. 30.3 (continued)

further resolution of the enhancement/necrosis with minimal residual enhancement (Fig. 30.3g). Serial imaging since that time has shown no evidence of recurrent tumor or necrosis.

She remains clinically and radiographically free of disease 11 years after the diagnosis of multiple brain metastases and more than 10 years after completion of treatment. Brain MRI on 8-2-17 showed no change in the minimal residual enhancement/scar tissue (Fig. 30.3h) and PET scan 8-2-17 showed no evidence of disease. She has remained asymptomatic for over a decade and continues to run marathons, as recently as 10-14-17. In November 2017, she completed the FACT-Brain questionnaire, a patient-reported QOL tool to reassess brain cognition. Her FACT-BR score was perfect (200 on a scale of 200), 11 years after diagnosis of her brain metastases. Notably, this patient never underwent craniotomy or whole brain radiation therapy and thus avoided the related long-term neurocognitive toxicity of these interventions.

To fully appreciate this patient's remarkable outcome, it is appropriate to review how her outcome compares to the best available evidence of survival for melanoma patients with brain metastases. We recently updated and published the melanoma-molGPA has recently been published [20, 21] based on a multi-institutional retrospective study of 483 melanoma patients with brain metastases diagnosed between 1/1/2006 and 12/31/15. Notably, the patient presented here was diagnosed in 2006, so she is a contemporary of the patients in the melanoma-molGPA update study. The study showed five prognostic factors significant for survival (Table 30.5).

Overall median survival for melanoma patients with brain metastases has improved from 6 to 10 months since the 1980s, and the median survival by melanoma-molGPA groups for GPA of 0-1.0, 1.5-2.0, 2.5-3.0, and 3.5-4.0 was 4.9, 8.3, 15.8, and 34.1 months, respectively. The patient presented here had a Melanoma-GPA of 3.0 on a 4.0 scale on both the original and updated GPA index, correlating with an estimated survival of 8.8 and 15.8 months, respectively. This patient is disease-free and asymptomatic with a perfect FACT-Brain QOL score 11 years after the diagnosis of multiple brain metastases. Clearly, prognostic indices are imperfect but nonetheless provide our best estimate of survival for these patients.

30.4 Summary

Patients with brain metastases are a heterogeneous population and outcomes vary widely by diagnosis and diagnosis-specific prognostic factors. Because of this heterogeneity and the plethora of available treatment options, it is difficult to estimate survival. These problems have complicated clinical decision-making as well as interpretation of clinical trials. The Graded Prognostic Assessment (GPA) is a diagnosis-specific prognostic index which has been updated to reflect the current treatment era by incorporating diagnosis-specific prognostic factors including molecular factors such as tumor subtype and gene status. The GPA is useful for clinical decision-making as physicians determine whether and what treatment is appropriate for these patients. It can also be useful to stratify clinical trials to ensure those trials are comparing comparable patients, which is especially important in such a heterogeneous patient population. Without accurate stratification, the results of clinical trials are uninterpretable and a waste of resources.

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Prevention Strategies for Brain Metastasis

31

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31.1 Introduction

The brain has been increasingly recognized as a sanctuary site for harboring metastases despite an excellent control of the extracranial disease. The main reason is that drugs such as cytotoxic chemotherapeutics or monoclonal antibodies, which are effective against primary tumor and/or systemic metastases, are not able to adequately cross an intact blood-brain barrier and target micrometastases in the brain, thus evolving into macrometastases with clinical correlates. Moreover, it is well known that within the same tumor type, some subgroups of patients, as defined by clinical, pathological, and molecular factors, have a higher propensity to metastasize into the brain. Thus, the concept of prophylactic strategies to prevent the development of brain metastases in high-risk patients has gained attention since several years. Historically, the first approach has been the so-called prophylactic cranial irradiation (PCI), which is a technique that delivers radiation therapy to the whole brain (WBRT) to eliminate undetectable micrometastases before they become clinically apparent. PCI was initially demonstrated to significantly decrease the rate of CNS recurrences in childhood acute lymphoblastic leukemia [1] and then employed in SCLC [2] and non-small cell lung cancer (NSCLC) [3]. While showing effectiveness in preventing the intracranial disease development, PCI carries the risk of neurocognitive decline, affecting QoL, in long-term survivors. Pharmacologic prevention, which is of limited value with cytotoxic drugs, is now an attractive concept in the era of molecular agents and immunotherapies.

This chapter will review the current approaches that are available in the clinic, discussing the balance between expected efficacy and neurotoxicity, and will explore the new horizons.

31.2 Prophylactic Cranial Irradiation (PCI)

31.2.1 Small Cell Lung Cancer (SCLC)

CNS failure in SCLC occurs approximately in 50–60% of patients at 2 years following diagnosis [2] and carries poor prognosis [4]. Early trials did not show a clear benefit to the delivery of PCI in SCLC [5] as they included patients with both limited (LD) or extensive (ED) disease and/or did not perform an appropriate restaging for response to chemotherapy prior to PCI. What

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became evident in the trials conducted in the subsequent years was that patients with LD SCLC who had a complete response to chemoradiotherapy derived a significant benefit in both local control and survival. A seminal metanalysis of seven randomized trials conducted in 1977–1995 on PCI at varying dose and fractionation schedules showed a reduction in the cumulative incidence of brain metastases at 3 years and an improvement of survival by approximately 5% at 3 years (20.7% PCI vs. 15.3% observation) [6]. A second more recent metanalysis with nearly identical results confirmed that PCI reduces the incidence of BM and provides a survival advantage [7]. However, the benefit of PCI on survival was not significant in patients with less than a CR after chemotherapy. A recent study has hypothesized that PCI may not have a survival benefit in patients with LD SCLC with MRI-confirmed absence of BM after chemoradiotherapy [8], but this finding needs confirmation in prospective studies.

However, both meta-analyses did not address the potential for neurotoxicity of whole-brain radiotherapy (WBRT). PCI is known to be associated with acute toxic effects, such as alopecia, nausea, headache, and fatigue [9], which are self-limited and resolve overtime. However, data on long-term cognitive deficits are limited. An early retrospective study on 20 long-term survivors of SCLC showed memory loss, ataxia, and weakness in 15% (75%) [10]. Other studies have identified age >60 years, total dose >30 Gy, and concurrent chemotherapy as factors increasing the risk of neurotoxicity following PCI [11, 12]. In RTOG 0212, 62% of patients who received 25Gy of PCI developed chronic neurotoxicity, and increasing age was the most significant risk factor [13, 14]. A recent study [15] has reported that among patients ≥70 years with ≥5 cm tumors, PCI did not improve significantly OS, probably due to the higher risk of comorbidity or extracranial disease. Thus, in patients ≥70 years, which account for about 60% of new cases of LD SCLC, physicians should be prepared to discuss the relative benefits and risks of PCI on an individual basis [16, 17].

All these data emphasize the importance of investigating treatment strategies aimed at reducing PCI-induced neurotoxicity, such as WBRT with hippocampal sparing in the phase II–III NGR-CC003 trial. However, the risk of BM in the hippocampal regions in SCLC patients is still not clear [18, 19].

The recommendation for PCI in patients with extensive disease (ED) SCLC is less clear [20]. Aupérin's metanalysis reported that the small subgroup of patients with ED SCLC, who achieved a CR following systemic chemotherapy, had lower rates of BM and better survival when PCI was administered [6]. The EORTC performed a phase III trial investigating the role of PCI in patients with ED SCLC, who had PR or CR to chemotherapy [21]. The risk of brain metastases at 1 year was significantly reduced in the PCI group (16.4% PCI vs. 40% observation), and the 1-year survival rate was also superior (27.1% PCI and 13.3% observation). However, the main limit of this study was the lack of a mandatory pretreatment brain MRI in asymptomatic patients to exclude the presence of small BM that could have responded to WBRT.

