Cancer Metastasis – Biology and Treatment 18

Diane Palmieri *Editor*

Central Nervous System Metastasis, the Biological Basis and Clinical Considerations

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List of Abbreviations

ADC	Apparent diffusion coefficient
AED	Antiepileptic drugs
BBB	Blood–brain barrier
BED	Biologically equivalent dose
BLI	Bioluminescence imaging
BM	Brain metastasis/metastases
BRAF	v-RAF murine sarcoma viral oncogene homolog B1
BTB	Blood–tumor barrier
CEA	Carcinoembryonic antigen
CNS	Central nervous system
COX-2	Cyclooxygenase-2
CSF	Cerebrospinal fluid
CT	Computed tomography
CTLA	Cytotoxic T lymphocyte antigen 4
DCE-MRI	Dynamic contrast-enhanced magnetic resonance imaging
Dmax	Maximum dose
DTI	Diffusion tensor imaging
DWI	Diffusion weighted imaging
ECOG	Eastern Cooperative Oncology Group
ECM	Extracellular matrix
EGFR	Epidermal growth factor receptor
EGFRmut	EGFR mutations
FACT	Functional Assessment of Cancer Therapy
FCI	Flow cytometry immunophenotyping
EORTC	European Organization for Research and Treatment of Cancer
FDG	2-[^{18}F]Fluoro-2-deoxy-D-glucose
FDOPA	3,4-Dihydroxyl-6-[^{18}F]-fluoro-L-phenylalanine
FI	Fluorescent imaging
FIM	Functional independence measure
FITC	Fluorescein isothiocyanate
FIS	Functionally independent survival

FLT	3′-deoxy-3′-[18F]-Fluorothymidine
Gd	Gadolinium
Gd-DTPA	Gadolinium-diethylenetriamine penta-acetic acid
GDNF	Glial cell line–derived neurotrophic factor
GFAP	Glial fibrillary acidic protein
GFP	Green fluorescent protein
GPA	Graded Prognostic Assessment
Gy	Gray
HDAC	Histone deacetylases
HER2	Human epidermal growth factor receptor 2
HS	Heparan sulfate
ICP	Intracranial pressure
IL-1β	Interlukin-1β
IL-2	Interleukin-2
IL-6	Interleukin-6
iv	Intravenous
KPS	Karnofsky Performance Score
LEF	Lymphoid enhancer binding factors
L-End	Endoglin long
LMD	Leptomeningeal dissemination
mg	Milligrams
MAPK	Mitogen-activated protein kinase
MDASI	M.D. Anderson Symptom Inventory
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MPLSM	Multiphoton laser scanning microscopy
MV	Megavoltage
NAA	N-acetylasparate
NM	Neoplastic meningitis
NSCLC	Non–small cell lung cancer
PCI	Prophylactic cranial irradiation
PEDF	Pigment epithelium-derived factor
PET	Positron emission tomography
PSA	Prostate specific antigen
QOL	Quality of Life
RF	Radiofrequency
RFP	Red fluorescent protein
RO-VPS	Reservoir –on/off valve ventriculoperitoneal shunt
ROR	Receptor tyrosine kinase-like orphan receptor
RPA	Recursive partitioning analysis
RTOG	Radiation Therapy Oncology Group
SBRT	Stereotactic body radiotherapy
SCLC	Small cell lung cancer
SDF-1α	Stromal cell derived factor 1-α

S-End	Endoglin short
SOCS-1	Suppressor of cytokine signaling
SPECT	Single photon emission computed tomography
SPIO	Superparamagnetic iron oxide
SQLI	Spitzer Quality of Life Index
SRS	Stereotactic radiosurgery
SRT	Stereotactic radiotherapy
SSEP	Somatosensory evoked potentials
STAT3	Signal transducer and activator of transcription 3
SWOG	Southwest Oncology Group
TCF	T-cell factors
TGF-β	Transforming growth factor β
TK-1	Thymidine kinase
TKI	Tyrosine kinase inhibitors
TMZ	Temozolomide
TNF-α	Tumor necrosis factor α
uPA	Urokinase-type plasminogen activator
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptors
WBRT	Whole brain radiation therapy or radiotherapy

Chapter 1
An Introduction to Brain Metastasis

Diane Palmieri

Abstract The incidence of brain metastasis is increasing. In fact, the incidence of brain metastasis outnumbers that of primary brain tumors by a factor of ten and is by far the most common neurologic complication of cancer. The reasons underlying the increasing incidence of brain metastasis are unclear, but may be associated with increased patient survival, improved imaging techniques, and greater awareness of the disease. With the increasing incidence, however, it is apparent that our understanding of the biology and epidemiology of brain metastasis is limited. Although most solid primary tumors can develop metastatic disease in the brain, approximately 80% of all brain metastases arise from adenocarcinomas of lung (50–60%) and breast (15–20%) and from malignant melanoma (5–10%). Brain metastases can develop from renal or colon cancers and other solid tumors but do so less frequently than metastases from the lung or breast. Within the brain, metastatic cancer cells can seed and grow in the brain parenchyma and the leptomeninges. Risk factors associated with the development of brain metastasis may vary according to origin of the primary cancer, which also often dictates the clinical experience and prognosis for a patient with a brain metastasis. Recently, a Graded Prognostic Assessment tool was developed to aid in treatment decisions and brain metastasis specific clinical trial strategies. Historically, patients with brain metastases have been excluded from clinical trials that enrolled metastatic cancer patients. Regardless of the origin of the primary cancer, prognosis is poor for patients who develop brain metastases, with median overall survival ranging from 4.8 to 13.8 months across all primary tumor histologies.

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1 Introduction

Metastasis, the spread of cancer from the site of primary tumor growth to a distant organ or organs, is the major underlying cause of morbidity and mortality for cancer patients. Brain or central nervous system (CNS) metastases, the most common neurologic complication of cancer, are devastating because of their impact on quality of life and are associated with a dismal prognosis. Several factors combine to make the CNS a unique metastatic site. These include the microenvironment in which the metastases occur, the presence of the blood–brain barrier or the remaining functions of the blood-tumor barrier, and the neuro-cognitive consequences of metastases in the brain and their treatments.

The metastatic process is complex and inefficient. For cancer cells to metastasize, they must first invade the local tissue environment and break through any existing tissue basement membrane. Next, they must intravasate into blood or lymphatic vessels and survive in circulation until they can adhere to a vessel wall at a distant site and exit the circulation. Upon extravasation, the cancer cells must establish residence in the foreign environment and eventually begin to proliferate to colonize the new organ. Metastatic colonization is the final, critical step in the process to establish active metastatic disease. In addition to these general requirements, cancer cells may acquire the ability to preferentially colonize certain organs such as the brain (see Chap. 2). Although each organ provides a unique microenvironment, the brain is distinct from any other site in the body (see Chap. 3) because it is immunologically privileged and protected by the blood–brain barrier. For cancer cells to colonize this unique microenvironment, they must break through the blood–brain barrier (see Chap. 4).

The normal mammalian brain consists of a dense matrix of neurons and glial cells—a broad term that includes microglia, astrocytes, oligodendrocytes, and ependymal cells. Together these cellular components form discrete regions within the brain that are associated with specific neurological and cognitive functions. The adult mammalian brain consists of two major regions: the parenchyma and the leptomeninges. The parenchyma consists of five regions—the telencephalon or cerebral cortex, responsible for spatial memory; the diencephalon, which consists of the thalamus and hypothalamus and is responsible for regulating the neuro-endocrine system; the mesencephalon or midbrain, responsible for transmitting sensory information to the cerebral cortex and motor commands to the reflex center; the cerebellum, responsible for the precision in actions; the pons, responsible for relaying information between areas of the brain; and the medulla oblongata, which is located in the lower region of the brain stem and is responsible for involuntary body functions including blood pressure and respiration. The leptomeninges are a system of three connective tissue membranes (dura, arachnoid, and pia, from outside to inside) that surround and protect the entire brain.

The brain is the most highly vascularized organ in the body. The dense capillary network of the brain ensures that almost every neuron is perfused by it's own blood vessel. However, these capillaries are unlike capillaries that exist in the rest of the body.

The blood–brain barrier begins with the endothelial cells that form the capillaries connected to one another by tight junctions that limit passive diffusion into the brain. The endothelial cells express numerous transporter proteins that act to shuttle compounds into the brain by facilitated diffusion and also function as active efflux pumps to send compounds away from the brain and back into the circulation. The vasculature is then surrounded by a basement membrane and covered by pericytes and the feet of astrocytes. All of these components combine to form the blood–brain barrier.

The brain microenvironment, the protective leptomeninges, and the blood–brain barrier, all contribute to making the brain a sanctuary site that is immunologically privileged and pharmacologically protected from toxic substances, including conventional chemotherapies and some newer molecularly targeted therapies. Once a cancer cell has penetrated into the brain, metastases can develop in both the brain parenchyma and the leptomeninges. The majority of parenchymal metastases are thought to originate from solid tumors that spread via the blood. Brain metastases occur more frequently in the cerebral cortex (80%) than in the cerebellum (15%) or brainstem (5%), which is in accordance with blood flow and tissue volume for each region [1]. Some cancers are associated with multiple brain metastases (i.e., lung cancer, melanoma), whereas other cancers are typically associated with a single brain metastasis (i.e., breast or GI cancer) [1, 2]. At least three supportive microenvironments have been described for experimental parenchymal metastases: the perivascular niche, the neuro-inflammatory parenchyma and the cerebrospinal fluid or leptomeningeal niche [3]. Leptomeningeal metastases (also known as neoplastic meningitis, see Chap. 10) can develop on the pia or the arachnoid membranes, but can also develop in the subarachnoid space (the cerebrospinal fluid filled space between the arachnoid and pia membranes) [4]. Leptomeningeal metastases may also occur via direct extension from the parenchyma, from the venous plexus, and by extension along nerves or perineural lymphatics [5]. Leptomeningeal metastases often occur simultaneously with parenchymal brain metastases in more than 50% of patients with melanoma or lung cancer, and are the most common form of brain metastases to develop from hematologic cancers [5, 6–7].

2 Incidence

Although the exact incidence and prevalence of brain metastasis is not known, it is estimated that between 170,000–200,000 new cases of brain metastases are diagnosed annually in the United States. Most data available on the epidemiology of brain metastasis are derived from population and autopsy studies; no current data from national registries, such as the Surveillance Epidemiology and End Results (SEER) registry, are available. Although likely to significantly underestimate the true incidence, data derived from several population-based studies conducted between 1935 and 2001 reported that the incidence rates of brain metastasis range from 8.3 to 14.3 per 100,000 population, and from 8.5 to 9.6% among cancer

patients [8]. Autopsy studies typically reported higher rates of brain metastases than population-based studies. The difference in reported rates between population-based and autopsy-based studies may reflect a difference between symptomatic and asymptomatic disease. Moreover, historically, patients particularly with lung cancer were not screened for and imaging methodology was not effective at detecting brain metastases.

Whereas some of the most commonly detected cancers such as those from the lung, breast and skin (melanoma) readily metastasize to the brain and account for 67–80% of all brain metastases, other cancers such as those from the kidney and colon can metastasize to the brain but do so with low frequency. Although the actual percentages may differ among studies, the range or trend of brain metastases from different primary cancers are often consistent across studies that look at multiple cancers, with brain metastases always detected among more lung cancer patients than among breast cancer and melanoma patients; brain metastases from renal (range 2–6%) or gastrointestinal cancers (range 6–9%) occur in less than 9% of patients [8]. Hematologic malignancies can metastasize to the CNS, most commonly to the leptomeninges [7]. Pediatric primary tumors rarely metastasize to the brain. The biological and epidemiological reasons underlying why some cancers but not others metastasize to the brain are unclear.

2.1 Lung Cancer

Lung cancer is the most deadly form of cancer, accounting for more deaths per year than those from breast, colon, and prostate cancer combined. The incidence of brain metastasis is highest in patients diagnosed with primary lung cancers. At the time of their primary lung cancer diagnosis, approximately 10–25% of patients have brain metastasis [9]. An additional 40–50% of patients with lung cancer will develop brain metastases during the course of their disease [9].

Small cell (SCLC) and non-small cell (NSCLC) are the major histologic types of carcinoma of the lung. SCLC accounts for approximately 15–20% of all lung cancers and is classified as either oat cell carcinoma or combined small cell carcinoma. SCLC is typically far more aggressive than NSCLC, originating in the bronchi and rapidly metastasizing to the brain, liver, and bone. The brain is the most common site of metastasis for patients with SCLC, and this likely contributes to the dismal 5-year survival rate of approximately 6% [9]. Unlike NSCLC, SCLC seldom occurs in never smokers, and is the predominant form of lung cancer associated with cigarette smoking. Eighteen to twenty-five percent of SCLC patients already have CNS involvement at the time of primary diagnosis [10], and many of these patients also present with metastases at other extracranial sites [9]. SCLC patients who relapse after an initial treatment response in the lung have a 50–67% risk of developing brain metastases [11].

The majority of lung cancers are NSCLC, which present as adeno-, squamous cell, or large cell carcinomas. The 5-year survival rate for patients diagnosed with NSCLC is less than 15% [12], reflecting that many patients have advanced or locally advanced disease at the time of diagnosis. Adenocarcinomas often occur in the outer or peripheral areas of the lung, whereas squamous cell carcinomas often occur in the more central areas of the lung next to the bronchi. Large cell carcinomas can occur anywhere in the lung and typically grow faster than other forms of NSCLC. In NSCLC, 40% of patients develop brain metastases [13]. Brain metastatic disease is more common in patients with adenocarcinomas and large cell carcinomas than in patients with squamous cell carcinoma [14–16]. Newer molecular therapeutics taking advantage of epidermal growth factor receptor overexpression and mutation have been used in NSCLC with low but significant response rates. In these treated patients, a high incidence of brain parenchyma and leptomeningeal metastases were observed [17]. This increase in brain metastases suggests that the brain is a sanctuary site, colonized to evade systemic therapy. The increased incidence of brain metastases may then be associated with increased survival subsequent to use with newer molecular therapeutics. From data derived from prophylactic imaging scans, non-symptomatic brain metastases are being detected in NSCLC patients, and are hypothesized to be an important facet of overall survival [18].

Most lung cancer patients develop parenchymal brain metastases early in their disease and develop multiple metastatic lesions, many of which are often associated with edema. The presence of brain metastases is associated with decreased survival [19]. Indeed, overall patient survival ranges from 4 to 8 months after diagnosis of a brain metastasis. Favorable prognostic factors that affect survival include Karnofsky performance status, patient age (>65), control of primary tumor, and absence of extracranial metastatic disease [20]. The Graded Prognostic Assessment (GPA) metric demonstrates that few lung cancer patients survive more than 3 years post-diagnosis of a brain metastasis (Table 1.1).

Few studies have addressed the issue of risk factors for the development of brain metastases in lung cancer patients. In a retrospective study of 264 patients with NSCLC, a positive correlation was found between size of the primary tumor, the cell type (adenocarcinoma and undifferentiated vs. squamous), intrathoracic lymph node status, and the development of brain metastases [16]. Grinberg-Rashi et al. reported that the overexpression of twelve candidate genes was associated with brain or general metastasis in 142 NSCLC patients and could be used to identify a predictive pattern for those at high risk of developing brain metastases [21]. Multivariate Cox regression analysis showed the expression values of three genes (CDH2, KIFC1 and FALZ) in primary tumors had prognostic value, and the authors suggested that a gene expression signature predictive of brain metastasis may identify patients at high risk who may benefit from prophylactic therapy [21]. Prophylactic therapies directed to the CNS have been used in the treatment of childhood leukemias for many years to prevent brain metastases [22].

Table 1.1 Survival times post brain metastasis diagnosis by graded prognostic assessment (GPA) score[a]

		Percentage of patients who reach median survival (months) in each GPA category:			
Primary tumor diagnosis	Overall median survival (months)	0–1.0	1.5–2.0	2.5–3.0	3.5–4.0
NSCLC[b]	7.0	14 (3.0)	38 (5.5)	40 (9.4)	9 (4.8)
SCLC	4.9	23 (2.8)	42 (4.9)	30 (7.7)	5 (7.0)
Breast	13.8	6 (3.4)	26 (7.7)	35 (15.0)	33 (25.3)
Melanoma	6.4	17 (3.4)	31 (4.7)	28 (8.8)	23 (3.2)
Renal	9.6	15 (3.3)	27 (7.3)	36 (11.3)	22 (4.8)
GI cancer	5.4	36 (3.1)	31 (4.4)	24 (6.9)	9 (13.5)

[a]Adapted from Sperduto, P. et al., Journal of Clinical Oncology [40]
[b]*NSCLC* Non-small cell lung cancer, *SCLC* small cell lung cancer, *GI* gastrointestinal

2.2 Breast Cancer

Patients with breast cancer tend to have recurrent disease to the CNS after the development of systemic metastatic disease and multiple rounds of chemotherapy. Breast cancer brain metastasis can develop in the brain parenchyma and the leptomeninges, often as solitary lesions (but rarely associated with edema), which distinguishes them from those that develop in patients with lung cancer. Breast cancer is the most common solid tumor to metastasize to the leptomeninges [5].

The incidence of brain metastasis among women with breast cancer is historically reported as 15–20% [23]. However, this rate may underreport the percentage of women with breast cancer brain metastasis as an autopsy study of 1,044 patients who died of breast cancer found histologic evidence of brain metastasis in 29% of the cases [24]. More recent reports have estimated the incidence as high as 30% for advanced breast cancer overall and higher for specific subtypes of breast cancer [25–28].

Breast cancer is a heterogenous disease of subtypes that originates most often from the ductal epithelial cells. Histologically the disease is divided into three main subtypes: estrogen receptor positive (which can be subdivided into Luminal A and Luminal B based on molecular markers), HER2-positive (based on the amplification or overexpression of the HER2 gene), and triple-negative (estrogen receptor negative, progesterone receptor negative and HER2 normal). The latter two subtypes have been reported to have brain metastasis incidence rates that exceed 35% of patients with advanced disease [26–29].

Several risk factors for the development of brain metastases have been reported for breast cancer patients. In a cohort of 9,524 breast cancer patients diagnosed with early stage disease between 1978–1999, the 10-year incidence of brain metastasis was 5.2% and associated with lymph node positivity, estrogen receptor-negative tumors, young patient age, and HER2 positivity [30]. Other studies have confirmed

these findings [31, 32]. In a population of patients with metastatic breast cancer, the incidence of brain metastasis was 21% over 10 years, with similar risk factors [33]. Leptomeningeal metastases were more frequently diagnosed in breast cancer patients with triple-negative or HER2-positive tumors [34].

For patients diagnosed with the HER2-positive subtype of breast cancer, brain metastases are increasing as a first site of metastatic progression and threaten to limit the gains made by systemic therapy [29]. A recent prospective, observational study followed 1,023 patients newly diagnosed with metastatic HER2-positive breast cancer for a period of 3–6 years [26]. This large study evaluated the incidence and outcomes of the patients that developed brain metastases. In this cohort, 37% of patients developed brain metastases and these women were found to be younger in age, have hormone receptor negative primary tumors and have higher metastatic disease burden (≥2 metastatic sites) than their counterparts who did not develop brain metastases [26]. Additionally, of the 37% of patients who developed brain metastases, 20% had brain as a site of metastatic disease at the time of their initial metastatic diagnosis and 4% had brain metastasis as the only site of metastatic relapse. In this study, the median overall survival was 26.3 months for patients with any CNS involvement compared to 44.6 months for patients with no CNS involvement. The patients who fared the worst were those who had brain metastases at the time of diagnosis of metastatic disease—these patients had a median overall survival of 20.3 months.

Less is known about the incidence of brain metastasis and outcome of patients with triple–negative breast cancer. An analysis of 116 patients with metastatic triple-negative breast cancer revealed a median survival time from a diagnosis of metastatic disease until brain recurrence of 13.3 months [27]. Overall, 46% of patients were diagnosed with brain metastases before death. The median survival after diagnosis of a brain metastasis was 4.9 months [27]. In a study of more than 15,000 women with breast cancer in the National Comprehensive Cancer Network, those with triple–negative breast cancer were more likely to develop brain metastases than women with the HER2-positive subtype [35]. In contrast to patients with the HER2-positive subtype, patients with triple-negative breast cancer and brain metastases rarely had stable systemic disease [27]. Of the hereditary breast cancers, many are triple-negative. In a small study, 67% of patients with confirmed BRCA1 mutations developed brain metastases [36].

Although brain metastasis is relatively rare in patients with estrogen receptor-positive tumors, limited outcome data are available. In a multi-institutional retrospective analysis of 400 breast cancer patients with brain metastasis, patients with Luminal A estrogen receptor positive tumors survived a median of 9.7 months after diagnosis, which was substantially shorter than the 20.7 months for patients with Luminal B estrogen receptor positive tumors and the 13.8 months for the entire cohort [37].

Where investigated, it is agreed that occult or nonsymptomatic brain metastases are prevalent in many patients with advanced breast cancer. Results from an autopsy study found that, of those patients with histologically confirmed brain metastases, only 31% were diagnosed with symptoms associated with brain metastasis before

death [24]. When imaging was used as an enrollment criterion for clinical trial participation on patients without symptoms of brain metastatic disease, 15% of patients had occult brain metastases [25]. The clinical relevance of these occult lesions is unknown.

Several predictors of outcome after diagnosis of a brain metastasis are in development specifically for breast cancer. Nomograms take patient age, Karnofsky performance score, systemic metastases, number and size of CNS lesions, molecular characteristics and breast cancer stage into account to predict survival [38, 39]. A breast cancer specific GPA has also reported prognostic outcomes [40] [37].

2.3 Melanoma

Although melanoma is the third most common primary tumor to form brain metastases, it has the highest propensity to metastasize to the brain [41]. The incidence is estimated between 10 and 40% in clinical studies, but autopsy studies report the prevalence to be substantially higher at 55–75% of melanoma patients [23, 42–44]. Melanomas of the head and neck are more likely to metastasize to the brain than melanomas from other sites [45]. Risk factors for developing brain metastasis from melanoma include: gender (more frequent in males), stage IV disease, primary melanoma of mucosa or the head and neck, thick or ulcerated neoplasm, and acral lentiginous or nodal lesions [46].

The prognosis for melanoma patients with brain metastases is poor, with a median survival time of less than 1 year after diagnosis of the brain metastasis [47]. Approximately 20–55% of melanoma patients die as a result of brain metastases [48]. Predictors of poor survival in patients diagnosed with brain metastases include a high number of brain metastases, the development of brain metastases after systemic metastases, elevated lactate dehydrogenase levels, and the presence of bone metastases (reviewed in [49]). A small percentage of patients with brain metastases who survive more than 3 years are characterized by a locally treated single brain metastasis without other systemic disease [49]. The GPA assessment of 481 patients with melanoma metastatic to the brain showed a median survival of 6.7 months, although there was substantial heterogeneity in survival times ranging <1 to 4 years (Table 1.1) [40].

2.4 Trends

The incidence of brain metastasis appears to be increasing. Recent studies investigating metastatic lung and breast cancer patients reported alarming rates of brain metastasis [17, 23, 26, 35]. The causes of an increased incidence of brain metastasis are unknown but several theories have been posited that take into consideration the underlying biology and new therapeutic and imaging modalities. On one hand, as patients

live longer because of the use of new molecular therapies, the additional time may be sufficient to allow brain metastases to develop. This has been seen in patients treated with trastuzumab for metastatic HER2-positive breast cancer [50, 51]. The brain may represent a preferential site of metastasis because many of the new molecular therapies (and virtually all of the traditional chemotherapeutics) do not cross the blood–brain barrier or what is left of the blood–brain barrier once a tumor forms, the blood-tumor barrier. If this is true, then the possibility exists that cancer cells have to initiate expression and/or repression of a specific series of genes, markers, and events to target or direct them to the brain, i.e., execute a brain-specific signature. The brain-specific events could be triggered by selection pressures applied by the molecular therapies directly, mediated by a specific cell population either within the cancer or the microenvironment, or by some as-yet unknown pathway. It is anticipated that the incidence of brain metastasis may increase as more specific molecular therapies are designed for additional cancers. On the other hand, the incidence of brain metastasis may not be rising per se, but reflect that the increased detection may be facilitated by an increased use of refined imaging and greater attention and awareness to neurologic symptoms.

3 Diagnosis and Prognosis

Regardless of the primary cancer, a diagnosis of brain metastasis is most commonly made on the basis of patient symptoms. Some patients may present with a brain metastasis with no known primary cancer diagnosis. Symptoms include, but are not limited to: headaches, focal weakness and paralysis, alterations in cognition (cognitive decline), mental status and behavior, and seizure. In addition, these symptoms may be exacerbated by some of the prescribed treatments. Diagnoses are confirmed by neuroimaging, and usually with magnetic resonance imaging which can reliably detect lesions in the range of 3–5 mm.

Some cancers have a predilection for developing multiple brain metastases (i.e., lung cancer) that are detected simultaneously, whereas other cancers are more likely to develop a single brain metastasis (i.e., breast cancer). The number and location of brain metastases diagnosed is critical for prognosis and treatment schemes. Much of what we know about the location of metastatic disease in the brain comes from a 1978 landmark autopsy study by Posner and Chernik who reported data from 3,219 cancer patient autopsies conducted from 1970–1976 [7]. Although a third of cases had metastatic disease in multiple locations within the brain, the majority of brain metastases were present in only a single location. The location of brain metastases varied, with 39% of all brain metastases located in the parenchyma, 18% in the pachymeninges, and 12% present only in the leptomeninges [7]. This and subsequent studies highlight the importance of distinguishing between a solitary brain metastasis and a single brain metastasis because this too will impact prognosis and treatment regimens. A solitary brain metastasis is defined by the detection of only one brain lesion in the presence of controlled primary disease

and no other systemic metastatic disease, i.e., a solitary brain metastasis denotes control of extracranial disease. By contrast, a single brain metastasis is defined by the detection of only one brain lesion with either (or both) active primary disease or systemic metastatic disease. Multiple brain metastases may also be diagnosed initially or may develop later. A diagnosis of a brain metastasis is a risk factor for further brain metastases.

The prognosis after a brain metastasis diagnosis is grim. Mortality is the consequence of both the brain metastasis and systemic disease, and varies widely among types of cancer and among patients with the same cancer classification. The most widely validated indicator of prognosis for brain metastasis is the above mentioned Graded Prognostic Assessment (GPA) [40]. This prognostic index is diagnosis specific and based on more current data than the landmark Recursive Partitioning Analysis tool originally developed by the Radiation Therapy Oncology Group [52, 53]. The variables used in the GPA calculation differ among cancer types but all include patient performance status (Karnofsky performance score), which is the one major determinant that is prognostic for each patient. Other variables include age, presence on extracranial metastases, number of brain metastases, and the subtype of primary cancer. A GPA of 4.0 is associated with the best prognosis while a GPA of 0.0 indicates the worst prognosis, this is reflected in the increasing median survival times by GPA category shown on Table 1.1 for various primary tumor types. Overall median survival varied from 4.9 months in SCLC to 13.8 months in breast cancer (Table 1.1). The percentage of patients with the highest GPAs (3.5–4), were highest for those with breast cancer (33%), melanoma (23%), and renal cell carcinoma (22%) [40]. Other cancer type specific prognostic algorithms are under development.

4 An Overview of Treatment

Current treatments for brain metastases include surgical resection when one or a few lesions are located in an accessible region (see Chap. 7), limited systemic chemotherapy (see Chap. 8), and radiotherapy (see Chap. 9). The number of surgeries for brain metastases increased from less than 4,000 in 1988 to 7,000 in 2000 according to a retrospective cohort study from the Nationwide Inpatient Sample [54]. Radiotherapy can be either whole brain radiation or stereotactic radiosurgery. Whole brain radiation therapy delivers a relatively small dose of radiation (up to 3 gray [Gy]) to the entire brain in multiple doses (fractions) to treat multiple lesions and prevent occult tumor cells from colonizing. A role for whole brain radiation therapy for the prevention of brain metastasis has been validated in lung cancer [55, 56]. Stereotactic radiosurgery delivers a higher dose of radiation (> 4 Gy) to a focused area. Additionally, palliative care such as steroids and anticonvulsants are prescribed. In the era of molecularly targeted therapy, the development of blood–brain barrier permeable, small molecule inhibitors that will target brain metastases and improve survival is an intense research focus (see Chap. 6).

5 Conclusions

Brain metastasis may be increasing in incidence and confer significant morbidity and mortality. The clinical course of brain metastasis is heterogeneous even within similar cancer histologies, but increasingly may be contributing to patient deaths. Although most incidence data have been collected retrospectively, insufficient data exist at this time to identify a nonsymptomatic population of patients that should receive additional screening for brain metastases. Whether prophylactic CNS-directed therapies would reduce the incidence of brain metastasis is unknown, but determining who would best benefit from such treatment would require identifying predictors. Predictors that identify patients at high risk for developing brain metastases are severely lacking for patients with breast cancer or melanoma. A recently identified three-gene signature predictive of brain metastases for patients with lung cancer offers hope, but needs substantial further validation. Preclinical data from models of brain metastasis have suggested that some agents that can cross the blood–brain barrier are effective at preventing the outgrowth of metastatic tumor cells in the brain, but not treating established bulky disease. Thus, undertaking clinical trials that combine both predictors of brain metastasis that identify patients at high risk with blood brain barrier-crossing preventive agents may move us closer to the much needed goal of eradicating brain metastases.

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Chapter 2
The Molecular Biology of Brain Metastasis

Stephan Woditschka, Brunilde Gril, Lynda M. Evans, L. Tiffany Reed, and Patricia S. Steeg

Abstract An understanding of the molecular biology of brain metastasis development is critical to the development of new preventatives and therapeutics. Our current understanding is largely based on functional validation studies of candidate genes in animal models. These candidates were either identified by genomic profiling of clinical specimens or brain-tropic cell lines, or were suspected factors in key steps of the brain metastatic process. This chapter provides a summary of current *in vivo* brain metastasis models, explores the key steps of brain metastasis development and discusses the experimental evidence that links various genes functionally to brain metastatic progression. Animal models have been developed for lung and breast carcinoma, and melanoma metastasis to the brain. Most commonly these models involve hematogenous metastasis from carotid artery or left cardiac ventricle injection, but implantation and spontaneous animal models have also been reported. The steps involved in brain metastatic spread include extravasation from the brain vasculature, tumor cell dormancy, and outgrowth in the brain microenvironment. The brain parenchyma is altered by a potent neuroinflammatory response, involving activated microglia and astrocytes that accompanies brain metastasis development both clinically and in animal models. Alterations in the expression levels of individual genes have demonstrated functional roles in brain metastasis development in animal models. This includes genes driving metastatic spread in general, for which functions in brain metastatic spread have been demonstrated, as well as those who appear to have brain metastasis specific roles. Genes involved in cell signaling, angiogenesis, microenvironment modulation, cell adhesion and invasion as well as multiple transcription factors are discussed.