More evidence in support of PCI in ED SCLC comes from a pooled analysis of patient with LD and ED SCLC with stable disease following chemotherapy and thoracic radiotherapy that reported an improvement of survival at 1 and 3 years with limited toxicity [22]. Conversely, a Japanese phase III trial [23] reported a lower median OS for patients who received PCI compared to those with observation (11.6 vs. 13.7 months), even if PCI significantly reduced the rate of brain relapse at 1 year (from 59 to 32.9%).

Ongoing trials on PCI in SCLC are listed in Table 31.1.

Table 31.1 Ongoing trials on PCI in NSCLC, SCLC, and breast cancer

Study	Phase	Number of patients	Type of solid tumor	Treatment	Endpoints
NCT01290809	III	170	NSCLC (stage IIIA or IIIB)	*Experimental arm*: Prophylactic WBRT (30 Gy/10 fr) following platinum-based chemotherapy *No intervention arm*: Platinum-based chemotherapy alone	*Primary*: – To measure cognitive sequelae – QoL
NCT01282437	III	315	NSCLC (stage IIIA or IIIB)	*Experimental arm*: prophylactic WBRT – 18 fractions of 2Gy – 12 fractions of 2.5Gy – 10 fractions of 3 Gy *No intervention arm*: Observer group	*Primary*: – Proportion of patients developing symptomatic BM *Secondary*: – Time to develop neurological symptoms – Measurement of side effects (CTCAE 3.0) – QoL (EORTC questionnaires)
NCT01603849	III	128	NSCLC (high-risk stage IIIB or IV)	*Experimental arm*: Prophylactic WBRT (25 Gy/10 fr) *No intervention arm*: Observer group	*Primary*: – CNS PFS *Secondary*: – OS – QoL (EORTC questionnaires) – Neurocognitive assessment (MMSE)
NCT00048997	III	1056	NSCLC (stage IIIA or IIIB)	*Experimental arm*: Prophylactic WBRT (30 Gy/15 fr) *No intervention arm*: Observer group	*Primary*: – OS *Secondary*: – Percentage of patients with deterioration in the HVLT-R (recall score, delayed recall score) – QoL (EORTC questionnaires) – Percentage of patients with BM
NCT02448992	II III	90	NSCLC	*Experimental arm*: Hippocampal-sparing prophylactic WBRT (30 Gy/15 fr) *No intervention arm*: Observer group	*Primary*: – Time to development of BM, regardless of the absence of active neurological symptoms *Secondary*: – Neurocognitive assessment (WMS III Word list and visual reproduction score)

(continued)

Table 31.1 (continued)

Study	Phase	Number of patients	Type of solid tumor	Treatment	Endpoints
NCT00955695	III	242	NSCLC	*Experimental arm*: Prophylactic WBRT (30 Gy/10 fr) following gefitinib or erlotinib *No intervention arm*: First-line chemotherapy with gefitinib or erlotinib alone	*Primary*: – Time to symptomatic BM *Secondary*: – PFS – OS – QoL (EORTC, HVLT, and K-ADL questionnaires) – Tolerability of WBRT
NCT01158170	III	200	NSCLC	*Experimental arm*: Prophylactic WBRT (25 Gy/10 fr) following gefitinib or erlotinib *No intervention arm*: First-line chemotherapy with gefitinib or erlotinib alone	*Primary*: – Cumulative incidence of symptomatic BM *Secondary*: – OS
NCT02906384	II	154	SCLC	*Experimental arm:* Prophylactic WBRT (25Gy/10fr) with hippocampus avoidance *Control arm:* Routine WBRT (25Gy/10fr)	*Primary:* – Memory preservation (HVLT test) *Secondary:* – OS – Hippocampus metastases – Changes of functional brain MRI
NCT03514849	NA	360	SCLC (pT1–2 N0 stage)	*Experimental arm:* Prophylactic WBRT (25Gy/10fr) following surgery (lobectomy + mediastinal lymph node dissection) and adjuvant chemotherapy (etoposide + cisplatin) *No intervention arm:* Surgery (lobectomy + mediastinal lymph node dissection) and adjuvant chemotherapy (etoposide + cisplatin) alone	*Primary:* – 5-y OS% Secondary: – 5-y PFS% – Surgery complications
NCT02397733	III	150		*Experimental arm:* Prophylactic WBRT (25Gy/10fr) with hippocampus avoidance *Control arm:* Routine WBRT (25Gy/10fr)	*Primary:* – Neurocognitive functioning (FCSRT) – Hippocampus brain metastases – Hippocampus volume – Adverse events (CTCAE v 4.0) – QoL (EORTC questionnaires)
NCT01780675	III	168	SCLC (stage I–III or stage IV without BM)	*Experimental arm:* Prophylactic WBRT (25Gy/10fr) with hippocampus avoidance *Control arm:* Routine WBRT (25Gy/10fr)	*Primary:* – Neurocognitive decline *Secondary:* – Time to symptomatic BM

Table 31.1 (continued)

Study	Phase	Number of patients	Type of solid tumor	Treatment	Endpoints
NCT02635009	II–III	394	Limited and extensive stage SCLC	*Arm A:* WBRT using 3DCRT *Arm B:* WBRT with hippocampal sparing using IMRT	*Primary:* – Neurocognitive assessment (HTLV) – Intracranial relapse rate *Secondary:* – QoL – Time to neurocognitive decline – Adverse events
NCT00016211	III	287	SCLC	*Experimental arm*: Prophylactic WBRT (30 Gy/10 fr) following first-line chemotherapy *No intervention arm*: First-line chemotherapy alone	*Primary*: – Time to symptomatic BM *Secondary*: – OS – QoL (EORTC questionnaires) – Toxicity (according to NCI CTC)
NCT02448576	III	326	Breast cancer (triple negative)	*Experimental arm*: Prophylactic WBRT (30 Gy/15 fr) after first-line chemotherapy *No intervention arm*: Observer group	*Primary*: – BM-free survival *Secondary*: – Cumulative risk of BM within 1 year – PFS – OS – QoL (EORTC questionnaires)
NCT00639366	III	390	Breast cancer (HER2 positive)	*Experimental arm*: Prophylactic WBRT (30 Gy/10 fr) plus taxane/trastuzumab *Control arm*: Taxane/ trastuzumab alone	*Primary*: – Incidence of symptomatic BM *Secondary*: – OS – CNS toxicity – QoL

NSCLC non-small cell lung cancer, *WBRT* whole-brain radiotherapy, *Gy* gray, *fr* fractions, *BM* brain metastases, *OS* overall survival, *CNS* central nervous system, *EORTC* European Organisation for Research and Treatment of Cancer, *PFS* progression-free survival, *QoL* quality of life, *MMSE* Mini-Mental State Examination, *WMS* Wechsler Memory Scale, *HER2* human epidermal growth factor receptor 2, *SCLC* small cell lung cancer, *NCI CT* National Cancer Institute Common Toxicity, *HVLT* Hopkins Verbal Learning Test, *K-ADL* Katz Index of Independence in Activities of Daily Living, *NA* not applicable, *FCSRT* Free and Cued Selective Reminding Test

31.2.2 Non-Small Cell Lung Cancer (NSCLC)

CNS metastases represent the first site of recurrence following radical surgical treatment in 15–20% of NSCLC patients, while around 40–50% of NSCLC patients develop metastases during the course of the disease [24]. Stage III patients (locally advanced disease) have the highest risk of developing BM with an incidence around 30%. Outcome in patients with BM from NSCLC is unfavorable with severe morbidity and decrease in quality of life, and only patients with druggable molecular alterations (EGFR, ALK,

etc.) have a slightly better survival. Therefore, preventive strategies are of potential interest. Thus far, eight randomized controlled trials comparing PCI with observation in both patients with squamous and non-squamous histologic types and predominantly in stage III disease have been performed (Table 31.2) [24, 25]. Irrespective of the PCI dose and fractionation, the studies reported a significant decrease of the incidence of BM following PCI: the BM incidence in the PCI arm ranged from 0.9 to 12.3% as compared with 11% to 30.7% in the non-PCI arms. In this regard, the recently published phase III NVALT-11/DLCRG-02 trial [26], which used MRI of the brain for both patient selection and monitoring, showed that PCI reduces the incidence of symptomatic BM from 27.2 to 7%. However, this reduction did not translate into an increased overall survival, and the metanalysis of Xie in 2014 [27] suggested that PCI may even have a detrimental effect on OS (as reported in some retrospective or nonrandomized studies).

Few studies have analyzed the impact of PCI on neurotoxicity and QoL. However, there are some reports of a meaningful impairment of neurocognitive function and/or QoL [26, 28]. More information is needed on long-term survival and risk of cognitive defects following PCI. Meanwhile, due to lack of survival benefit, PCI is not a standard management in NSCLC patients regardless of the clinical stage [29].

Table 31.2 Trial designs to evaluate agents for prevention of brain metastases

Primary chemoprevention studies
• Selection of patients in a specific cancer category on the basis of one or more risk factors • Designed as randomized studies because historical data on the expected natural incidence of CNS metastases are not well defined • Choice of agents aimed to prevent the metastatic process
Secondary chemoprevention studies
• Selection of patients with a limited number of brain metastases treated with SRS followed by an agent meant to treat the micrometastatic CNS disease • More efficient design as these patients have a higher risk of developing new brain metastases than high-risk patients with no history of CNS involvement

Ongoing trials on PCI in NSCLC are listed in Table 31.1.

31.3 Pharmacologic Prevention

31.3.1 Chemotherapy

The role of cytotoxic chemotherapy in terms of pharmacologic prevention is limited. Maintenance temozolomide monotherapy after surgical resection of locally advanced or stage IV advanced NSCLC after platinum-based chemotherapy did not decrease the incidence of brain metastases [30]. Conversely, the post hoc analysis of two randomized trials on pemetrexed showed a reduction in the risk of brain metastases as the first site of disease progression (3.2 vs. 6.6%) [31]. The positive effect of pemetrexed on brain metastases was confined to patients with non-squamous NSCLC.

In experimental models of breast cancer, temozolomide, a lipophilic drug that can cross an intact blood-brain barrier (BBB), has been reported to significantly reduce the occurrence of micrometastases in an MGMT-dependent manner [32], but thus far, there is lack of confirmation by clinical trials.

31.3.2 Targeted Therapies and Immunotherapy

Monoclonal antibodies, such as trastuzumab in breast cancer, do not seem to be able to adequately target micrometastases.

Conversely, anti-VEGF-A agents, such as bevacizumab, could have the potential to prevent brain metastases in non-squamous NSCLC [33], but clinical trials are needed to prove this hypothesis.

With the advent of small TKI for an effective treatment of systemic disease in druggable subgroups of patients in NSCLC and breast cancer, the issue of a potential activity in terms of prevention, instead of treatment, of BM of new targeted agents has become relevant [34]. In this regard, several recent randomized and nonrandomized

studies showing the efficacy of targeted agents in several solid tumors, either with or without brain metastases at baseline, have released data on the rate of incidence and/or time to CNS relapse following treatment, thus giving some information of the preventive capabilities of the molecular compounds.

Regarding EGFR-mutated NSCLC, a lower CNS progression rate following first-line gefitinib and erlotinib as compared with first-line chemotherapy (33 vs. 48%) has been reported [35]. Erlotinib has a slightly better CSF penetration than gefitinib [36] and thus could be more effective at least in terms of secondary prevention [37]. The risk of CNS metastases is lower in patients treated with first-line EGFR TKIs than in patients treated with second-line therapy [38]. The second-generation EGFR TKI afatinib has been reported to lower the risk of CNS progression as compared with chemotherapy [39]; however, the preventive efficacy seems equivalent to that of gefitinib and erlotinib [40]. The third-generation EGFR TKI osimertinib, which displays a higher ability to cross an intact BBB in preclinical models [41], has been shown to significantly reduce the risk of CNS relapse as compared with gefitinib or erlotinib (12 vs. 30%) [42].

Few data are available on the potential preventive effect of ALK inhibitors in ALK-rearranged NSCLC [43–45]. A dramatic reduction of 12-month incidence of relapse into the brain (9.4 vs. 41.4%) has been reported following the second-generation compound alectinib as compared to the first-generation crizotinib [43, 45]. This is in line with the better CSF penetration of alectinib in preclinical models [46].

Durvalumab, a PDL-1 inhibitor, has been recently reported to lower the CNS incidence of brain metastases as compared with placebo (5.5 vs. 11%) in patients with stage III NSCLC without disease progression after platinum-based chemoradiotherapy [47].

Regarding HER2-positive breast cancer, the small TKI HER2 inhibitor lapatinib, which is registered for breast cancer, has a limited CSF penetration [46] and, as a consequence, a limited preventive ability. In both CEREBEL [48] and EMILIA [49] trials, lapatinib in association with capecitabine failed to show a superior efficacy in reducing the CNS relapses as compared with either trastuzumab + capecitabine (3.5 vs. 5%) or TDM1 (0.7 vs. 2%).

Compared with lapatinib, neratinib is an irreversible inhibitor that targets both the amplified HER2 receptor and activating HER mutations in HER2 gene amplification-negative breast cancer and is able to reverse ABCBI-mediated chemoresistance [50]. A randomized clinical trial in previously untreated metastatic HER2-positive breast cancer showed that symptomatic or progressive CNS recurrences occurred in 8.3% of patients of the neratinib-paclitaxel group versus 17% in patients of the trastuzumab-paclitaxel group [51]. These data could suggest a potential preventive effect of neratinib. The ongoing post hoc analysis of PUMA-NER5210 trial in metastatic HER2+ breast cancer looking at time to CNS relapse following neratinib could provide more firm data.

31.3.3 Trial Designs for Prevention of Brain Metastases

Three issues are critical when designing clinical trials aimed to test the preventive capabilities of an antineoplastic agent. First, a subgroup of patients at high risk of CNS relapse needs to be identified. Second, the investigational agent should adequately cross an intact BBB, as demonstrated by preclinical and possibly human models. Last, specific endpoints (time to relapse in the brain at different time points, cumulative incidence of relapses in the brain, intracranial PFS) should be chosen in relation with the natural history of the disease. Overall, there are two types of studies aimed to evaluate either primary or secondary chemoprevention [52] (Table 31.2).

31.4 The Issue of Screening

Guidelines recommend staging brain MRI for patients with newly diagnosed SCLC, stages I B through IV NSCLC, and stage IV melanoma. A debate is ongoing on HER2-positive breast cancer which is at high risk of developing brain metas-

tasis at first recurrence. The ASCO Guidelines [53] do not recommend the routine surveillance with MRI in asymptomatic patients due to "a low quality of evidence," and the same is true for ESMO Guidelines [54]. Conversely, a recent population-based study in the USA is performed on a sample of 238,726 adult patients [55]. A potential advantage of an early diagnosis of brain metastases in asymptomatic patients could be to avoid neurosurgical procedures needed for bigger lesions and treat with SRS smaller lesions with an increased probability of success and less toxicity [56]. On the other hand, routine surveillance imaging in large population raises the question of cost-effectiveness.