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1 Animal Models of Brain Metastasis

The use of animal models has been crucial to elucidate the cellular and molecular biology of brain metastasis development and validate expression trends from human craniotomy samples. The cancer cell lines used in brain metastasis assays are either derived from an experimental or spontaneous model of metastasis. Some brain metastatic (also called 'BR') lines, such as the 231-BR breast cancer cells or A549-BR lung cancer cells, were derived by repeated *in vivo* selection. In order to derive brain-tropic tumor cell lines, cells are injected into the left ventricle of the heart or into the carotid artery, to bypass the capillary beds of the lung, in which the cells would otherwise arrest. This is done by hand or under stereotactic guidance. The brains are harvested at necropsy, sterilely minced and tumor cells grown out in culture. This process is repeated until one or more endpoints are reached – the cell line produces brain metastases in all animals injected, it produces few systemic metastases, and/or it produces greater numbers of brain metastases. Other cell lines, such as the TXM-18 melanoma cell line and the MDA-MB-361 breast cancer cell line, will give rise to brain metastases in the majority of mice following intracardiac or intracarotid injection, without further *in vivo* selection.

The most commonly used brain metastasis models, utilizing both autonomously brain-tropic or *in vivo* selected brain-tropic cells are (1) implantation models, in which tumor cells are inoculated directly into the brain parenchyma, (2) hematogenous models, in which tumor cells are injected into the animals' arterial circulation, and (3) spontaneous models, in which cells are shed from primary tumors (reviewed by [1]). Implantation models, in which a bolus of tumor cells or tumor fragments is inoculated directly into the brain, are one of the simplest models. Because only a single lesion develops in a known location, it is the model of choice for close follow-up through a cranial window or for manipulation with radiation therapy. Implantation models do not require the use of brain-tropic cell lines. In a brain metastasis model from melanoma, a specialized inoculation technique using a subarachnoid catheter, which is passed through the magna cisterna along the spinal cord to the cerebrospinal fluid, allows for the study of leptomeningeal melanoma. The implanted catheter can subsequently be used for therapeutic drug delivery (reviewed by [2]). Implantation models invariably bypass important steps of the brain metastatic cascade, such as cell dissemination, blood-brain barrier (BBB) crossing and outgrowth from a solitary cell in the brain microenvironment and, increasingly, are not accepted as valid readouts of metastasis.

In hematogenous brain metastasis models, tumor cells are injected into the left ventricle of the heart or into the carotid artery. The time to histologically detectable metastatic formation varies depending on the model. Some models, such as the 4T1-BR require only 2 weeks, whereas others such as the MDA-MB-361 take 7–8 months [3, 4]. The majority of models, however, require approximately 4–8 weeks. These varying lengths of time may facilitate different types of experiments. Shorter time courses would be optimal for drug studies to minimize the amount needed, while neurocognitive endpoints may require 6–12 months. The morphology

of the brain lesions also varies. Some models produce round, circumscribed lesions typical of that seen on human scans, while other models produce clusters of very infiltrative tumor cells that, given time, may coalesce to form a more typical rounded shape. Endpoints of these assays vary and include live animal and *ex vivo* imaging to confirm the presence of metastases, histological counts of lesions in brain sections, and mouse survival. For histological counting, we routinely obtain a saggital section every 300 μm through one hemisphere of the brain an H&E stained. Using an ocular micrometer, all lesions greater than 300 μm in a single dimension are enumerated as "large" metastases – these are comparable to MRI-detectable several millimeter lesions in a human brain – and smaller lesion as micrometastases. The reason for this dichotomization is that the fate of micrometastatic tumor cells is unknown, as they could lie dormant or continue to grow. Genes such as HER2, when overexpressed also showed different effects on micro- versus large metastases [5]. Imaging endpoints, while easy and quantitative, may be the least relevant in brain metastases, as they fail to discriminate large and micrometastatic lesions and only work to a limited depth in the brain. Caution must also be taken when analyzing survival data. Because many brain metastatic cell lines may also give rise to systemic metastases, this endpoint does not currently allow for sole determination of survival due to brain metastases. Consequently, survival data are often used in conjunction with histologic confirmation of brain metastases.

While hematogenous models recapitulate the cancer cells' BBB crossing, invasion, and outgrowth in the brain microenvironment, they bypass precolonization steps such as dissemination, intravasation, and homing. Also, the tumor cells in hematogenous models are injected all at once, as opposed to being continuously shed from a primary tumor. This process only occurs in spontaneous metastasis models, which recapitulate the complete brain metastatic cascade.

Spontaneous models, in which brain metastases develop subsequent to growth and removal of primary tumors from an orthotopic or subcutaneous site, are the most complicated to run as a controlled experiment but provide a high level of evidence for confirming hypotheses. Spontaneous metastasis models are an exquisite balance of allowing primary tumor growth to proceed so that many tumor cells are shed, and then having brain lesions form before systemic lesions force the sacrifice of the mice. In contrast to hematogenous models, only a fraction of animals in spontaneous models develop brain metastases, ranging from 20% in models of low-dose metronomic chemotherapy [6] to 80% in G3.5 melanoma models [7]. The percentage of positive animals, rather than a full histological count is often the experimental endpoint.

Few analyses have asked how relevant experimental brain metastasis models are to human disease. Experimental brain metastases of the triple negative breast cancer cell line 231-BR exhibited similar patterns of proliferation, apoptosis and neuroinflammatory responses to a cohort of resected human brain metastases of breast cancer [8]. Figure 2.1 presents this comparison between the 231-BR mouse model and human samples. Most interesting is the prominent neuroinflammatory response surrounding the experimental lesions, consisting of activated microglia and astrocytes. Similar "fingers" of neuroinflammatory cells are observed in the human craniotomy specimens, suggesting that they also formed from coalescence of smaller lesions,

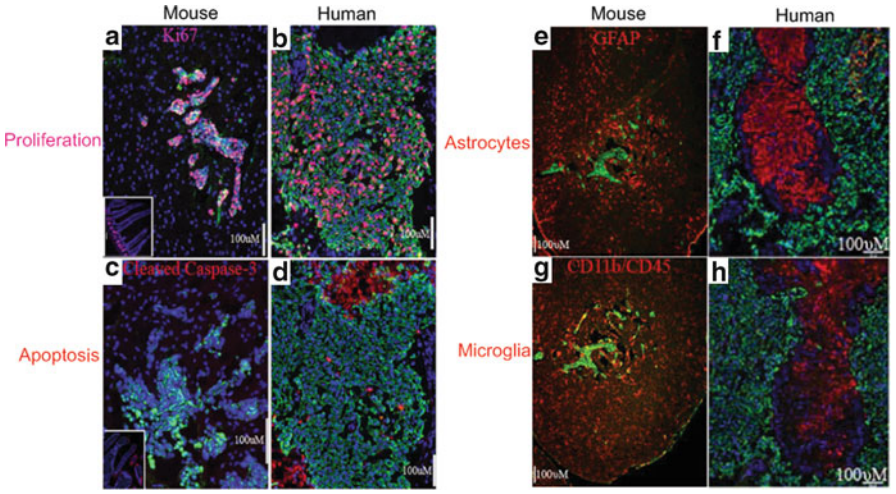

Fig. 2.1 The Brain metastatic 231-BR mouse model is similar to human brain metastases in proliferation, apoptosis and the neuroinflammatory response (Figure adapted from Fitzgerald DP et al. [8]). Cytokeratin-positive tumor cells are stained *green* in all panels, and nuclei are counterstained with DAPI in *blue* in panels (a), (d), (f) and (h). (**a**) Cluster of 231-BR cell metastases proliferating (Ki67; pink) in the mouse cerebral cortex. (**b**) A surgical sample from a brain metastasis of ductal carcinoma showing many Ki67-positive tumor cells (Ki67; pink). (**c**) The lack of staining for Cleaved Caspase-3 (*red*) demonstrates that apoptotic cells in the xenograft model are rare. (**d**) Few apoptotic cells are visible among the proliferating carcinoma cells from a surgical specimen of brain metastasis of ductal carcinoma. Necrotic areas, at the top and bottom left of (d) nonspecific show reactivity to the anti- Cleaved Capsase-3 antibody. (**e**) Numerous reactive astrocytes, visualized by staining for GFAP-positive cells (*red*), are visible around the cluster of metastases (*green*). (**f**) Large islands of GFAP-positive astrocytes trapped between clusters of cytokeratin-positive carcinoma cells are observed in the surgical specimen of human brain metastasis. (**g**) Reactive microglia (CD11b and CD45; *red*) surround the metastases in the mouse cerebral cortex. (**h**) In the human brain metastases tissues, CD68-positive microglia/macrophages co-localize to the islands of astrocytes

entrapping surrounding inflammation. A brain-tropic subline of A549 lung cancer cells derived from grafting parental cells onto the lung was resistant to conventional therapies including oxaliplatin and taxol, in keeping with clinical experience [9]. In essence, each model system represents the characteristics of a single patient, highlighting the importance of establishing a molecular pathway in multiple models to ascertain its generality.

2 Steps in Brain Metastasis

Tumor cells enter the circulatory system from primary tumors and also from metastatic sites, and can arrest and extravasate into the brain. Brain metastases arise from specific primary tumor sites, which are mainly cancers of the lung or breast, or from melanoma. Other tumor types that can spread to the brain are kidney and bladder

cancers, certain sarcomas, testicular and germ cell tumors and less frequently cancer of the colon, ovaries and prostate. Based on clinical observations, different latency for brain metastasis progression had been observed depending on primary tumor sites. For example, lung cancer patients develop brain metastases rapidly, simultaneously with or within the first 2 years after primary tumor diagnosis; brain metastases in breast cancer patients appear as a late event in the course of the disease, after the development of systemic metastases and multiple rounds of chemotherapy [10]. Two hypotheses have been generated to explain the late formation of brain metastases: (1) the brain microenvironment expresses factors that might delay the outgrowth of the metastases (parallel progression model), and (2) brain metastases derive from other metastases (linear progression model) (reviewed by [11]).

Intravital microscopy has demonstrated that tumor cells, after extravasation, crawl on the outside of blood vessels, the perivascular niche. Figure 2.2 presents immunostaining to characterize the blood vasculature and the brain microenvironment interaction with metastatic cells. The metastatic lesions (cluster of blue nuclei stained with DAPI) grow along blood vessels (CD31 in red), which appear more dilated compared to the blood vessels in areas of normal brain. For breast and lung cancer and melanoma cell lines, tumors elongate on the blood vessel surface, using integrins for attachment. Tumor cells move along these "highways" and proliferate along the way. Human brain metastatic specimens from various primary sites also showed this vascular association [12].

Eventually a proliferating mass of tumor cells will encounter the brain parenchyma and continue to colonize in this niche. The brain microenvironment is covered in detail in Chap. 3. During metastasis development, the brain parenchymal microenvironment is altered by neuroinflammation. Microglia (Fig. 2.2g, red) are macrophage-like resident cells of the brain that normally sit behind the BBB to monitor synaptic functional status and respond to injury or infection [13, 14]. Activated microglia express higher level of CD11b and CD45 compared to resting microglia [8, 15]. Microglia in close proximity to the metastases can display amoeboid morphology or a dendritic/stellate appearance. When tumor cells embedded in matrix were cultured next to a brain slice *ex vivo*, microglia accumulated at the point of contact, associated with the tumor cells and facilitated their invasion into the slice [16]. Astrocytes form a physical and metabolic support system for neurons while releasing communicative transmitters. When activated in neuroinflammation, astrocytes upregulate expression of glial fibrillary acid protein (GFAP) intermediate filaments (Fig. 2.2h green), nestin and proteases, and shield neurons from oxidative and other damage [8, 17, 18]. *In vitro* co-culture experiments indicate that brain metastatic 231-BR cells colonized preferentially in response to astrocyte conditioned medium as compared to lung fibroblast conditioned medium [8], suggesting the active participation of the neuroinflammatory response in brain metastatic colonization. The brain microenvironment also contains damaged axons, edema and vascular changes. Activation of microglia and astrocytes is seen around and within the lesions. Some brain metastases acquire a necrotic core while others do not. This is in keeping with the varying roles of angiogenesis, new blood vessel formation, versus co-option of the dense vasculature already present.

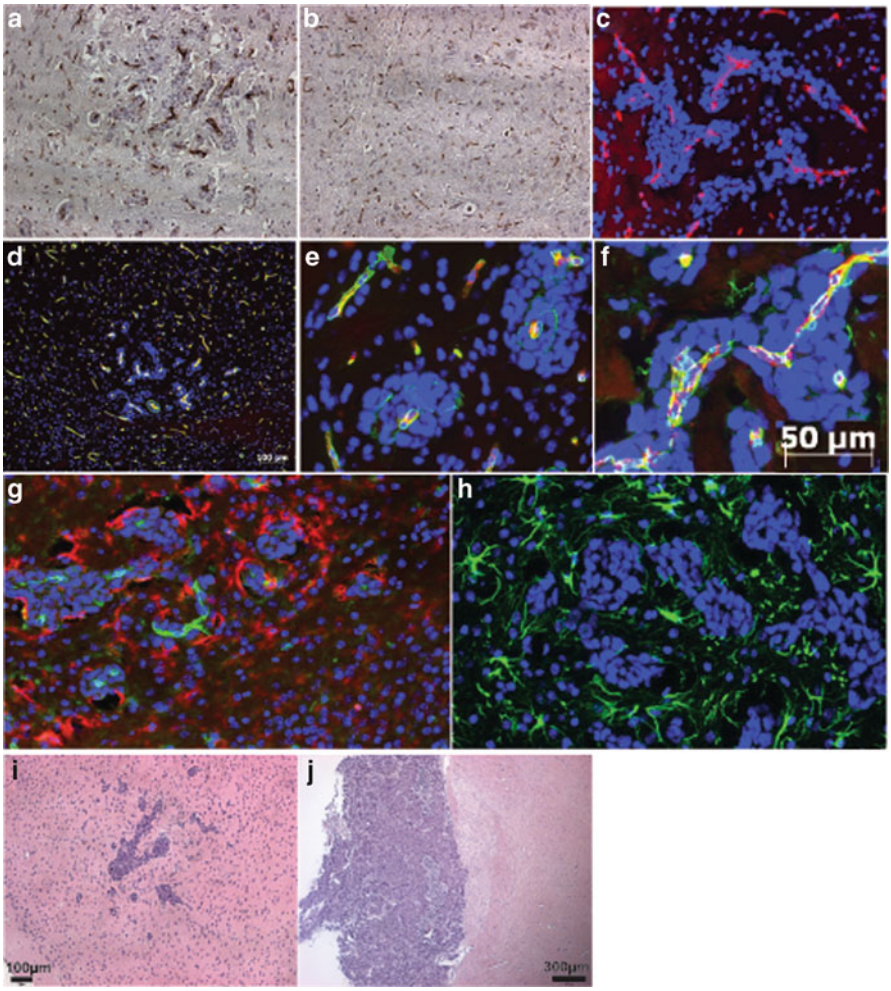

Fig. 2.2 Characterization of the microenvironment in mouse models of brain metastasis. (**a** and **b**) Immunohistochemistry using CD31 antibody, a marker of endothelial cells, to stain blood vessels (brown staining). In (**a**), metastatic lesions (large *gray-blue* nuclei) are growing along dilated blood vessels (CD31; *brown*). (**b**) Normal brain parenchyma with no metastases. (**c** to **h**) Immunofluorescence staining using different markers to characterize the blood vasculature. Clusters of cell nuclei stained with DAPI (*blue*) are metastatic lesions; the individual smaller *blue dots* are neurons and glial cells. (**c**) Metastatic lesions growing along blood vessels (CD31; *red*). (**d** and **e**) Every blood vessel (CD31; *red*) is surrounded by a collagen type IV + basement membrane (*green*), seen as yellow. **e**. Larger magnification. (**f**) NG2+ pericytes (*green*) cover blood vessels (CD31; *red*). Metastases grow along pericyte-covered blood vessels (*yellow*). Basement membrane and pericytes are components of the blood–brain barrier. (**g**) CD11b and CD45 double-stained activated microglia/macrophages (*red*) localize in direct contact with metastases. (**h**) Hypertrophic active GFAP + astrocytes (*green*) localized abundantly near metastases. (**i** and **j**) Hematoxilin and Eosin staining: metastatic lesions are in *purple*. (**i**) Intraparenchymal metastases. (**j**) Leptomeningeal metastases