31.5 Conclusions

PCI is standard of care in patients with SCLC as it is able to reduce the rate of relapses into the brain and improve overall survival while the role in NSCLC and breast cancer remains to be evaluated. In this regard, the balance between the improvement of outcome and the risk of cognitive deficits in long surviving patients will be a crucial issue.

In the future, with the development of targeted agents for druggable molecular subgroups of solid tumors, the concept of a pharmacologic prevention of brain metastases will probably grow.

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32 Clinical Trials: Endpoints and Outcome Assessment

Nancy U. Lin

32.1 Introduction

Over the past several decades, clinical trials have become firmly established as a gold standard in assessing the value of novel therapeutic interventions in cancer patients. Innovations, iterative improvements, and standardization in statistical methods, response assessment (e.g., through criteria such as the Response Evaluation Criteria in Solid Tumors [RECIST]), and study designs have contributed to progress against cancer [1].

Historically, clinical trials in oncology have rarely included patients with active CNS metastases, thus leaving gaps in the development of standard methodology by which to assess trial endpoints. Not only have trial endpoints been variably assessed and defined, but the most clinically relevant outcomes may differ by type of trial. This chapter (1) provides recommendations for more active inclusion of patients with brain metastases into prospective clinical trials, (2) summarizes measures that could be considered as primary or secondary trial endpoints, (3) reviews efforts to develop more standard definitions of trial endpoints, and (4) discusses the selection of trial endpoints most appropriate for the given target population and proposed intervention.

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32.2 Incidence of CNS Metastases in Patients with Solid Tumors

Brain metastases are the most common cause of central nervous system (CNS) malignancy in adults, far outpacing the incidence of primary brain tumors. Among over 1.3 million patients included in the Surveillance, Epidemiology, and End Results (SEER) registry with a diagnosis of nonhematologic malignancy between 2010 and 2013, brain metastases were noted on initial presentation in significant proportions of patients with de novo stage IV melanoma (28.3%), lung adenocarcinoma or non-small cell lung carcinoma (NSCLC) (25.6–26.8%), small cell lung cancer (23.5%), squamous cell carcinoma of the lung (15.9%), bronchoalveolar carcinoma (15.5%), and renal cancer (10.8%) [2]. Notably, these figures severely underrepresent the impact of CNS metastases over the course of a patient's disease, as the SEER registry only captures sites of distant relapse at the time of initial cancer diagnosis. Thus, patients with de novo stage IV disease who develop CNS involvement later in their disease course and patients who present with early-stage disease and subsequently relapse in the CNS do not have their events captured in the SEER incidence estimates.

Other sources of data have uncovered very high rates of CNS involvement in specific tumor subtypes, particularly as patients are followed longitudinally over time. For example, in

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several studies of alectinib for crizotinib-refractory ALK-rearranged NSCLC, 61% of patients had CNS metastases at study entry [3, 4]. In patients with metastatic HER2-positive breast cancer, or metastatic triple-negative breast cancer, up to half will eventually present with brain metastases [5–8].

The incidence of leptomeningeal disease (LMD) in patients with solid tumors is less well characterized; however, it is estimated that 4–15% of cancer patients will develop LMD, most commonly from breast cancer, lung cancer, and melanoma [9].

32.3 Inclusion and Exclusion of Patients with CNS Metastases in Clinical Trials

Patients with active brain metastases are frequently excluded from clinical trials. Many contemporary trials persist even in excluding patients with treated, stable brain metastases from participation. Notably, exclusion of patients with brain metastases from trials may mean that half to two-thirds of intended use disease populations are not included in either early- or late-stage clinical trials, leading to many outstanding questions regarding safety and efficacy even after phase 3 trials have been completed and reported.

For example, McCoach and colleagues performed a search of clinicaltrials.gov for interventional drug trials enrolling adult patients with advanced NSCLC as of September 2014. Of 413 open trials, 14% strictly excluded patients with any history of CNS metastases, and only 26% of trials allowed patients with untreated brain metastases [10]. Costa and colleagues performed a similar analysis of published phase 1 and 2 clinical trials for patients with metastatic breast cancer [11]. Among over 1400 clinical trials published until June 2016 and indexed in PubMed, only 39 (2.6%) of trials specifically required CNS disease for entry (i.e., were designed specifically to evaluate the CNS efficacy of a therapeutic regimen), of which only 16 (1%) were restricted to breast cancer patients. Nearly one-third of trials excluded patients with any known history of brain metastases. Even among trials restricted to patients with HER2-positive, metastatic breast cancer, a population in which it has been known for over a decade that brain metastases are especially frequent, 48.5% of trials excluded patients with any history of CNS metastases. Finally, an internal analysis of Investigational New Drug (IND) submissions to the United States Food and Drug Administration (FDA) found that as recently as 2015, among 250 new IND submissions, less than half allowed patients with stable, treated brain metastases to enroll, and very few included patients with active brain metastases (Jin et al., manuscript submitted).

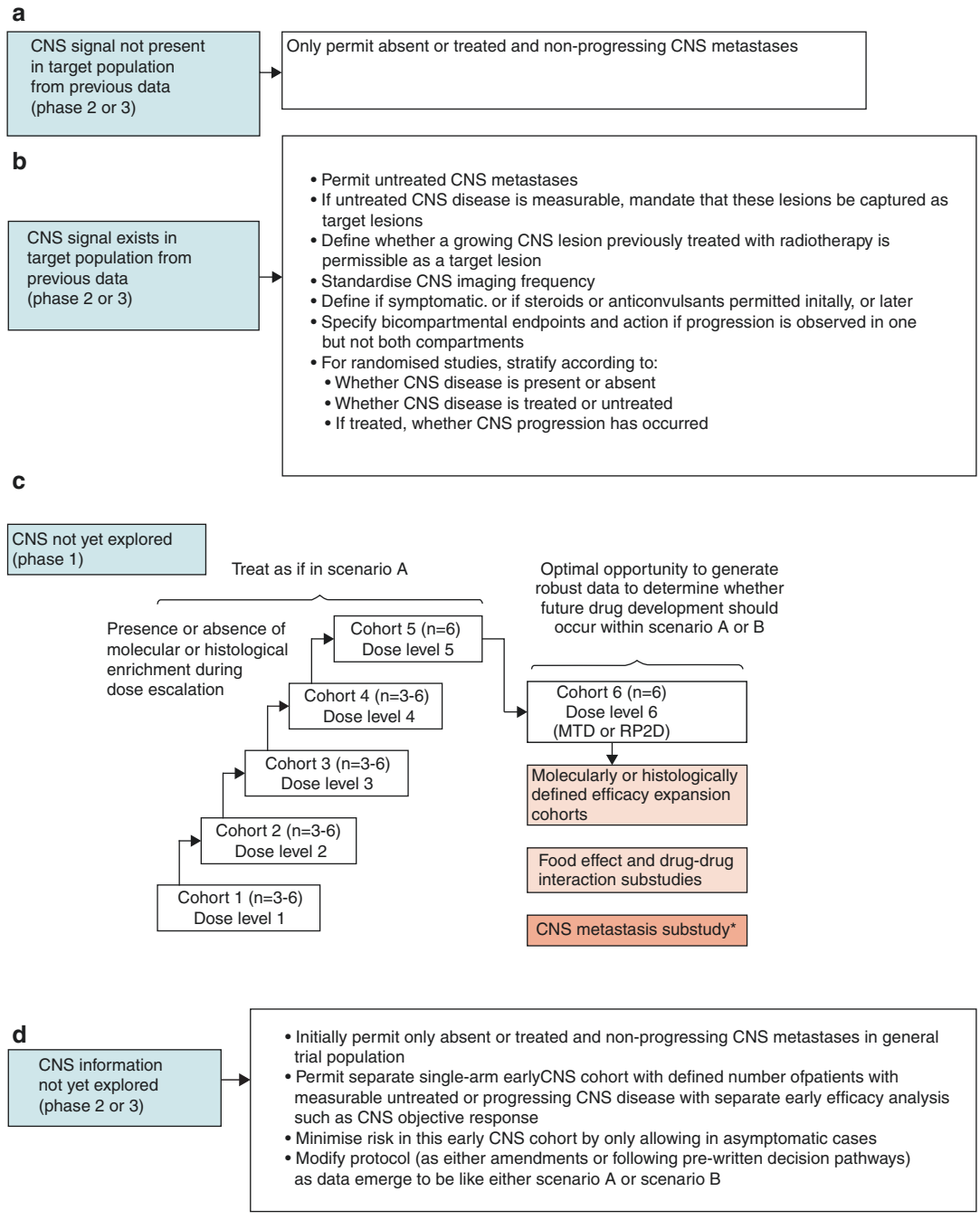
In response to concerns that overly restrictive trial eligibility criteria may be causing harm and impeding progress, the American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (FOCR) convened investigators, industry representatives, patient advocates, and members of the US FDA in a collaborative effort to modernize eligibility criteria for the twenty-first century [12–14]. Key recommendations of the ASCO-FOCR Brain Metastasis Working Group are shown in Table 32.1 [15]. While trial investigators have often focused on perceived risks of patients with brain metastases in clinical trials (e.g., due to concerns about life expectancy, differential toxicities, lower efficacy, or challenges in response assessment), in fact, there have been several notable successes, including the demonstration of clinically meaningful CNS efficacy with ALK inhibitors in lung cancer, BRAF inhibitors in melanoma, and immune checkpoint inhibitors in both lung cancer and melanoma [16–19]. In HER2-positive breast cancer, a variety of HER2 inhibitors appear to hold promise in the treatment of CNS metastases [20–23].