The leptomeninges – linings of the brain and cerebrospinal system – comprise a third niche for colonization. Figure 2.2i, j show representative pictures of intraparenchymal and leptomeningeal metastases, respectively. In humans, spread to the leptomeninges can be accomplished by several routes including hematogenous, direct extension from the brain, or from the venous plexus, nerves, perineural/perivascular lymphatics, or choroid plexus. The cerebrospinal fluid (CSF) compartment serves as a microenvironment for leptomeningeal metastases and may be altered by immune cell infiltration, elevated protein concentrations and reduced glucose concentrations [19]. When co-cultured with leptomeningeal tissues, metastatic melanoma and lung cancer cells invaded into and degraded the leptomeninges, in contrast to glioma (primary brain tumor) cells that sat atop the tissue [20]. This observation suggests that glioma and brain metastases, while sharing the same "soil", may be distinct in important facets of their colonization.

In addition to the continuously colonizing tumor cells, dormant tumor cells have been described in the brain. Using DC-MRI of EGFP labeled 231-BR cells loaded with micron sized iron oxide particles, "signal voids," the size of single tumor cells were serially imaged in the mouse brain through an experimental metastasis assay. Proliferation of the tumor cells would dilute out the particles to undetectable levels and progressive colonization produced a fluorescent EGFP lesion. For every overt brain metastasis formed, three dormant cells remained [21], providing a significant pool of tumor cells to potentially awaken and lead to further relapses (reviewed by [22]). The existence of a pool of dormant tumor cells in the brain provides the rationale for whole brain radiation therapy and explains, at least in part, the observation that patients with a brain metastasis are at high risk for subsequent development of additional lesions.

Whether all metastatic tumor cells are capable of spawning a brain metastasis is debatable. To successfully form metastases, tumor cells from the primary tumor undergo a very inefficient cascade of events (extravasation, survival, proliferation). Indeed, preclinical studies and clinical observation suggest that only a small proportion of cells escaping the primary tumor will generate metastases. It has been hypothesized that this small population of tumor cells constitutes "cancer stem cells" or tumor-initiating cells [23]. These potential cancer stem cells might be able to maintain their tumor-initiating and metastasis-initiating capacity at a secondary site and therefore create a "metastatic niche". Another "unknown" is the degree to which the brain microenvironment is modified by systemic factors, known as the premetastatic niche in brain metastasis [24, 25].

3 Molecular Pathways Mediating Brain Metastasis

Characterization of a limited number of matched sets of primary tumors and brain metastases from the same patient has revealed distinctions. Genomic analyses show increased rates of genomic alterations. Among the EGFR (*E*pidermal *G*rowth *F*actor *R*eceptor) superfamily, EGFR was overexpressed in breast and lung cancer brain

metastases; in the lung cancer brain metastases multiple aspects of the EGFR pathway were up-regulated, including EGFR, phospho-EGFR, and the ligand amphiregulin [26]. HER2 was comparably expressed between primary breast tumors and brain metastases, but HER3 was overexpressed in the latter, as well as in lung brain metastases [26, 27]. Estrogen receptor varied in 26% of matched breast cancer sets [28]. Two DNA repair enzymes, O6-methyleguanine-DNA methyltransferase and ERCC1, were overexpressed in lung brain metastases [29, 30]. The DNA methylation patterns of genes such as HIN-1 and RAR-beta were increased in brain metastases [31]. Among unlinked cohorts of brain metastases, low expression of metastasis suppressor genes [32], apoptotic genes [33] and the Notch target HES1 [34] was reported. Conversely, high expression of Hexokinase 2 [35] and phospho-Stat3 [36] were observed in brain lesions. The microarray data files of these referenced human cohort specimens are publically accessible through the Gene Expression Omnibus (GEO) at the National Center for Biotechnology Information (NCBI) and, given the scarcity of human samples, can serve as a valuable resource for hypothesis generation purposes.

More commonly, brain-tropic and parental tumor cell lines were profiled to reveal candidate brain metastasis pathways that were then validated in gene knockdown or overexpression studies. Many of the genes identified to date have been studied in other metastatic sites. This chapter will focus on those pathways that have been validated functionally in brain metastasis model systems. A summary of these genes along with a brief description of the functional evidence linking them to brain metastasis development is presented in Table 2.1.

3.1 HER2

The HER2 (*H*uman *E*pidermal Growth Factor *R*eceptor) tyrosine kinase receptor is an oncogene, belonging to the EGFR superfamily. Its overexpression and/or gene amplification occurs in about 25% of primary breast carcinomas and it is a validated marker for breast cancer prognostic and therapeutic guidance [37, 38]. HER2 homodimerizes or heterodimerizes with other superfamily members. Up to 38% of advanced HER2+ breast cancer patients will develop brain metastases [39, 40]. HER2 gene amplification and/or overexpression in breast cancer has been associated with increased cell proliferation, cell motility, tumor invasiveness, metastases development, angiogenesis, and reduced apoptosis [41]. Trastuzumab is a recombinant monoclonal humanized murine antibody targeting the extracellular domain of HER2. It has activity in combination with chemotherapy in the adjuvant and metastatic settings for breast cancer. Lapatinib is a small molecule, competitive tyrosine kinase inhibitor that binds reversibly to the cytoplasmic ATP binding site in the kinase domains of EGFR and HER2 [42]. It is approved for metastatic breast cancer patients following trastuzumab therapy, in combination with capecitabine, the prodrug of 5-fluorouracil that blocks DNA synthesis.

The incidence of brain metastases in HER2+ metastatic breast cancer patients, currently 38%, is high and may be rising. The reasons for the increase in brain

Table 2.1 Genes functionally demonstrated to contribute to brain metastasis in model systems

Gene	Gene function	Primary tumor type	Functional evidence
HER2	Oncogene, tyrosine kinase receptor of the EGFR family	Breast	HER2 overexpression increased the multiplicity of large brain metastases [5], lapatinib decreased brain metastasis outgrowth by 53% [47]
VEGF	Vascular endothelial growth factor, responsible for angiogenesis, the creation of new vessels	Melanoma Breast Lung Colon	VEGF inhibitor PTK787 treatment resulted in lower brain metastasis burden [54]
$\alpha_V\beta_3$ *integrin*	Cell surface receptor for adhesion to the matrix, supports metastatic growth and vasculature development in the brain microenvironment	Breast Glioma	Activation of β3 in intracranial lesions derived from MDA-MB-435 cells resulted in increased brain metastases growth [57]
Notch 1	Transcription factor	Breast Glioma	Inhibition of Notch1 by γ-secretase inhibitor DAPT or shRNA knockdown reduced brain metastasis formation [60]
Wnt/β-catenin	Transcription factor	Lung Breast	Knockdown of transcription factors known to function through β catenin reduced brain metastasis formation [68]
STAT-3	Transcription factor	Breast Melanoma	STAT-3 overexpression increased the incidence of brain metastases; knockdown of STAT3 or overexpression of an inhibitor reduced brain metastases [74, 75]
COX2	Inducible isozyme, responsible for prostaglandin production	Breast	ShRNA mediated COX2 knockdown reduced brain metastasis-free survival [82]
ST6GALNAC5	Sialyltransferase, catalyzing the transfer of sialic acid to oligosaccharides, altering cell-cell and cell-extracellular matrix interactions	Breast	ShRNA mediated ST6GALNAC5 knockdown reduced brain metastasis-free survival [82]

(continued)

Table 2.1 (continued)

Gene	Gene function	Primary tumor type	Functional evidence
PEDF	Pigment epithelium-derived factor, non-inhibitory member of the SERPIN serine protease inhibitor gene family	Breast	PEDF overexpression in 231-BR and 4T1-BR cells decreased the multiplicity of large and micrometastasis [86]
Heparanase	Proteolytic enzyme cleaving heparan sulfate side chains, roles in tumorigenesis, ECM degradation	Melanoma Breast	Heparanase repression by mir-1258 reduced multiplicity of brain metastasis [91]
TGFβ	Tumor suppressor and oncogene, depending on context. Activates major signaling cascades such as ERK, AKT, and Src. Can also regulate transcription through Smad proteins	Melanoma Breast	*TGFβ* overexpression assisted in tumor growth in the brain parenchyma [104]

metastasis incidence in HER2+ metastatic breast cancer patients are likely complex and include (1) protection from drug entry by the BBB, (2) improved treatment of systemic disease by trastuzumab, prolonging survival and unmasking a new population of patients with brain metastases, and (3) HER2 overexpression itself induces a more aggressive brain metastatic phenotype.

The brain is protected by the BBB, described in Chap. 4. The limited disruption of the BBB by a developing brain metastasis may be particularly acute for the entry of large therapeutics such as trastuzumab. In patients, trastuzumab levels in CSF has been shown to be 300-fold lower than those in plasma [43–45], creating a "sanctuary site" from chemotherapy in the brain. Preclinical studies, using experimental models of brain metastases from breast cancer demonstrated that lapatinib, had only limited access to the brain. As compared to paclitaxel (widely used mitotic inhibitor blocking cell division by stabilizing microtubules) the uptake of lapatinib in experimental brain metastases was greater, with 17% of the lesions demonstrating drug uptake comparable to systemic lesions and 70% with 5-fold improved uptake over normal brain [46]. Thus, even a "brain-permeable" therapeutic may be only partially available to brain metastatic tumor cells.

The functional role of HER2 overexpression in brain metastasis development was investigated in a preclinical model. Brain metastatic 231-BR breast cancer cells were transfected to overexpress HER2. In hematogenous brain metastasis assays, both vector and HER2 transfectants produced the same number of micrometastases, however the HER2 expressing clones induced a 2.5- to 3-fold increase in the number of large metastases [5] demonstrating that HER2 overexpression promotes the outgrowth of tumor cells in the brain. The functional role of HER2 overexpression was confirmed using lapatinib in preclinical experiments. When given early after tumor cell injection, lapatinib prevented the formation of 231-BR-HER2 large brain metastases by 53%, while it prevented by only 17% the formation of 231-BR (without HER2 overexpression) large brain metastases. Lapatinib induced a significant decrease in staining for phospho-HER2 (i.e. decrease in HER2 activation), indicating that the drug hit its target [47]. However, phospho-Akt, a marker of cell survival, remained expressed in 36% of the metastatic lesions after lapatinib treatment *in vivo*, suggesting that additional brain-permeable drugs will be needed for complete prevention (Gril et al., unpublished observation).

3.2 VEGF

The brain is a very well vascularized organ (see Chap. 3 for a detailed discussion of the brain microenvironment). In general brain metastases have fewer vessels that are more dilated, with prominent peritumoral edema compared to normal brain parenchyma. The contribution of the existing, remodeled or new vasculature to a developing brain metastasis is therefore complex.

Multiple active processes affect brain metastasis vasculature. Angiogenesis, the creation of new vessels, is fueled by Vascular Endothelial Growth Factor (VEGF) as well as other angiogenic factors. Vascular co-option is the use of the existing vasculature; it facilitates tumor growth in the brain, and allows proliferation of tumor cells along the periphery of existing blood vessels [1, 48, 49]. The existing vasculature can also be remodeled. Mechanisms of vascular branching and outgrowth, that are not specific to brain metastasis but can occur, include vascular intussusception, vasculogenic mimicry [49], and vasculogenesis [1].

Angiogenesis is controlled by intracellular and extracellular signals within the brain parenchyma. Cellular signals upregulating angiogenesis are typically released from hypoxic inflammatory or neoplastic cells. Primary angiogenic signals include, but are not limited to VEGF-A, VEGF-C, ANG2, FGFs, $\alpha_v\beta_3$, and various chemokines [50]. Evidence of the clinical significance of VEGF overexpression for brain metastasis development came from an analysis of CSF from 37 patients with leptomeningeal metastases [51]. There was a 14-fold increase in the median VEGF value from the CSF of patients with leptomeningeal metastases, compared to the CSF of patients with other neurological diseases [51].

Investigations of VEGF in mouse models of brain metastatic melanoma have further elucidated the role of this gene in brain metastatic progression. In a hematogenous model of brain metastatic melanoma the effects of VEGF overexpression were compared to the low endogenous levels of the Mel57 cell line. The VEGF overexpressing brain metastases were significantly larger, had higher proliferation indices and exhibited a more solid morphology compared to the control lesions, which grew in a more infiltrative pattern [52].

Two types of therapeutics are approved for anti-angiogenic therapy. Bevacizumab is a monoclonal antibody against VEGF, while a number of small molecules inhibit the VEGF receptors (VEGFRs). In a 2010 study by Kienast et al., VEGF-A was inhibited by bevacizumab, resulting in reduced angiogenesis in lung carcinoma metastases to the brain. Despite VEGF-A inhibition, the lung carcinoma cells were eventually able to proliferate due to co-option of the existing brain vasculature and development of capillaries. In contrast, brain metastatic growth of MDA-MB-435 cells, which do not express the target protein VEGF-A, was unaffected by bevacizumab treatment [53]. In a hematogenous mouse model of brain metastatic 231-BR cells, administration of the VEGFR tyrosine kinase inhibitor vatalanib (PTK787/Z 222584) resulted in marginally increased survival and a 2.6-fold reduction in brain metastasis burden compared to vehicle controls [54]. This was associated with reduced angiogenesis within brain lesions, as well as decreased proliferation and increased apoptotic indices [54].