The ASCO-FOCR working group recommendations align well with recommendations from the Response Assessment in Neuro-Oncology (RANO) brain metastases working group [24]. The RANO guidelines provide one potential framework for more active inclusion of patients with brain metastases in clinical trials (Fig. 32.1).

Table 32.1 Key recommendations of the ASCO-FOCR Brain Metastasis Working Group regarding inclusion of patients with brain metastases in clinical trials [15]

Type of patient	Recommendation	Suggested inclusion criteria template
Treated/stable brain metastases	Should be routinely included in prospective clinical trials of all phases and only excluded if there is a compelling rationale for exclusion. If there are specific safety concerns, tailoring eligibility criteria to the concern is preferable to general exclusion of all patients with brain metastases.	Patients with treated brain metastases are eligible if there is no evidence of progression for at least 4 weeks[a] after CNS-directed treatment, as ascertained by clinical examination and brain imaging (MRI or CT) during the screening period.
New, active, or progressive brain metastases	Should be included early in clinical development when there is a strong scientific rationale for likelihood of benefit, based on molecular pathways, histology, and/or preclinical data. For drugs/modalities with less robust preclinical data, inclusion should still be considered, especially if brain metastases are common in the intended use population. The inclusion of a CNS-specific cohort can provide valuable dosing and preliminary efficacy data to either support or refute inclusion in later-phase trials. For later-phase trials, ideally, data from earlier-phase trials, in concert with the strength of the scientific rationale and preclinical data, can inform decisions on inclusion. When such data are not available, several potential trial designs could allow patients with active brain metastases to enroll, either as a parallel cohort or as a defined subset within the larger clinical trial.	Tailor to specific situation (see recommendation)
Leptomeningeal disease	Recommend inclusion of an LMD cohort in early-phase trials when CNS activity is anticipated. When possible, inclusion of an LMD cohort in later-phase trials may be useful to provide access to investigational agents and to generate additional safety and efficacy data. If patients with LMD are to be excluded, justification should be provided, and use of the wording in the next column recommended, to avoid unnecessary exclusion of patients with imaging-only equivocal findings.	If LMD is to be excluded, the following language is recommended: LMD is a clinical diagnosis, defined as positive CSF cytology and/or unequivocal radiologic or clinical evidence of leptomeningeal involvement. Patients with leptomeningeal symptoms in the setting of leptomeningeal enhancement would be considered to have LMD even in the absence of positive CSF cytology, unless a parenchymal lesion can adequately explain the neurologic deficit. In contrast, asymptomatic or minimally symptomatic patients with mild or nonspecific leptomeningeal enhancement would not be considered to have LMD. In such patients, CSF sampling is not required to formally exclude LMD but can be performed at the investigator's discretion on the basis of level of clinical suspicion.

[a]Both ASCO-FOCR [15] and RANO [27] guidelines note that shorter than a 4-week interval could be considered on a case-by-case basis. For example, RANO guidelines suggest shorter intervals may be appropriate in first-line trials or trials in highly aggressive extra-CNS disease



Abbreviations: MTD, maximum tolerated dose; RP2D, recommended phase 2 dose. *Only consider if evidence of a high systemic response exists in the target (molecularly or histologically defined) population—eg, if ≥ 40% of patients achieve a high systemic response—and the same population is at substantial risk of CNS disease.

Fig. 32.1 Trial designs to address brain metastases. Recommended trial designs for patients with CNS metastases for drugs considered very unlikely to have CNS antitumor activity or efficacy, applicable mostly to phase 2 or phase 3 trials (**a**); considered very likely to have CNS antitumor activity or efficacy, applicable mostly to phase 2 or phase 3 trials (**b**); with minimal baseline information on CNS antitumor activity or efficacy during the initial first-in-human cancer trial (**c**); or with minimal baseline information on CNS antitumor activity or efficacy, applicable mostly to phase 2 or phase 3 trials (**d**). Reproduced from Camidge et al., Lancet Oncol 2018 [24]

32.4 Outcome Measure: Criteria for Response

Historically, there has not been a single accepted standard definition for tumor response or progression in clinical trials of patients with solid tumor brain metastases [25]. The Macdonald criteria were originally developed primarily to assess high-grade gliomas and thus focus only on the CNS compartment [26]. In contrast, the Response Evaluation Criteria in Solid Tumors (RECIST) criteria were developed primarily to evaluate extracranial metastases; patients with either primary brain tumors or brain metastases from solid tumors were not well represented in the development of RECIST [1].

To address the gap in trial methodology, investigators have frequently adapted existing response criteria or even developed entirely new criteria, when designing clinical trials [25]. The criteria have varied according to imaging requirements (e.g., CT versus MRI), minimum size of a target lesion (ranging from unspecified to 1 cm), maximum number of target lesions (ranging from 2 to undefined), type of measurement (longest diameter, bidimensional, or volumetric), degree of shrinkage or growth to qualify as a partial response (PR) or progressive disease (PD), the need for confirmatory scans (required versus not), corticosteroid use (included versus not), neurological symptoms (included versus not), and status of extracranial disease (included versus not, summation of intracranial and extracranial target lesions versus CNS and extracranial compartments assessed separately). Clearly, the dramatic variation between trials affects the ability to place trial results into their proper context.