The variable contribution of angiogenesis to brain metastasis formation may impact imaging. In a mouse model of melanoma brain metastasis, Mel57 brain metastatic lesions with upregulated VEGF-A contained dilated and permeable co-opted vessels at the tumor periphery. This cell line often produced lesions that were identifiable with T1 and T2 weighted images (see Chap. 5 for a detailed discussion of imaging modalities), likely due to peritumoral and intra-tumoral

edema. Additionally, these lesions were associated with large amounts of hemorrhage, which may have occurred as a result of vascular permeability. In mice with parental Mel57 brain metastasis, the lesions were not visible on MRI. The absence of the tumor on MRI may occur because the tumor contains pre-existing brain capillaries and the BBB is intact. In patients who receive antiangiogenic therapy it is possible that their brain metastasis may appear invisible with MRI due to vessel co-option and not necessarily due to cessation of tumor volume [55].

3.3 $\alpha_v\beta_3$ Integrin

Integrins are transmembrane cellular receptors that bind to the extracellular matrix and facilitate cell-cell adhesion. Many different types of integrins exist which bind to a variety of extracellular matrix proteins. Integrins contribute to the growth, survival, and proliferation of the cell [56]. For example, the β1 integrin is involved in initiation, proliferation, and metastasis of tumor cells. β1 integrin mediates binding of tumor cells to the vascular basement membrane, and can facilitate cell proliferation and brain micrometastases. The interaction of β1 integrin and brain vasculature has been confirmed in mouse models of lymphomas and carcinomas, following intraparenchymal injection [12].

The $\alpha_v\beta_3$ integrin supports metastatic growth of neoplastic cells and vasculature development in the brain microenvironment in gliomas, metastatic breast cancer and melanomas [57]. Upregulation of $\alpha_v\beta_3$ results in adhesion of endothelial cells to the extracellular matrix (ECM) [50, 57]. Tumor cells containing activated $\alpha_v\beta_3$ have increased VEGF mRNA translation following the release of the eIF4E transcription factor. In the brain, $\alpha_v\beta_3$ integrin activation precludes tumor cell growth arrest and apoptosis associated with hypoxia [57].

Experimental evaluation and validation of $\alpha_V\beta_3$ confirms the importance of this gene in vascular development in metastatic brain lesions [57]. To elucidate the diagnostic significance of $\alpha_V\beta_3$ in brain metastasis, MDA-MB-435 cells were injected intracerebrally into the striatum of CB17/SCID mice. One subset of these cells contained activated integrin (D723R) while another subset contained shRNA mediated $\alpha_V\beta_3$ gene knockdown. The growth of β_3D723R cells was markedly increased in comparison to β_3 knockdown cells. Integrin activation markedly increased the growth of the implanted tumors, resulting in greater blood vessel density, new vessel formation, and metastatic growth of tumor cells in the brain. Additionally, β_3D723R tumors lacked large regions of hypoxia that contributed to tumor cell proliferation. In normoxic tumor conditions, β_3D723R cells expressed higher levels of VEGF than β_3 knockdown cells. Given the heterogeneity of phenotypic outcomes with VEGF in brain metastasis, the role of this integrin in additional model systems is awaited. Development of $\alpha_v\beta_3$ as a therapeutic target may serve as a vehicle to control angiogenesis in these metastatic lesions [57].

3.4 Transcription Factors

Transcription factors are proteins that control the expression of specific target genes by facilitating RNA polymerase binding at the target gene promoters. To date, three categories of transcription factors have been characterized: (1) steroid receptors which are present at the cell membrane and translocate to the nucleus following ligand binding, (2) resident nuclear proteins which are present in the nucleus and are activated following signaling, and (3) latent transcription factors. Latent transcription factors are located in the cytoplasm prior to activation by a signaling cascade. Following activation, they translocate to the nucleus to mediate transcription [58]. Interestingly, the transcription factors that have been found to associate with brain metastases are resident nuclear proteins or latent transcription factors whereas the steroid receptors (such as the estrogen receptor) are the only ones that have been successfully targeted pharmacologically [59].

Notch, a transmembrane receptor that undergoes proteolytic cleavage to generate an intracellular fragment with transcriptional activity, has been hypothesized to be involved in the maintenance of cancer stem cells during tumor growth and development, thereby promoting tumor growth and an aggressive phenotype. Supporting this hypothesis, analysis of Notch1 expression in 295 breast cancer patients from the Netherlands Cancer Institute found elevated expression of Notch1 was associated with a 23% decrease in overall survival [60]. The four known human Notch proteins (Notch 1 – Notch 4) are transmembrane receptors activated by binding to one of five ligands (Jagged 1, Jagged 2, Delta-like 1, Delta-like 3, and Delta-like 4) (Fig. 2.3). Upon ligand-Notch binding, Notch undergoes a series of proteolytic cleavages, first by one of the ADAM proteins and then twice by γ-secretase. These cleavages generate an intracellular protein fragment known as the Notch intracellular domain (NICD), which can translocate to the nucleus and induce transcription [61, 62]. Two Notch-target genes commonly used to assess Notch transcriptional activation are Hey1 and Hes1.

When comparing brain metastatic 435-BR cells to the parental MDA-MB-435 (435-P) cell line via microarray, Nam et al. found that Jagged2 and the γ-secretase catalytic domain presenilin1 were increased in expression, suggesting a role of the Notch pathway in the development of brain metastases. The Notch regulated genes Hey1 and Hes1 were also found to be upregulated in the 435-BR cells while the NICD was upregulated in both the 435-BR and 231-BR cell lines relative to their parental counterparts, indicating an increase in Notch1 activity in brain-tropic breast cancer cell lines [60, 63].

Experimental data indicates that Notch signaling is involved in cell migration, invasion, and proliferation. All three of these metastatic phenotypes are reduced *in vitro*, when Notch is targeted by either shRNA or the γ-secretase inhibitor N-[N-(3,5-Difluorophenacetyl)-L-alanyl]-S-phenylglycine t-butyl ester (DAPT) in brain metastatic 231-BR or 435-BR cells [60, 63]. While it is clear that Notch1 is increased in these experimental brain metastasis models, the molecular mechanisms by which the protein affects migration, invasion and proliferation, remains to be determined.

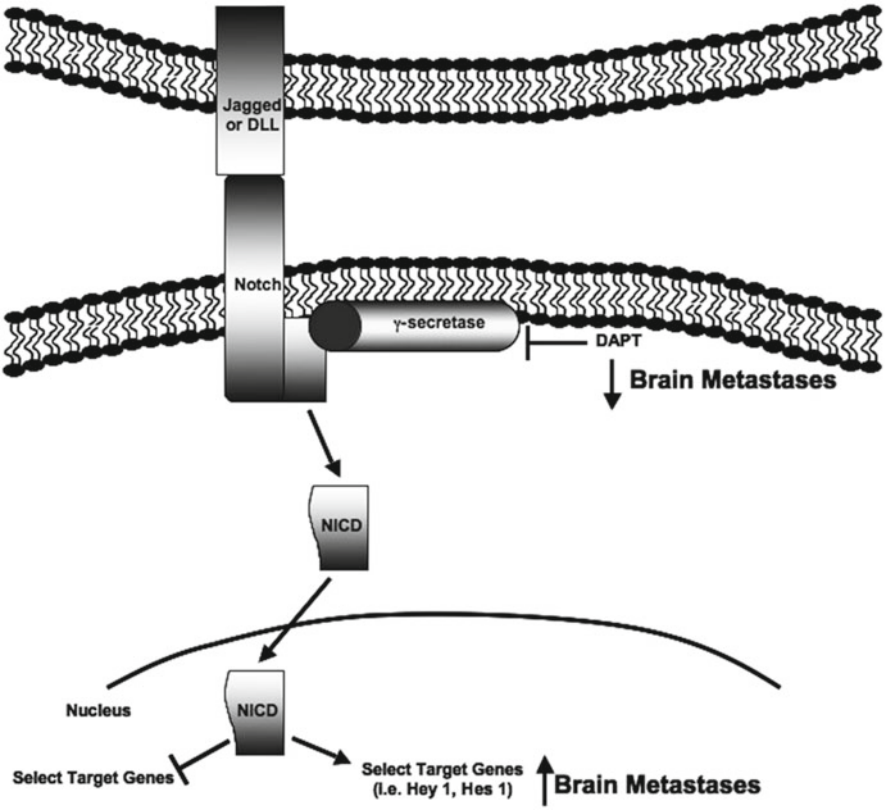

Fig. 2.3 The involvement of Notch signaling in the development of brain metastases. Following binding to a delta-like (DLL) or jagged receptor on an opposing cell, Notch under goes a series of proteolytic cleavages to generate the Notch intracellular domain (NICD). NICD then translocates to the nucleus where it can regulate transcription. Implicating the importance of Notch 1 signaling in the development of brain metastases, knockdown of expression with shRNA constructs or inhibition of signaling with the compound DAPT both significantly reduced the development of brain metastases in murine models

Following the evidence from their *in vitro* studies, McGowan et al. determined whether Notch affects the development of brain metastases *in vivo*. Using the 231-BR brain metastasis assay, DAPT treatment, starting day 14 post-injection, resulted in a 25% reduction in the number of both large metastases and micrometastases. Furthermore, shRNA-mediated Notch1 knockdown caused a greater than 75% decrease in large metastases and micrometastases compared to the scrambled shRNA control [60].

Because Notch1 inhibition was efficacious both when started at the time of injection (via shRNA) and when acting on established lesions (via DAPT treatment) the transcription factor likely has roles in both the initial colonization and the outgrowth of brain metastases as well as the growth and maintenance of brain metastases (Fig. 2.3).

Both principles lend to the use of γ-secretase inhibitors in patients with brain metastases although caution is still advised in extrapolating the results from a non-clinical candidate molecule such as DAPT to clinical inhibitors. We found that the Roche Ro4929097 γ-secretase inhibitor did not prevent brain metastasis formation in the 231-BR model ([64], Evans et al., unpublished observation), suggesting that DAPT may have off target effects. Additionally, not all brain metastases may respond to inhibition of γ-secretase. In contrast to the breast cancer model, brain metastases from colorectoral cancers may have decreased Notch signaling relative to the primary tumors as determined by decreased Hes1 expression [65].

A second transcriptional pathway active in brain metastasis formation is Wnt/β-catenin. Activation of Wnt signaling and β-catenin occurs in many cancer subtypes and may be a common event in brain metastases. During activation of the canonical Wnt signaling cascade, β-catenin translocates from the cytoplasm to the nucleus where it can bind to T-cell Factors (TCFs)/lymphoid enhancer binding factors (LEFs), inducing transcription [66]. To date, 4 TCF genes have been identified in humans – TCF1, TCF3, LEF1, and TCF4. TCF3 acts solely as an inhibitor of the Wnt/β-catenin pathway whereas LEF1 is solely an activator. TCF1 and TCF4 have been shown to serve as both activators and repressors of Wnt/β-catenin responsive genes. (Reviewed in [67]).

To determine whether Wnt/TCF signaling was involved in the development of brain metastases from lung cancer, Nguyen et al. analyzed TCF activity using a luciferase reporter assay [68]. Both the brain-tropic H2030-BrM3 cells and PC9-BrM3 cells exhibited greater activity than their parental counterparts. When TCF4 activity was inhibited in the brain tropic cells by transfection of a "dominant negative" (function inactivating) TCF4 construct, there was an increase in metastasis-free survival to all metastatic sites, including the brain. Knockdown of the Wnt3A targets LEF1 and HOXB9 via shRNA in the H2030-BrM3 and PC9-BrM3 cells also increased metastasis-free survival suggesting they are potential downstream targets of TCF4 [68].

A second role for the Wnt/β-catenin pathway may involve the microenvironment. The infiltration of activated microglia into a breast cancer metastasis has been documented in both animal models and human metastases [8]. Placing a tumor plug of MCF-7 breast cancer cells next to a brain slice, microglia were found to migrate to and infiltrate the tumor cells. Interestingly, when slice co-cultures were performed in the presence of the Wnt inhibitor DKK-2, there was a significant decreased in MCF-7 cell invasion into the brain slice. Although not conclusive, these results suggest that Wnt may play a role in invasion.

In addition to the canonical pathway, there is also evidence that β-catenin independent Wnt signaling pathways may be involved in brain metastasis development. Alternative Wnt signaling pathways include a Wnt/Ca2+ cascade and the receptor tyrosine kinase-like orphan receptors (ROR) 1 and 2. When Klemm et al. examined β-catenin expression in breast cancer brain metastases, they found it was not nuclear in the majority of samples. Analysis of human brain metastases relative to MCF-7 breast carcinoma cells found Wnt5a and Wnt5b, were upregulated 1.4-fold, and 2.9-fold, respectively. ROR-1 and ROR-2 were upregulated 3.3-fold and 20.2 fold relative to MCF-7 suggesting the involvement of β-catenin independent Wnt signaling [69].

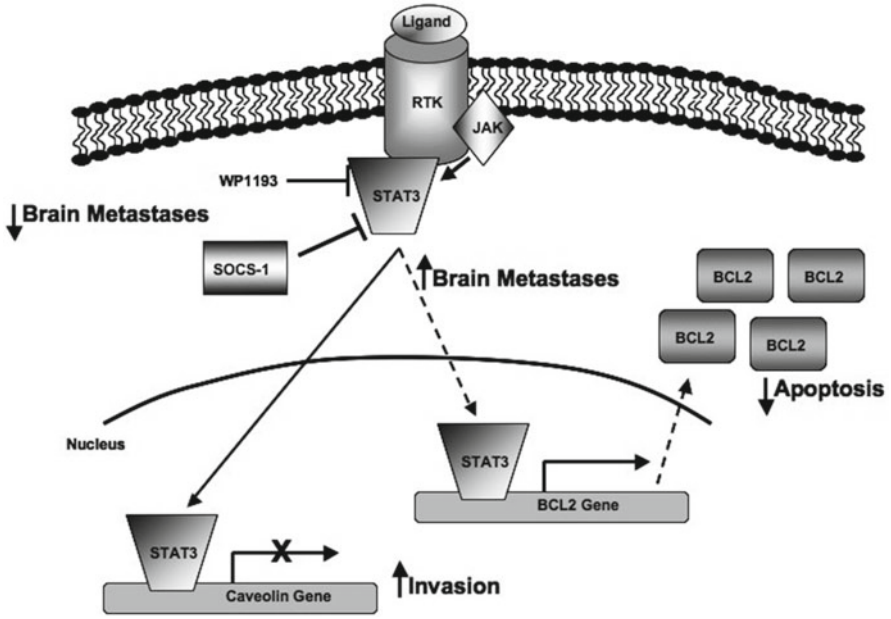

Fig. 2.4 The involvement of STAT3 in the development of brain metastases. Following ligand binding with its receptor tyrosine kinase (RTK), the complex recruits and activates JAK. JAK then phosphorylates STAT3. Upon activation of STAT3 by JAK, the protein translocates to the nucleus where it can regulate transcription of various proteins. STAT3 expression has been found to increase the development of brain metastases, whereas inhibition of STAT3 using either physiological (SOCS-1) or pharmacological (WP1193) means has the opposite effect. STAT3 activation has also been associated with an increase in BCL-2 expression (indirectly) and a decrease in caveolin expression (directly through binding to the promoter), and decreases apoptosis and increases invasion of cancer cells, respectively

In conclusion, the exact effects of β-catenin dependent and independent Wnt signaling on the development of brain metastases have yet to be determined but may influence tumor cell invasion through activation of microglia in the neuronal microenvironment.

A third transcriptional pathway involved in brain metastasis is the Signal transducer and activator of transcription 3, more commonly known as STAT3. Genes regulated by STAT3 are involved in a variety of functions including cell proliferation, survival, angiogenesis, metastasis and immune response [70]. Canonical cascade activation occurs when intracellular JAK kinases activate STATs by phosphorylation. Activated STATs are able to translocate to the nucleus where they can regulate transcription [71]. Increased expression and activation is often associated with an upregulation of known activators, such as EGFR, Src, IL6 receptors, and G-coupled protein receptors, or with the downregulation of known inhibitors, such as SOCS (Suppressor of cytokine signaling), PIAS (Protein inhibitors of activated STATs) and SHPs (Scr-homology 2 (SH2)-containing protein tyrosine phosphatases) [72, 72] (Fig. 2.4).

Clinical data indicates that STAT3 may be involved in the development or maintenance of brain metastases. Analysis of phospho-STAT3 demonstrated increasing STAT3 activation with breast cancer aggressiveness, from 22% strongly positive in noninvasive ductal carcinomas in situ to 32% in infiltrating ductal carcinomas and 68% in brain metastases [73]. Analysis of primary melanoma and brain metastases from patients also found a 57% increase in strong phospho-STAT3 staining in the brain metastases [36].

The experimental brain metastasis data, like the human data, showed compelling evidence for the involvement of STAT3 in brain metastases. Comparing a brain-tropic A375 melanoma cell line to the parental line (A375-BR vs. A375-P), the authors found that mice injected with A375-BR did not survive past day 60 and 100% of mice developed brain metastases; in comparison, mice injected with the parental cells were still alive at day 90, without developing brain metastases. Following overexpression of STAT3 in the A375-P cell line, incidence of brain metastases rose from 0 to 60–100%. Conversely, when a dominant-negative STAT3 was overexpressed in the A375-BR cell line, the incidence of brain metastases decreased from 100 to 20% or less. The authors also analyzed another brain metastatic melanoma cell line TXM-18, in which expression of the dominant-negative STAT3 decreased the incidence of brain metastases from 100 to 40% or less [36]. Additionally, inhibiting activation of STAT3 by overexpressing its inhibitor SOCS-1 reduced the incidence of brain metastases by 50–78.8% in A375-BR cells and completely inhibited formation in the 231-BR cell line [74]. Due to potential artifacts in incidence data from failed injections, an analysis of brain metastasis numbers is awaited.

In vitro evidence suggests that STAT3 may control brain metastasis by inhibiting the gene expression of caveolin-l, thereby promoting cell invasion. Caveolin-1 was shown to be inversely correlated with STAT3 activation in a variety of breast cancer cell lines and normal mammary epithelial cells and STAT3 binding at the caveolin promoter prevents transcription of this potent inhibitor of cell invasion [73]. STAT3 may also promote tumor cell survival following chemotherapy through upregulation of Bcl-2 [75], which in turn inhibits proteins known to induce apoptosis (reviewed in [76]). Confirmation of these potential mechanisms *in vivo* is awaited.

Multiple mechanisms have been employed to inhibit STAT3 (Fig. 2.4). The current strategies include inhibiting the upstream receptor tyrosine kinase receptors, thereby inhibiting STAT3 activation, nuclear translocation, and DNA binding. To date, however, each strategy has had its share of difficulties and downfalls [70]. WP1193 was identified as a third generation, BBB permeable STAT3 inhibitor, which has shown synergistic effects with interferon alpha treatment in a B16 melanoma cell brain metastases model, but was without significant activity as a single agent [77].

3.5 COX-2 and ST6GALNAC5

Cyclooxygenase-2 (COX-2) is an inducible isozyme, responsible for prostaglandin production during inflammation. COX-2 has well documented roles in promoting tumor progression and metastasis (reviewed by [78]). Of particular interest is the

fact that prostaglandin production during inflammation has been reported to increase BBB permeability [79]. ST6GALNAC5 is a relatively unstudied sialyltransferase, a group of enzymes which transfer sialic acid to oligosaccharides. In this way, ST6GALNAC5 appears to modify proteins and lipids on the cell surface, which in turn can alter both cell-cell and cell-ECM interactions [80].

Overexpression of COX-2 was identified as part of a 17-gene signature predictive of brain relapse in a cohort of 368 annotated breast tumors, in which COX-2 overexpression was a significant independent predictor [81]. ST6GALNAC5 was found to be highly upregulated in cell lines selected for brain metastatic growth, such as brain metastatic 231-BR cells and patient-derived CN34 cells. In these brain-tropic derivatives, ST6GALNAC5 was overexpressed 30-fold and >100-fold respectively, compared to the parental cell lines. The gene was also highly overexpressed in two additional pleural-derived samples, 95-fold and 72-fold, after just one round of *in vivo* selection in mice for brain tropism. This rapid and striking upregulation of ST6GALNAC5 is intriguing, and suggests that overexpression of this relatively unknown gene may be beneficial to cancer cell survival for outgrowth in the brain microenvironment. Based on preliminary evidence, ST6GALNAC5 may also be highly overexpressed in at least a subset of clinical breast cancer brain metastases (and possibly some lung metastases), while it is virtually absent in bone and liver metastases [81].

ShRNA-mediated COX-2 knockdown in brain metastatic 231-BR and patient-derived CN34 cells significantly increased brain metastasis-free survival ($p=0.02$ and $p<0.00001$, respectively) compared to control shRNAs. Similarly, knockdown of ST6GALNAC5 in CN34 cells also increased brain metastasis free survival ($p=0.0001$) [81]. Brain metastasis free survival was further increased by adding cetuximab, an EGFR inhibitor, to the ST6GALNAC5 knockdown group ($p=0.02$ compared to ST6GALNAC5 knockdown alone), suggesting potentially additive effects of ST6GALNAC5 and EGFR functions in brain metastasis development.

These findings suggest potential rationale in targeting COX-2 and ST6GALNAC5 for prevention or treatment of brain metastasis. However, despite the intriguing discovery that COX-2 overexpression might mediate brain metastasis development, and the availability of COX-2-specific inhibitors, no preclinical or clinical data on brain metastases exists today. Also, there are currently no strategies for targeting ST6GALNAC5.

3.6 PEDF

Pigment epithelium-derived factor (PEDF) is a secreted glycoprotein and a non-inhibitory member of the SERPIN, serine protease inhibitor gene family. PEDF had been shown to possess a wide range of functions such as tumor suppressive, neuroprotective, anti angiogenic, anti oxidative, and anti inflammatory properties [82–84]. More recently, PEDF had been shown to play a protective role against brain metastases of breast cancer, acting simultaneously as a pro apoptotic factor for cancer cells and a neuroprotector in the brain microenvironment.

PEDF's association with brain metastases of breast cancer was shown using a gene expression analysis comparing resected breast cancer specimens. PEDF mRNA levels were downregulated by approximately 14-fold in resected human brain metastases of breast cancer compared to unlinked primary breast tumors [35]. To evaluate the hypothesis that PEDF could have specific implications in brain metastasis protection, different breast cancer cell lines (231-BR and 4 T1-BR) and mouse models were studied [85]. Overall, significant decreases in the number of large metastases and in the number of proliferating cancer cells was observed in the mice injected with PEDF-expressing clones compared to vector controls.

Perhaps the most unique aspect of PEDF is its simultaneous neuroprotective activity, which is hypothesized to be mediated by different cellular receptors. Investigation of neuronal damage using silver staining and fluorojade-B staining showed that the intracranial injection of cancer cells induced a 15-fold increase in neuronal damage surrounding the brain lesion, compared to a saline control injection. A 3.5-fold diminution in neuronal damage was observed in the brains of mice injected with the cancer cells expressing PEDF compared to the mice injected with the vector transfected cancer cells.

These results indicated that PEDF can simultaneously act to promote neuronal survival while activating cell death in cancer cells in the brain. The tumor-suppressive properties were not specific to the brain microenvironment as it can affect cancer cells in other organs. However, the neuroprotective effect of PEDF is an important advantage for the management of brain metastases, because patients with brain metastases undergo significant cognitive declines associated with brain metastatic disease itself or treatments. Therefore, further investigating the use of PEDF as a potential factor for the treatment of brain metastases seems pertinent.

PEDF is already under investigation to treat neurodegenerative diseases [86]. However, the development of PEDF as an agent for the treatment of brain metastases require further investigations into different aspects of PEDF: the specificity of its different functional domains, the cell-type-specific activities, its receptor expression pattern and mechanism of action, as well as a better understanding of brain permeability to deliver PEDF into the brain microenvironment.

3.7 Heparanase

Heparanase is a proteolytic enzyme, which cleaves the side chains of heparan sulfate (HS), a component of the extracellular matrix. Since HS plays important roles in cell–cell and cell–ECM interactions, cleavage of HS by heparanase alters the structural integrity of the ECM and releases a multitude of growth factors, chemokines, cytokines and enzymes that are tethered to the ECM and cell surface by HS chains. Heparanase is overexpressed in essentially all major types of human cancer: carcinomas, sarcomas and hematological malignancies, and is generally associated with reduced survival, increased tumor metastasis and higher microvessel density (reviewed by [87]). In melanoma, specifically, heparanase expression correlates with

disease progression: with low levels in normal skin and tumor radial growth phase, increased levels in vertical growth phase (9-fold) and the highest levels in metastatic melanoma (10-fold), especially brain metastasis (12-fold) [88].

Heparanase aids invasion of tumor cells into the brain architecture by degrading extracellular matrix components and basement membranes during colonization. When the effects of heparanase on invasion of B16B15b murine melanoma cells were investigated in a brain slice model, recombinant heparanase treatment increased invasion in a dose-dependent manner, while pre-treatment with the specific inhibitor, suramin, blocked invasion [89]. These data suggest that heparanase degrades ECM and basement membranes, thereby compromising the structural integrity of the brain architecture, ultimately leading to invasion and metastatic spread.

Targeted inhibition of heparanase by microRNA-1258 (mir-1258) suppressed brain metastasis development in a hematogenous xenograft model of brain metastasis from breast cancer [90]. Mir-1258 binds to a conserved binding site in the 3′ UTR of heparanase and represses the enzyme's expression. Lentiviral expression of mir-1258 in brain-tropic 231-BR breast cancer cells resulted in 4-fold fewer brain metastases in a hematogenous mouse xenograft model. It should be noted that mir-1258 is not a specific inhibitor of heparanase, as it is known to regulate the expression of other key proteins important to metastasis development, such as COX-2, MMP-9 and EGFR.

In addition to heparanase's role in invasion, the enzyme has known functions that could potentially affect brain metastasis development at multiple steps, including shedding from primary tumors by increasing microvessel density (reviewed by [91]), evasion of immune response by removal of HS-bound cell surface proteoglycans [92], upregulation of Akt survival signaling [93, 94] and by stimulating angiogenesis [95, 96].

Because of its multifaceted role in the metastatic cascade, heparanase is currently being pursued both as a marker [97] and molecular target of metastatic spread. A number of targeted approaches against heparanase are under investigation, including small molecules, sugar inhibitors, and heparins [98] as well as natural product inhibitors and neutralizing antibodies.

3.8 TGFβ

Originally described as an inhibitor of malignant transformation, Transforming Growth Factor β (TGFβ) is now understood to serve as both a tumor suppressor and an oncogene depending upon the context of activation [99]. Three isoforms of TGFβ have been identified in human cells and these are known as TGFβ1, 2, and 3. To induce signaling, TGFβ binds to a heterodimeric complex of two serine/threonine receptors known as TGFRβI and TGFRβII. To date, 7 TGFRβI and 5 TGFRβII receptors have been identified in the human genome [100]. A third receptor, either endoglin or betaglycan, has also been identified and appears to assist in ligand binding. Betaglycan promotes TGFβ2 binding to the receptor whereas Endoglin binds

TGFβ1 and 2 [100]. Two Endoglin isoforms have been identified – Endoglin Long (L-End) which can bind TGFβ and Endoglin Short (S-End) which cannot bind TGFβ [100]. Following ligand binding, the receptors induce phosphorylation of Smad2 and Smad3, which can then heterodimerize with Smad4 and translocate to the nucleus thereby regulating gene expression [101, 102]. TGFβ signaling has also been shown to act independently of the Smad proteins and signal through common signaling mediators such as PI3K/AKT, Ras/ERK, and Src [101, 102]. Although much remains to be elucidated, research indicates that TGFβ may promote brain metastatic growth.

Using two brain metastatic melanoma cell lines, B16-BL6 and K-1735, Zhang et al. demonstrated that TGFβ2 promotes the development of parenchymal brain metastases. The K-1735 cells produced metastases only in the brain parenchyma following injection in the intracarotid artery whereas the B16-BL6 cells produced only leptomeningeal and ventricle metastases. When secreted TGFβ2 was measured, over 50 pg/ml was detected in the K-1735 cells whereas the protein was undetectable in the B16-BL6. Following intracarotid injection of B16-BL6 cells overexpressing TGFβ2, mice began to develop parenchymal metastases. Decreasing TGFβ2 expression by approximately 5-fold in the K-1735 cells resulted in a significant reduction in brain metastasis development and an increase in overall survival. Interestingly, decreasing TGFβ2 did not induce leptomeningeal or ventricle metastases in the K-1735 cell line [103]. Taken together, these results suggest TGFβ2 may be important in the development of parenchymal metastases.

Further implicating the TGFβ-mediated signaling pathway in the development of brain metastases, Oxmann et al. found an approximately 100-fold increase in Endoglin RNA expression in the brain metastatic 231-BR cells relative to the parental 231-P cells. Confirming these results, protein levels were undetectable in the 231-P cells whereas the brain metastatic 231-BR cells expressed substantial amounts of Endoglin protein. When both the L-End and S-End were exogenously overexpressed in parental 231-P cells, only overexpression of the TGFβ-binding L-End resulted in increased TGFβ1-dependent invasion phenotypes *in vitro*. Consistent with a role of Endoglin in tumor cell invasion, when cancer cell spheroids were incubated on brain slices, the L-End overexpressing 231-P cells remained attached to the neuronal tissue and invaded into the slices whereas the control 231-P cells dissociated from the slice [104].

Currently, a number of large and small molecule inhibitors to target TGFβ are in clinical development [106]. However, to date, no targeted TGFβ therapies have been shown to be BBB permeable or tested preclinically in brain metastases.

4 Conclusions

Brain metastases appear as a devastating final event in the progression of cancer. Not only do they affect physical functions of patients but they also induce severe cognitive impairments. Brain metastases are expected to increase in incidence as chemotherapies improve and lead to better systemic disease control. This chapter

largely summarized studies on brain metastases from breast cancer, lung cancer and melanoma, as those primary tumors are the major contributors of brain metastasis cases. However, it is noteworthy to mention that the rise in brain metastasis incidence is now also observed in various cancer types such as renal cell carcinoma, prostate and gastrointestinal cancer [106–108], as systemic treatments prolong patient life span.

Basic and translational research, supported in some cases by clinical observations, reveal important underpinnings of the brain metastatic process. However, despite those advances, a better understanding of the mechanism underlying brain metastatic progression and its interaction with the brain microenvironment is needed to develop efficient therapies. The brain offers a unique microenvironment in which the BBB appears as a major obstacle for drug delivery. Therefore, deciphering the mechanism of BBB permeability is one of the priorities of the field. Meanwhile, preventive approaches for the development or the progression of brain metastases seem the more immediate possibility for clinical application. Close collaboration between researchers and medical oncologists will be needed to address these challenges brought on by this growing and incurable disease.