In response to this heterogeneity, the RANO group convened an international, multidisciplinary group of investigators to propose consensus criteria which could serve as a useful starting point in an effort to optimize response and progression criteria for the evaluation of treatments in patients with brain metastases from solid tumors. Criteria were reviewed with industry and government partners for feedback prior to publication. The first proposed version of the RANO-BM (brain metastases) criteria was reported in 2015 [27]. Key elements of the RANO-BM criteria are shown in Table 32.2. Gadolinium-enhanced MRI is strongly encouraged as the standard imaging technique, due to its demonstrated higher sensitivity for detection of CNS lesions [28, 29]. Measurable disease is defined as a contrast-enhancing lesion that can be accurately measured in at least one dimension, with a minimum size

Table 32.2 Response assessment in neuro-oncology brain metastases (RANO-BM) criteria

	Complete response	Partial response	Stable disease	Progressive disease
Target lesions	None	≥30% decrease in sum longest distance relative to baseline	<30% decrease relative to baseline but <20% increase in sum longest distance relative to nadir	≥20% increase in sum longest distance relative to nadir[b]
Nontarget lesions	None	Stable or improved	Stable or improved	Unequivocal progressive disease[b]
New lesion(s)[c]	None	None	None	Present[b]
Corticosteroids	None	Stable or decreased	Stable or decreased	Not applicable[a]
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse[b]
Requirement for response	All	All	All	Any[a]

[a]Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration

[b]Progression occurs when this criterion is met

[c]A new lesion is one that is not present on prior scans and is visible in minimum two projections. If a new lesion is equivocal, for example, because of its small size, continued therapy can be considered, and follow-up assessment will clarify if the new lesion is new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan showing the new lesion. For immunotherapy-based approaches, new lesions alone do not define progression

of 10 mm. While lower minimums were debated (e.g., a 5 mm cutoff), the consensus was that to maintain reproducibility and interpretation of small changes in measurements, a 10 mm cutoff is favored, particularly when objective response is chosen as the primary endpoint. Trials with primary endpoints other than objective response (e.g., progression-free survival, overall survival, neurocognitive function, etc.) do not necessarily need to require measurable CNS disease for study entry, thus allowing patients with smaller lesions to enroll. Guidance is provided in the publication for investigators who choose to lower the minimum size limit of measurable disease to 5 mm, including mandated use of MRI imaging with slice thickness of 1.5 mm or less, without skips. Given the lack of data comparing response evaluation on 2 versus 5 target lesions, the group elected to allow up to 5 CNS target lesions to be designated at baseline. Lesions not previously treated with stereotactic radiosurgery or surgical resection are preferred as target lesions; however, previously treated lesions could be considered if there is clear progression since the time of local treatment.

Similar to RECIST 1.1, RANO-BM proposes a ≥30% decrease in the sum of longest dimensions of target lesions (in the case of RANO-BM, considering only the CNS target lesions), whereas an increase of ≥20% in the sum of longest dimensions of target lesions relative to the nadir is deemed radiographic progression. In contrast to RECIST 1.1, RANO-BM explicitly takes into account corticosteroid use and clinical status in the assessment of response (Table 32.2). At the time of the original publication, the definition of clinical deterioration was left to the discretion of the treating physician, but it was recommended that patients with a substantial decrease in performance status (Karnofsky Performance Status—decrease from 90–100 to ≤70, or decrease from 80 to ≤60, or decrease from any baseline to ≤50, for at least 7 days, unless attributable to comorbid events, treatment-related toxicity, or changes in corticosteroid use) be considered as having a clinical deterioration event. Moving forward, investigators could also elect to utilize the Neurologic Assessment in Neuro-Oncology (NANO) scale (discussed below) to assess changes in clinical status [30].

The RANO investigators fully acknowledge that the RANO-BM criteria have not yet been validated relative to the relationship between response and long-term outcomes such as overall survival, nor has the performance of RANO-BM been formally compared to preexisting criteria such as RECIST 1.1. To this end, a collaborative effort between the RANO and RECIST working groups has been initiated and is working toward compiling a large, central database including deidentified clinical data, outcomes data, and imaging files, with the ultimate goal of refining response criteria in the future.

32.5 Outcome Measure: Progression-Free Survival (PFS)

Progression-free survival (PFS) is a common endpoint in oncology clinical trials. Inclusion of patients with brain metastases in clinical trials has implications on how PFS might be defined, particularly if patients with active/progressive brain metastases are entered. In addition, the treatment modality (e.g., localized treatment such as stereotactic radiosurgery) may influence which sites of progression are most relevant to evaluate treatment efficacy.

Notably, the current RECIST 1.1 criteria take a summation approach, such that a maximum of two lesions per organ and a maximum of five lesions overall are to be selected as target lesions [1]. All target lesions are summed, and if the sum of the longest dimension of target lesions is 20% or greater than the nadir, disease progression on the basis of radiologic progression of target lesions is declared. Patients may also progress on the basis of unequivocal progression of nontarget lesions or new lesion(s).

If, as frequently occurs in clinical practice, a patient experiences a “mixed response” with

Table 32.3 Bi-compartmental progression-free survival (PFS) per RANO-BM

CNS (RANO-BM)	Non-CNS (RECIST 1.1)	Bi-compartmental PFS	Note
Complete response, partial response, or stable disease	Progressive disease	Log as a PFS event	Log as non-CNS progressive disease
Progressive disease	Complete response, partial response, or stable disease	Log as a PFS event	Log as CNS progressive disease
Progressive disease	Progressive disease	Log as a PFS event	Log as both CNS and non-CNS progressive disease

stable/responsive disease in target liver metastases, but clear progression of one or more target brain metastases, the patient might still be considered to have stable disease by RECIST 1.1, if the increase in the linear dimension of the brain metastases is not sufficient to drive an overall 20% increase in the sum of all target lesions. This is despite the fact that from a clinical standpoint, the patient would likely be recommended some form of treatment, whether local or systemic, to manage his or her CNS progression.

In trials of local therapies such as surgery or stereotactic radiosurgery, endpoints such as disease status at the treated site (often deemed "local control" or "local recurrence-free survival) and disease status in non-treated intracranial sites (often deemed "distant brain control" or "distant brain progression-free survival") are frequently reported. These endpoints do not include any assessment of extracranial disease status, given that local modalities are not typically expected to affect extracranial disease control.

One potential approach to harmonize endpoint definitions across local therapy and systemic therapy trials, and to take into account the reality of how brain metastases are managed in clinical practice, is to assess the CNS compartment independently from the extracranial compartment—a so-called bi-compartmental model. Using this approach, CNS metastases are assessed separately from extracranial metastases. In reporting bi-compartmental PFS, a progression event in either the CNS (as assessed using RANO-BM criteria) or extracranial compartment (as assessed using RECIST 1.1) counts toward an overall progression event (Table 32.3) [27]. The RANO group also proposed a set of PFS endpoints that could take into account only CNS progression, non-CNS (extracranial) progression, and progression at locally treated sites (Table 32.4). The hope is that providing investigators a range of PFS endpoints that could be selected to be most appropriate to the patient population and modality under study, while standardizing the definitions of each endpoint, could provide a balance between flexibility and harmonization.

Table 32.4 Sites of inclusion for assessment of progression-free survival per RANO-BM

Endpoint	Sites included
Bi-compartmental progression-free survival	CNS lesions and non-CNS lesions
CNS progression-free survival	CNS lesions only
Non-CNS progression-free survival	Non-CNS lesions only
CNS_{local} progression-free survival	Local CNS lesions only[a]

[a]Local CNS lesion refers to a CNS lesion treated with a local therapy (e.g., surgery, stereotactic radiosurgery). In general, the endpoint of CNS_{local} progression-free survival will be most relevant to trials evaluating local approaches to the treatment of CNS disease

32.6 Outcome Measure: Overall Survival (OS)

Overall survival measures the interval from a predefined time point (within the context of a prospective study, typically study entry) and death due to any cause. Patients lost to follow-up are censored at the date last known alive. While overall survival is frequently considered a gold stan-

dard on oncology clinical trials, several issues when considering patients with brain metastases merit specific discussion.