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Chapter 3
The Brain Microenvironment

Mami Noda

Abstract The incidence of brain metastasis is increasing, however, little is known about the molecular mechanisms responsible for metastasis of peripheral tumor cells and their colonization of the brain. After tumor cells metastasize to the brain, they encounter a completely different microenvironment from that in the periphery. The interactions between tumor cells and glial cells, mainly astrocytes and microglia, including soluble factors released from these cells, are still under investigation. However this knowledge will contribute to understanding the mechanisms of cell-cell interactions in the brain and identify possible therapeutic targets on resident brain cells that could effect brain metastasis formation and treatment. In addition to the complex interactions between metastatic tumor cells and the brain's resident cells, factors from endothelial cells and endogenous plasma factors also affect the blood-brain barrier and may change tumor cell characteristics. Therefore the totality of the brain microenvironment must be considered. The cell types and soluble factors that contribute to the brain microenvironment surrounding metastatic tumor cells are discussed herein.

1 Introduction

In the metastatic process, the microenvironment of the metastatic site plays an important role in tumor cells invasion and proliferation in the target tissues [1]. Such a microenvironment contains many resident cell types in addition to tumor cells as

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well as migratory hematopoietic cells. In the brain or central nervous system (CNS) the microenvironment is composed of neurons and glial cells (microglia, astrocytes, and oligodendrocytes). Endothelial cells and pericytes that compose the blood-brain barrier (BBB) are also present.

In the CNS, activated glial cells contribute to the innate immune response and produce a large variety of different inflammatory mediators as a chronic inflammatory reaction [2]. A similar mechanism could function in mediating tumor cell survival, proliferation and colonization, and invasion and motility in the microenvironment of brain metastases [3, 4]. The involvement of brain-resident and infiltrating cells in the pathology of primary and metastatic brain tumors is poorly understood. Therefore, a better understanding of the tumor microenvironment in the brain and interactions between each cell type is necessary. Accordingly, some of the known interactions between metastatic tumor cells in the brain and different stromal cells were already described [5]. These understandings and additional information would be expected to contribute to the development of improved therapies for brain metastasis that are urgently needed due to poor treatment options for these malignancies.

Experimental models of brain metastasis will aid in our study of the brain as a microenvironment to support metastatic growth (see Chap. 2 for a discussion of experimental models of brain metastasis). In brain metastasis mouse models using human lung cancer cell lines, tumor cells metastasized to whole regions of the brain. At 3 weeks after the inoculation of tumor cells into the cardiac ventricle, metastatic foci were found in midbrain-lateral cortex (Noda, unpublished observation). At 4–6 weeks, metastatic foci of various sizes were found throughout the brain. It is important to understand the interactions between invaded tumor cells and resident brain cells to understand how tumor cells grow and rapidly colonize the brain. Similar results were seen with breast cancer brain metastasis models [4, 6]. Further, this understanding could help prevent the growth of metastatic tumors in the brain. In this chapter, cell types in the brain are defined, pathology of invaded tumor cells and surrounding cells are described and the interactions between tumor cells and individual resident brain cells are discussed.

2 Cell Types in the Brain

2.1 Neurons

Neurons are the fundamental cells in the brain and all other cells are mainly devoted to the support of neurons. This traditional concept is, however, only partially correct under certain physiological condition, especially from a synaptic point of view [7]. Under many pathological conditions, including brain metastases, neurons are damaged and destined to die, leading to neuronal loss. The fate of damaged neurons is controlled by interactions between the metastatic tumor cells and neuron-supporting cells, mainly glial cells.

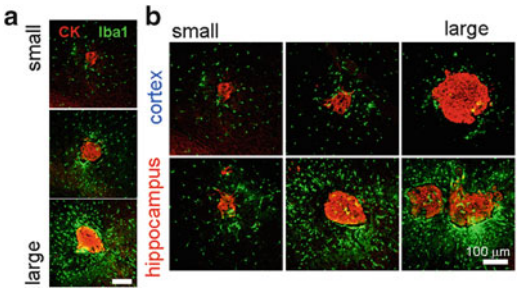

Fig. 3.1 In a mouse xenograft model of brain metastasis, microglia accumulate around lung cancer cells in the brain parenchyma. (**a**) Typical example of microgliosis (*green*) around the tumor (*red*), and microglia accumulate in relation to the size of the metastatic foci. *Red*; cytokeratin. *Green*; Iba1. (**b**) Typical example showing that more microglia accumulated around metastatic foci in the hippocampus than in the cerebral cortex. Staining antibodies the same as in (a) (Reproduced from Noda et al. 2009)

2.2 *Microglia*

In the brain, microglial cells are considered as the pathologic response element [8–10]. They are sometimes referred to as the macrophage of the brain, however, when the brain is damaged, blood monocyte-derived macrophages are also present [11, 12]. Microglial cells are dispersed throughout the entire CNS, exhibiting a ramified morphology under normal conditions, and their physiological role is gradually becoming unveiled [13]. Recently it was shown that microglial processes are highly dynamic in the intact brain, suggesting that microglial cells scan the brain parenchyma with their processes and potentially shield it from injury [14, 15]. Under pathologic conditions such as a lesion (traumatic brain injury), stroke, neurodegenerative disorder or tumor cell invasion, activated microglia migrate rapidly to the affected site of the CNS. At the same time, microglial activation is accompanied by the release of immunocompetent molecules such as cytokines or chemokines, and other molecules such as growth factors [16].

In brain metastasis mouse models, bigger metastatic foci attracted increased numbers of microglia (Fig. 3.1a). Though the incidence of brain metastasis was different in each mouse, the highest incidence was generally observed in the cerebral cortex and the hippocampus [17]. In the cerebral cortex, less activated microglia were often observed around large metastatic foci (Fig. 3.1b), the reason for this is being still interrogated.

2.3 *Astrocytes*

Among the glial cells, astrocytes are the characteristically star-shaped cells in the brain and are the most abundant glial cell population. Astrocytes play an important role in maintaining homeostasis of the brain [18], including biochemical support of

endothelial cells that form the BBB, provision of nutrients to the nervous tissue, maintenance of extracellular ion balance, and they also play a role in the repair and scarring process of the brain and spinal cord following traumatic injuries. Recently, the function of astrocytes has been reconsidered, and they are now thought to play a number of active roles in the brain as well, including the secretion or absorption of neural transmitters and maintenance of the BBB [13]. Astrocytes, therefore, may be considered one of the most influential cell types in the brain, and they interact with metastatic tumor cells. In brain metastasis mouse models using lung cancer cells, glial fibrillary acidic protein (GFAP)-positive astrocytes, so-called "activated astrocytes", accumulated according to the size of the metastatic tumor [19]. Similarly, accumulation of astrocytes around brain metastases was also observed in surgical specimens from breast cancer patient craniotomies [4] and autopsy cases from a number of primary tumor types [20]. These observations suggest that astrocytes may be essential to metastatic tumor cells in the microenvironment of brain metastases.

2.4 Oligodendrocytes

The main function of oligodendrocytes in the brain is the insulation of axons (the long projection of nerve cells) [21]. The same function is performed by Schwann cells in the peripheral nervous system. This functional importance is obvious in myelination. Although the role of oligodendrocytes in pathology is unclear, it is suggested that they may participate at an early stage in amyotrophic lateral sclerosis [22]. The role of oligodendrocytes in brain metastasis is unknown.

2.5 Pericytes

Pericytes are specifically located surrounding the endothelial cell layer of the capillary network in the brain. Pericytes play an integral role in the maintenance of the BBB as well as several other homeostatic and hemostatic functions of the brain [23]. These cells regulate capillary blood flow and BBB permeability, and are responsible for clearance and phagocytosis of cellular debris. Pericytes are also a key component of the neurovascular unit, which includes astrocytes and neurons as well as endothelial cells [24]. Recent studies suggest that pericytes in the CNS are bone marrow derived, although a respective precursor still remains enigmatic [25]. It has also been revealed recently that a lack of pericytes in the CNS can cause a breakdown of the BBB and lead to other degenerative changes in the brain [23, 26, 27]. As well as leakage of neurotoxins due to pericyte dysfunction and BBB breakdown, a role for pericytes in limiting tumor cell metastasis was demonstrated [28].

3 Cancer Stem Cells

Neoplastic clones are maintained exclusively by a rare fraction of cells with stem-like properties, known as cancer stem cells. It is believed that tumors grow from a type of "cancer stem cell" that gives rise to other cancerous cells and the identification of brain tumor initiating cells provided insight into human brain tumor pathogenesis, giving strong support for the cancer stem cell hypothesis as the basis for many solid tumors [29]. The role of cancer stem cells in the organ tropism of breast cancer metastasis as well as brain tumors was recently reported [30]. Additionally, Calabrese et al., reported the existence of a perivascular niche for brain tumor stem cells [31] and it is tempting to speculate that this niche in the microenvironment may also exist for metastatic tumor cells in the brain. Therefore, a better understanding of the interactions between cancer stem cells in invading tumor cell populations in the brain and other organs is essential for the development of novel therapeutic targets for metastatic disease. However, an in depth discussion of this is beyond the scope of this chapter.

4 Interactions Between Cell Types

4.1 Metastatic Tumor Cell-Neuron Interactions

The neuronal network in the brain has a highly compact framework devoid of large amounts of extracellular space thus the presence of a growing metastatic lesion is thought to cause neuronal damage and death as it displaces this network. Direct interactions between metastatic cells and neurons have not been fully elucidated, and whether the damage to neurons is the result of direct cell-to-cell contact or the result of toxic soluble factors secreted by tumor cells is not known. In a model on lung cancer brain metastases, a correlation was observed between the size of the metastatic lesion that was present and a vacant area of brain surrounding the lesion, suggesting neuronal loss in the brain (Noda, unpublished data). Using an intracranial implantation model with breast cancer cells, neuronal death was quantified by the identification of Fluorojade-B positive neurons [32]. The injection of the breast cancer cells induced a 15-fold increase in neuronal damage compare to a saline control injection [32]. Similarly, *in vitro* co-culture of primary neurons with lung tumor cells or addition of conditioned medium of lung tumor cells showed that tumor cells released factors that were toxic for neurons. The addition of the lung tumor cells inhibited the survival of primary cultured neurons depending on the number of tumor cells (Fig. 3.2). When the number of lung tumor cells was five times of that of neurons (T5 in Fig. 3.2a), the number of neuronal cells decreased to almost 50%. Importantly, tumor cell-induced neuronal damage may be responsible for cognitive symptoms experienced by some brain metastasis patients.

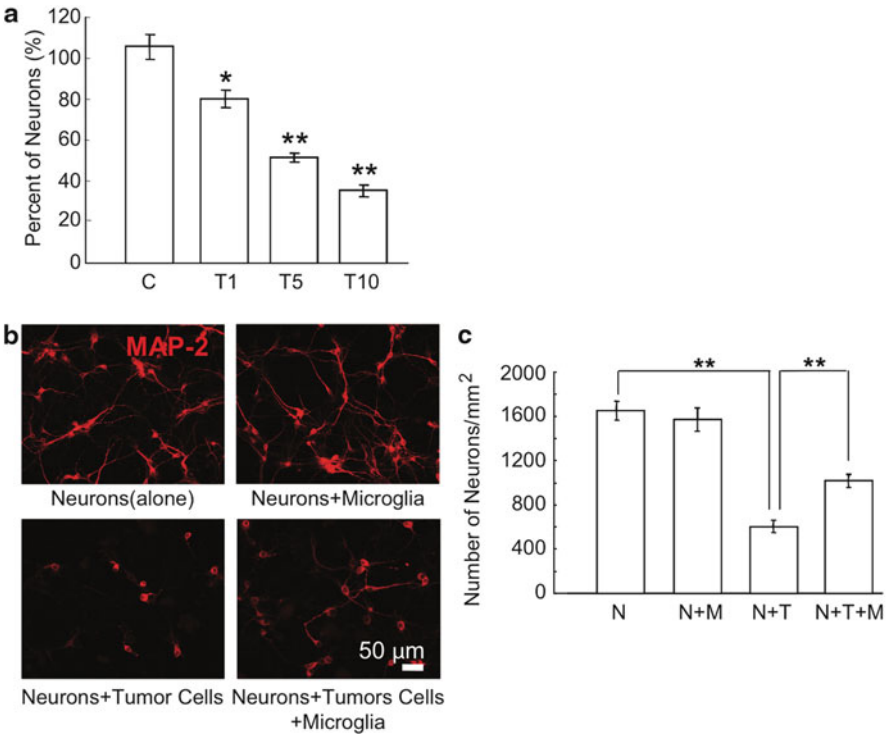

Fig. 3.2 The influence of microglia on the interactions between tumor cells and neurons. (**a**) Lung tumor cells inhibited neuronal survival in a dose-dependent manner *in vitro*. C; no tumor cells. T1; equal amounts of tumor cells and neurons. T5; Fivefold the number of tumor cells compared to neurons. T10; Tenfold the number of tumor cells compared to neurons. (**b**) Primary cultured neurons from mouse cerebral cortex (*top left*) were co-culture with tumor cells without microglia (*bottom left*) or with microglia (*top right*) and microglia and tumor cells (*bottom right*). Neurons are seen as MAP2 -positive red staining cells. (**c**) Number of neurons present in each culture from (b). Neurons were counted in 4–7 images per condition. *$p<0.05$, **$p<0.01$. *N* neurons, *T* tumor cells, *M* microglia (Modified from Noda et al. 2009)

4.2 Metastatic Tumor Cell-Microglia Interactions

The importance of microglia in the brain necessitates that these cells would interact with invading metastatic tumor cells. In 3 experimental models of brain metastasis, activated microglia were seen surrounding single or small clusters of tumor cells just 7 days after the tumor cells were injected into the circulation [33]. Exactly what the microglia is doing at the metastatic site is still under investigation. In *in vitro* co-culture experiments with lung cancer cells and microglia or just by the addition of microglial conditioned medium to the lung cancer cells, tumor cell proliferation was significantly inhibited by unknown microglial factors [17].

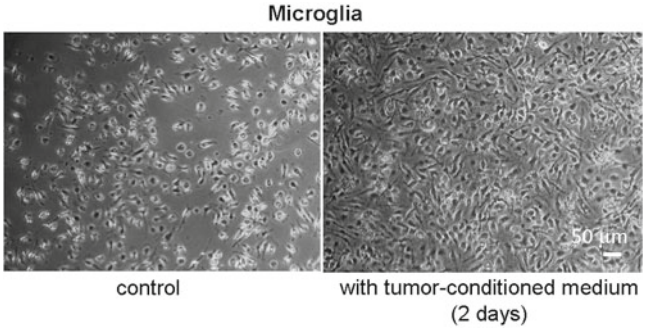

Fig. 3.3 Cultured mouse microglia with or without tumor-conditioned medium. Microglial cell were seeded on 35 mm dish at 8×10^5 cells/dish and were cultured for 2 days after addition of medium (control) or tumor cell-conditioned medium

Importantly, no significant TUNEL staining was observed in the tumor cells exposed to microglial conditioned medium, while BrdU-positive cells decreased over time, this suggested that inhibition of tumor cell proliferation by microglial factors may due to cell-cycle arrest but not apoptosis [17]. In contrast, when breast cancer cells were grown in soft agar in the presence of microglia, colony formation was increased almost fivefold compared to breast cancer cells in soft agar alone [4]. These differing effects could be primary tumor cell type specific or result from experimental differences, such as purity of the microglial cultures, and should be further investigated.