First, multiple randomized trials comparing local therapy approaches have demonstrated better CNS control with more extensive CNS-directed therapy (e.g., whole brain radiotherapy [WBRT] versus stereotactic radiosurgery [SRS], or WBRT versus cavity-RT) [31–34]. However, in these trials, improved CNS control did not translate to any statistically significant differences in overall survival. Furthermore, despite improved CNS control with WBRT, and no differences in survival, the trials have been largely interpreted to favor more targeted approaches, due to their lesser impact on neurocognitive decline and quality of life. Second, patients with brain metastases frequently also have coexisting extracranial metastases which represent a competing cause of mortality. Interventions that do not impact extracranial disease control are less likely to impact overall survival.

Even with these caveats, overall survival may still be an appropriate primary or key secondary endpoint. In trials testing "de-escalation" of therapy (e.g., SRS versus WBRT), demonstrating similarity of OS with improved functional outcomes has already been practice-changing. In trials of systemic therapies expected to control both CNS and extracranial disease, clinically meaningful improvements in OS would likely be practice-changing.

32.7 Neurological Outcomes Assessment

CNS metastases (as well as their treatments) can lead to profound alterations in neurological function, cognition, and quality of life. More than for virtually any other involved organ site, an assessment of the impact of CNS metastases can help to define the clinical value of a new intervention. As shown in Table 32.5, a wide variety of domains and assessment tools have been incorporated into clinical trials. The following sections provide further details on selected scales for each domain.

Investigators planning to incorporate neurological outcomes in a clinical trial should plan in advance how they will minimize differential dropout from assessments [35]. For example, patients with clinical deterioration may be less likely to adhere to a demanding neurocognitive testing schedule. Dropout from study assessments can dilute any positive effects of an intervention and can drastically reduce the power of the study to compare groups. For example, in the EORTC 22993–08993 study of prophylactic cranial irradiation for patients with extensive-stage small-cell lung cancer, of 286 patients initially included,

Table 32.5 Selected neurologic outcome assessment tools

Endpoint	Tools
Performance status	• Karnofsky Performance Status (KPS) • Eastern Cooperative Oncology Group (ECOG) performance status
Symptom assessment	• M.D. Anderson Symptom Inventory Brain Tumor Module (MDASI-BT) • Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE)
Neurological exam assessment	• Neurologic Assessment in Neuro-Oncology (NANO) scale • Medical Research Council (MRC) Scale for muscle power[a]
Quality of life	• European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) • EORTC QLQ-BN20 (specifically for brain tumor patients) • EORTC EuroQOL (EQ)-5D • Functional Assessment of Cancer Therapy-Brain (FACT-Br)
Neurocognitive assessment	• Mini-Mental State Examination (MMSE) • Montreal Cognitive Assessment (MOCA) • Wechsler Adult Intelligence Scale-Revised (WAIS-R) • Hopkins Verbal Learning Test-Revised (HVLT-R) • Trail-Making Tests (TMT) • Controlled Oral Word Association (COWA)

[a]Covers muscle strength only

only 54.5% completed QOL surveys at 3 months; at 12 months, only 45 patients (16% of the initial study population) were still alive, of which less than half completed the QOL survey [36]. In the randomized trial evaluating the effects of memantine on neurocognitive outcomes associated with WBRT, only 149 of 554 accrued patients (29% of the study population) had analyzable data for the primary endpoint at 24 weeks, due to poorer-than-expected survival in both arms [37]. A number of studies have implemented centralized call centers to assist in tracking of expected time points and to provide reminder calls and other interventions to reduce missing data [38].

Careful attention to the life expectancy of the patient population, timing of assessments, reminders of upcoming assessments, tracking of missed assessments, respondent burden, education of investigators and study personnel, and monitoring of compliance can all be considered in an effort to optimize adherence rates and optimize interpretability of data results.

32.8 Outcome Measure: Neurological Function

CNS metastases can be associated with abnormalities on neurological examination, including strength, sensation, gait, cranial nerve function, and other domains. Both the Macdonald and RANO criteria incorporate clinical status within the definitions of response and progression; however, they do not provide specific guidance on how to do so in an objective and reproducible manner. Historically, few trials have prospectively specified the minimum components of a neurological examination that should be performed and recorded at each assessment time point. Transfer of routine neurological examination findings from a typical clinic note into the codified format required in case report forms can be challenging. These factors result in data that is frequently either not captured or uninterpretable due to issues with data quality or missing data.

Other neurological subspecialties have previously developed standard scales to assess neurological function in patients with stroke, multiple sclerosis, Parkinson's disease, and other diverse neurological disorders. To fill a gap in the availability of a disease-specific, clinician-reported assessment tool for patients with brain tumors, the Neuro-Oncology Assessment in Neuro-Oncology (NANO) working group was convened [30]. The purpose of the scale is to provide an objective, reproducible measurement of neurological function relative to underlying tumor activity.

The NANO scale covers gait, strength, upper extremity ataxia, sensation, visual fields, facial strength, language, level of consciousness, and behavior. Each domain is subdivided into 3 or 4 levels of function. Neurological response is defined as a ≥2-level improvement in at least one domain without worsening in other domains from baseline or best level of function not attributable to change in concurrent medications or recovery from a comorbid event. Neurological progression is defined as a ≥2-level worsening from baseline or best level of function with at least one domain or worsening to the highest (worst) score within at least one domain that is felt to be related to underlying tumor progression and not attributable to a comorbid event or change in concurrent medication. In a multicenter study including 220 patients across North America and Europe, each assessed independently by two clinicians, the percent agreement between observers was >90% for all domains, with kappa statistics ranging from 0.35 (fair agreement) for behavior to 0.83 (near perfect agreement) for language. The median time for completion of the instrument was 4 min. Thus, data from this initial study supports consideration of inclusion of the NANO scale in prospective studies in which neurological function is selected as an endpoint.

32.9 Outcome Measure: Neurocognitive Function

Neurocognitive function is a critical contributor to quality of life. Deficits in neurocognitive function can often precede changes in overall health-related quality of life and functional independence [39]. In clinical trials including patients

with brain metastases, inclusion of tools to assess neurocognitive function may serve to provide additional data on the potential risk-benefit ratio of an intervention, either as a primary or secondary endpoint. Table 32.5 provides a listing of several of the most frequently selected tools for assessment of neurocognitive function in prospective studies.

The Mini-Mental State Examination (MMSE) is a 30-item measure used widely in oncologic and non-oncologic conditions [40]. Strengths of the MMSE include low respondent burden and short test time, as well as limited training required to administer the instrument. Limitations of the MMSE include relatively poor sensitivity to change in brain tumor patients, particularly when compared to tests such as the Hopkins verbal learning test [39, 41]. Similarly, the Montreal cognitive assessment is simple and brief to administer but is not as sensitive as formal neuropsychological assessments in detecting neurocognitive deficits and change over time [42].

To better assess neurocognitive outcomes in clinical trials, the International Cognition and Cancer Task Force, RANO, the Radiation Therapy Oncology Group (RTOG), and many industry sponsors have converged on a uniform core battery of cognitive tests. As summarized in Table 32.6, these include the Hopkins verbal learning test-revised (HVLT-R); trail-making tests (TMT), parts A and B; and controlled word association test (COWA) [35, 43–47]. The instruments cover the domains of memory, executive function, and processing speed. The assessment can be administered by trained research personnel and takes approximately 25–30 min to complete. Each of the instruments displays high test-retest reliability, validity, and sensitivity to change, and multiple language versions are available. The feasibility of including this battery in multicenter, prospective trials has been demonstrated [34, 37].

Table 32.6 Neurocognitive battery incorporated in many prospective clinical trials

Instrument	Domains tested
Hopkins verbal learning test-revised (HVLT-R)	Learning and memory
Trail-making test, parts A and B	Processing speed and executive function
Multilingual aphasia examination and controlled word association test (COWA)	Verbal fluency and executive function

32.10 Outcome Measure: Patient-Reported Symptom Burden

Patient-reported outcomes (PROs) are being increasingly incorporated into the design of prospective studies in oncology. PROs may be used to measure tumor-related symptoms, treatment-related toxicity, functional independence, and quality of life.

The M.D. Anderson Symptom Inventory Brain Tumor Module (MDASI-BT) includes the core MDASI's 13 symptom items and 6 interference items. In addition, it includes 9 additional symptoms specific to patients with brain tumors, including weakness on one side of the body, difficulty understanding, difficulty speaking, seizures, difficulty concentrating, problems with vision, change in appearance, change in bowel pattern, and irritability [48]. Regression analysis conducted as part of the development of the instrument demonstrated that 56% of the variability in symptom severity was explained by the brain module items. Reliability was high (0.91), and scores were sensitive to performance status and tumor recurrence. The MDASI-BT has also been validated in patients with brain metastases [49]. An advantage is the low respondent burden (typical completion time of 5 min) and ability to be adapted for paper-, electronic-, or telephone-based administration.

Historically, symptom and toxicity assessments in clinical trials have been rated by investigators using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE). More recently, a patient-facing version of the CTCAE, termed the PRO-CTCAE, has been developed. The PRO-CTCAE has favorable measurement properties across individuals from diverse educational, ethnic, and geographic backgrounds [50, 51]. A library of over 120 adverse event (AE) items is now

available. Investigators may select items of highest salience to the patient population under study. Paired surveys of patients and clinicians demonstrated relatively good concordance of investigator-reported versus patient-reported symptom severity for items such as vomiting and diarrhea but lower concordance in items such as fatigue or dyspnea, such that PROs do appear to provide valuable and additional information beyond investigator assessments alone [52]. Feasibility within prospective multicenter studies has been demonstrated [38, 53].

32.11 Outcome: Quality of Life

Physical well-being, cognitive function, psychological well-being, social functioning, physical security, and existential well-being all contribute to overall quality of life. Table 32.5 lists some of the more commonly included instruments in clinical trials.

The EORTC QLQ-C30 plus EORTC-BN20 and the FACT-Br have been specifically validated in patients with brain tumors [54–56]. The EORTC QLQ-C30 addresses four major domains: physical functioning, emotional functioning, pain, and fatigue. The EORTC-BN20 includes 20 items that assess future uncertainty, visual disorder, motor dysfunction, and communication deficits [54]. The FACT-Br includes 23 items that ask about general well-being, concentration, memory, seizures, vision, hearing, speech, personality, ability to express thoughts, weakness, coordination, and headaches [56].

Another tool which has been frequently included in oncology clinical trials is the EQ-5D. The EQ-5D covers five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. A visual analogue scale also records the patient's self-rated overall health. The very low respondent burden makes the EQ-5D highly appealing for inclusion in trials of patients with limited life expectancy or functional status. In addition, the EQ-5D can be mapped to obtain health utilities in order to capture the outcome of quality-adjusted survival [57, 58].

32.12 Leptomeningeal Disease (LMD): Special Considerations

A critical review of randomized, controlled trials evaluating treatment of LMD noted substantial variation in the choice of endpoint and definition of response [9]. Response criteria were based on varying combinations of clinical, radiologic, and cytologic data and differed across all studies. Not only are response definitions important in clinical trials, but in the case of LMD, lack of consensus on what findings constitute response also makes routine clinical management challenging.

To address this problem, the RANO group has recently proposed new response criteria for LMD [59]. The criteria take into account practical considerations, including (1) the reality that may neurological deficits due to LMD are fixed and irreversible and anticipate that the best clinical response to treatment may be stabilization of neurological function rather than resolution of neurological signs or symptoms, (2) the nonquantitative nature of CSF cytology assessments, and (3) the varying sensitivity of MRI for detecting LMD and frequent lack of large tumor deposits that would ordinarily constitute "measurable disease" by RECIST 1.1 or other standardized criteria. Key features of the RANO-LMD criteria are shown in Table 32.7**.** Notably, the criteria allow for a distinction between different types of progressive disease, including neurological examination-defined, CSF-defined, radiologic-defined, and symptom-defined progression, which can provide further granularity in evaluating the efficacy on novel therapeutic approaches. The publication also provides a scorecard to aid in the radiographic assessment. The group acknowledges that prospective validation is required to understand both the feasibility and clinical relevance of the proposed criteria; however, prospective trials are beginning to incorporate the criteria into study designs, and these should provide rich data for further iterations to the criteria in the future.

Table 32.7 RANO proposal for response determination for leptomeningeal metastases [59]

Assessment	Response	Progressive or refractory disease				Stable disease
		Neurological examination-defined progression	CSF-defined disease progression	Radiologic-defined disease progression	Symptoms	
Neurological exam	Improved	Worse	Stable	Stable	Stable	Stable
CSF cytology (all cancers)	Negative	Negative	Positive (lack consensus)	Negative	Negative	Negative or positive (solid tumors only)
CSF flow cytometry (hematologic cancers only)	Negative	Negative	Positive (lack consensus)	Negative	Negative	Negative or positive
CNS imaging	Definite improvement	Stable	Stable	Definite worsening	Stable	Stable or equivocally worsening or improved
Steroid dose (in hematologic cancers only)	None or decreased	Stable or increased	Stable or increased	Stable or increased	Stable	Stable or decreased
Symptom assessment	Improved	Worse or stable	Worse or stable	Worse or stable	Worse	Stable

CSF cytology negative, defined as either true negative or atypical cells. CSF cytology positive, defined as true positive or suspicious cells. Stable, defined as stable or indeterminate. Symptoms: Stable, defined as no change (−1 to +1 in symptom inventory); worse, defined as −2 to −3 in symptom inventory; improved, defined as +2 to +3 in symptom inventory

32.13 Putting It All Together: Optimizing Endpoint Selection for Patients with Brain Metastases

In an initial dose-finding study, the primary objective is typically determination of the recommended phase 2 dose (RP2D), and this is the case whether the study actively includes patients with brain metastases or not. While determination of maximum tolerated dose (MTD) remains the most typical method by which the RP2D is selected, increasingly, early-phase studies are incorporating pharmacodynamic and/or biomarker endpoints in order to refine dose selection. For nonrandomized, phase 2 studies in patients with brain metastases in which preliminary assessment of efficacy is a primary objective, CNS objective response (e.g., using RANO-BM) criteria is frequently selected as an endpoint for interventions postulated to have a cytotoxic effect, whereas clinical benefit may be more appropriate for interventions postulated to have a cytostatic effect. PFS, OS, neurocognitive function, or QOL can also be considered as primary endpoints, but in the absence of a comparator arm, heterogeneity in patient selection and lack of clear data in a historical control population can sometimes limit their use in practice. Finally, the primary purpose of phase 3 trials is to demonstrate clinical benefit relative to standard of care. As discussed above, while overall survival is one important endpoint, other endpoints including PFS, neurological function, neurocognitive function, or QOL may also be appropriate, either as primary or secondary endpoints, and contribute to the understanding of whether an intervention delivers clinically meaningful benefits to patients.

32.14 Summary

The ultimate goal of conducting clinical trials in patients with brain metastases is to develop interventions which will meaningfully improve the length and/or quality of patients' lives. For any individual study, the most appropriate primary and secondary endpoints will vary according to the primary purpose of the study, whether it is for initial dose finding, preliminary exploration of efficacy, or a more definitive comparative assessment versus current standard of care. Regardless of the endpoint(s) selected, consistent assessment of endpoints across clinical trials, using validated tools when available (and expert consensus guidelines when validated tools are not available), will improve the interpretability of study results and provide a more robust evidence based upon which to make clinical decisions and decisions regarding further development of novel interventions.

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