Since microglia inhibited the proliferation of lung tumor cells, it could be hypothesized that microglia may rescue damaged neurons and promote their survival. The addition of microglia to neurons in the absence of tumor cells did not show any significant effect on the neurons (Fig. 3.2b, Neuron/microglia; N/M in Fig. 3.2c), assessed by counting MAP2 (microtubule-associated protein 2, a neuronal cell marker)-positive cells. However, when microglia were added to the co-culture of neurons with lung tumor cells (Fig. 3.2b, Neuron/tumor/microglia; N/T/M in Fig. 3.2c), the number of MAP2 positive cells present in the culture was significantly increased compared to the neurons cultured with the tumor cells in the absence of microglia (Fig. 3.2c, N/T/M vs N/T).

On the contrary, microglia exposed to tumor cell-conditioned medium appeared to have a stimulated morphology and increased proliferation (Fig. 3.3). This is not unexpected as the metastatic lesion is an insult in the brain and should trigger a host cell response. In line with this, as noted above, when neurons were cultured with tumor cells and microglia, the microglia appeared to support neuronal cell viability (Fig. 3.2). This suggests that microglia, at least *in vitro*, serve in their immune cell function rescuing neurons from harm. These results indicate that there are not only cell-cell interactions but also complex multi-cell interactions at play in the presence of a metastatic lesion in the brain.

4.3 Metastatic Tumor Cell-Astrocyte Interactions

Since astrocytes, in conjunction with microglia, play a critical role in neuronal cell survival, it has been postulated that they can also support tumor cell survival in the brain. Activated astrocytes produce a number of inflammatory cytokines. IL-1, one such inflammatory cytokine, has been shown to stimulate the growth of tumor cells in hepatic and/or lung metastases of melanoma cells *in vivo* [34–36]. *In vitro,* astrocytes through secretion of IL-6, TGF-β and/or IGF stimulated the growth of a breast cancer cell line, which was derived from a brain metastasis [37]. In brain metastasis of melanoma, it was reported that astrocytes produce neurotrophin-regulated heparanase which was shown to increase tumor cell invasion [38, 39].

Using lung tumor cells, astrocytes were activated by tumor cell-oriented factors; MIF, IL-8 and PAI-1. These activated astrocytes then produced IL-6, TNF-α and IL-1β, which in turn promoted tumor cell proliferation. The addition of mouse recombinant IL-6, TNF-α and IL-1β to human lung cancer cells mimicked the effects of activated astrocytes [19]. Semi-quantitative immunocytochemistry showed that expression of receptors for IL-6 and its subunits gp130 on human lung cancer cells were up-regulated with time, while receptors for TNF-α and IL-1β were down-regulated after co-culture with astrocytes. These results suggest that astrocyte-derived inflammatory cytokines and their receptors, especially IL-6 receptors, may have an important role on the development of metastatic lesions in the brain and therefore might be therapeutic targets in brain metastases of lung cancer and other cancers.

Aside from those mentioned above astrocytes have been also been shown to produce IL-3, TNF-α, TGF-β, IGF-1 and PDGF [40–43]. Among them, it was suggested that IL-6, TGF-β and IGF-1 may contribute to the development of brain metastasis by breast cancer cells [37].

In the human brain, an immunohistochemical study was conducted on the peritumoral gliosis which is produced around hematogenous metastases. Eighty-five percent of the cases with metastases showed expression of endothelin-like immunoreactivity in the peritumoral astrocytes. Activation of microglial cells was another frequent and widespread glial cell alteration around the metastases [20]. Recently, it was also reported that co-culture of human breast cancer cells or lung cancer cells with murine astrocytes (but not murine fibroblasts) led to the up-regulation of survival genes, including GSTA5, BCL2L1, and TWIST1, in the tumor cells [44].

Astrocytes not only interact with and affect tumor cells at the site of metastatic growth, they also interact with microglia and neurons at the site. Activated astrocytes express glial cell line-derived neurotrophic factor (GDNF) followed by releasing of TNF-α and IL-1β by astrocytes then promotes the survival and growth of dopaminergic neurons [45]. Cultured astrocytes activated by lung tumor cells also express GDNF (Noda et al., unpublished data). Though which factors released from activated astrocytes are responsible is unknown, these factors attenuated microglial-tumor cell interactions and tumor cell proliferation showed less inhibition with microglia-astrocyte co-culture medium than that with microglia-conditioned medium alone

(Noda et al., unpublished data). There results suggest that there are complicated cell-cell interaction between tumor cells and glial cells that remain to be fully understood.

5 Soluble Factors in the Brain Microenvironment

In addition to cell-cell interactions and the soluble factors mentioned above, numerous other soluble factors have been shown to play a role in influencing metastatic tumor growth in the brain microenvironment. Bradykinin, a plasma protein, has been shown to be involved in tumor metastasis by increasing BBB permeability mediated by adenosine 5'-triphosphate-sensitive potassium channel [46] and TNF-α [47], or blood-tumor barrier permeability [48]. It was suggested that bradykinin, acting via bradykinin-2 receptors (B2R), acts as an important signal for directing the invasion of glioma cells toward blood vessels [49]. These results suggest that not only brain tumor cells but also invaded peripheral tumor cells may show increased chemotaxis in the brain. Therefore, clinically approved B2R antagonists could be used as anti-invasive drugs in the future.

Recently, the cytokine pigment epithelium-derived factor (PEDF) was shown to affect both metastatic tumor cells in the brain and neurons [32]. PEDF is a secreted factor that was down regulated in a cohort of human breast cancer brain metastasis specimens compared to unlinked primary tumors [50]. When breast cancer cells were forced to overexpress PEDF and implanted into the brains of nude mice, PEDF expressing tumor cells showed increased apoptosis compared to control cells. Additionally, when the amount of neuronal damage surrounding the implanted cells was quantified by fluorojade B staining, there was a 3.5-fold decrease in damaged neurons surrounding the PEDF expressing cells compared to the control cells [32]. These data suggest that restoring the expression of PEDF in metastatic tumor cells might limit their spread. Additionally, PEDF peptides, if delivered to the brain, might help alleviate neuronal damage and thus cognitive symptoms in brain metastasis patients.

6 Summary

Figure 3.4 illustrates the cell-cell interactions and their effects discussed herein. Much of what was discussed has only been elucidated in the last decade and we still have much to learn about the brain microenvironment during metastatic tumor cell colonization and growth. Interestingly, competitive cross-species hybridization of microarray experiments showed that the brain microenvironment induces complete reprogramming of metastasized cancer cells residing there, resulting in a gain of neuronal cell characteristics and mimicking neurogenesis during development [51]. This suggests that identifying target molecules on tumor cells that could restrict these characteristic changes would be a useful strategy to prevent brain metastasis in the future.

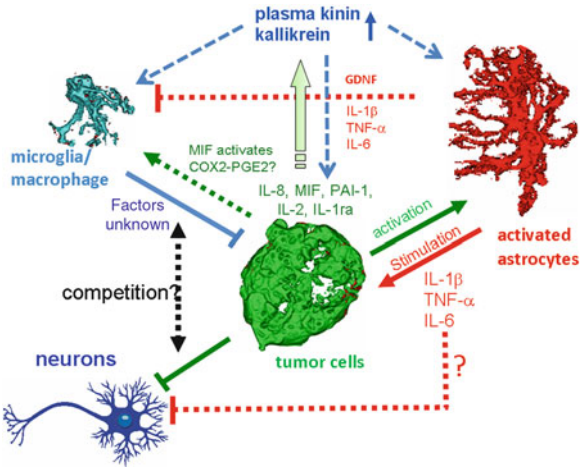

Fig. 3.4 Proposed schema for neuron-glia-tumor cell interactions. Microglial cells release soluble factors that suppress the proliferation of tumor cells by inducing cell-cycle arrest. Tumor cells, in turn, release soluble factors that activate astrocytes and suppress neuronal survival. Astrocytes are also involved in the regulation of tumor cell proliferation by the release of various soluble factors. Astrocytes may interact with microglia and neurons surround the metastatic lesion. In addition, plasma kinin and kallikrein increase blood-brain and blood-tumor permeability and may influence resident brain cells, too. *Arrows* indicate activation or stimulation and *dotted lines* are speculated signaling interactions

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Chapter 4
Vascular Permeability Within Brain Metastases

Chris E. Adkins, Rajendar K. Mittapalli, Kaci A. Bohn, Amit Bansal, Vinay K. Venishetty, and Paul R. Lockman

Abstract The vasculature within the normal brain is structurally unique compared to blood vessels found throughout the rest of the body. This unique structure highly regulates which molecules and or drugs can enter into brain tissue. However, when a brain metastasis is formed, the vasculature becomes compromised, and as a result is much more permissive in allowing molecules and or drugs to move from the blood into the brain metastasis. Quantifying these changes allow significant insight into the ability of chemotherapeutics to penetrate into a brain metastasis. Herein, we discuss the vascular structural changes that are present within a brain metastasis, clinical and preclinical differences between observed permeability in a primary tumor and a metastasis, and lastly the most common methods to determine permeability changes within a central lesion.

1 Blood–Brain Barrier

The blood–brain barrier (BBB) is a unique vascular interface which restricts the blood to brain paracellular diffusion of numerous drugs [1, 2]. A hallmark structural feature of the BBB is the near complete sealing of the luminal vascular endothelial cells by tight junction protein complexes (Fig. 4.1). These complexes are made up of multiple integral membrane proteins; including claudins 3, 5, and 12, zona occludins-1,-2, and -3 [3], occludin, and intercellular junctional adhesion molecules [4]. The sealing of the luminal endothelial cells of the BBB is so effective that transendothelial electrical resistance is orders of magnitude higher than peripheral

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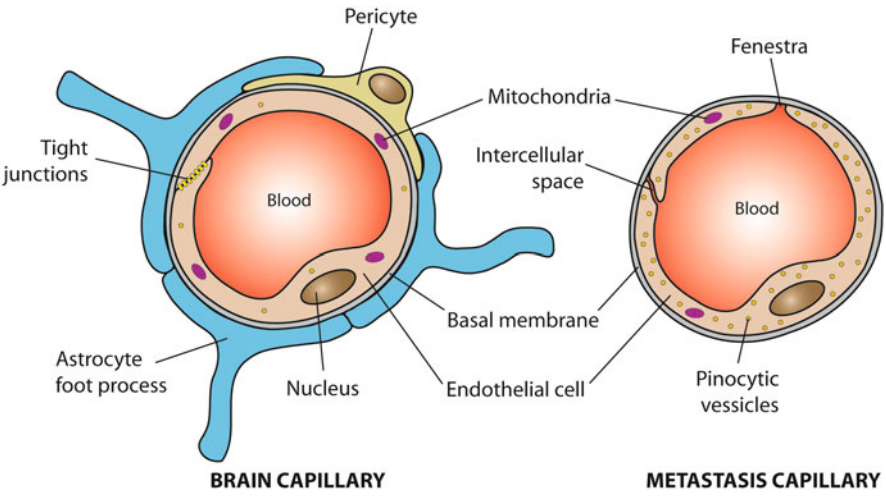

Fig. 4.1 Cartoon illustrating the blood–brain barrier versus the blood-tumor barrier. A major structural difference between the two vessels is the decreased expression of tight junction proteins, which leads to an incomplete sealing of the metastatic vasculature, and an increased permeability of the lesion

capillaries [5]. Further, unlike peripheral capillaries, brain capillaries are distinguished by their lack of fenestrations [1, 2] and low pinocytic activity. The net effect is that in order for a drug to gain access to the central nervous system (CNS) it must dissolve or diffuse through the endothelial cell membrane or utilize a transport protein mechanism [2, 6]. In addition to the endothelial cells, astrocytic foot processes, pericytes, and neuronal input further restricts paracellular diffusion of polar and or large molecules between the blood and brain [7–9].

To complement the physical barriers of the BBB, there are numerous efflux transporters and enzymatic proteins that are highly expressed in the BBB vascular endothelia, which also constrain the entry of molecules into brain parenchyma [10–12]. Numerous chemotherapeutics, including paclitaxel and doxorubicin, are subject to active efflux transport mechanisms including p-glycoprotein, breast cancer resistance protein and the family of multi-drug resistance proteins [13, 14]. Similarly, the BBB is rich in numerous enzymes (e.g., phosphatases), which cause biotransformation or inactivation of several molecules including peptides and neuropeptides [15–17] as they attempt to cross the BBB into the brain parenchyma.

While there are significant restrictions at the BBB that limit brain access for drugs, there are pathways that can facilitate brain penetration. The BBB richly expresses a number of influx transporters (receptor mediated, facilitated and active carrier mediated systems) that selectively move needed nutrients into the brain from the vasculature. For example, essential small molecule nutrients such as glucose (*GLUT1*) and amino acids (*LAT*, cationic amino acid transporter, lactate transporter) utilize carrier mediated transporters to enter into brain parenchyma. These compounds would normally have significantly restricted brain entry because of their

polarity [18]. Large endogenous molecules use receptor mediated endocytosis mechanisms to enter brain. For example, insulin is transported by the insulin receptor [19], iron utilizes the transferrin receptor [20], both of which are highly expressed in the capillary endothelium.

2 Blood-Tumor Barrier

2.1 Functional Changes

While the BBB serves as a structural and functional barrier to limit passive diffusion of hydrophilic and charged compounds into brain [21], the presence of an intracranial metastasis alters the vascular integrity both within and around the lesion. These blood vessels (blood-tumor barrier; BTB) compared to the normal BBB, generally have increased permeability, reduced blood flow [22–24] and an increased or decreased expression of influx or efflux transporters.

The changes in BTB vascular permeability are usually not homogenous throughout the lesion. It is generally accepted that if there is necrosis within the metastatic lesion it has highly permeable blood vessels [25]. In contrast, the blood vessels that are immediately adjacent to the lesion have permeability values that are similar to the normal BBB, or at most, permeability values that are somewhere between the normal BBB and the main body of the lesion [26–32]. Determining vascular permeability on the edge of the metastasis is critical, since this is the one of the main infiltrating and proliferating areas of the lesion.

Vascular permeability is also not homogenous between metastatic lesions in the same brain. Recently, we have demonstrated that permeability of brain metastases of breast cancer in two experimental model systems are highly heterogeneous, ranging nearly 30-fold between various lesions. A representative image of lesion permeability compared to normal brain is shown in Fig. 4.2. While nearly all lesions have some degree of increased permeability, permeability changes are typically less than 10-fold above normal brain (~80% of lesions). Similarly, permeability values within a single lesion are highly variable ranging from minimal changes to 30-fold. However, it is not clear that the areas of increased permeability are attributable to necrotic portions of the lesion. It is of interest to note, that for the ~2,000 preclinical metastatic lesions for which we have evaluated previously, there is not a clear correlation of increased permeability with increased lesion size [33, 34].

2.2 Structural Changes

The BTB is structurally different from the BBB, which may contribute to increased vascular permeability. A hallmark structural feature of the BBB is the sealing of the vascular endothelial cells with tight junction proteins. A primary protein in the tight

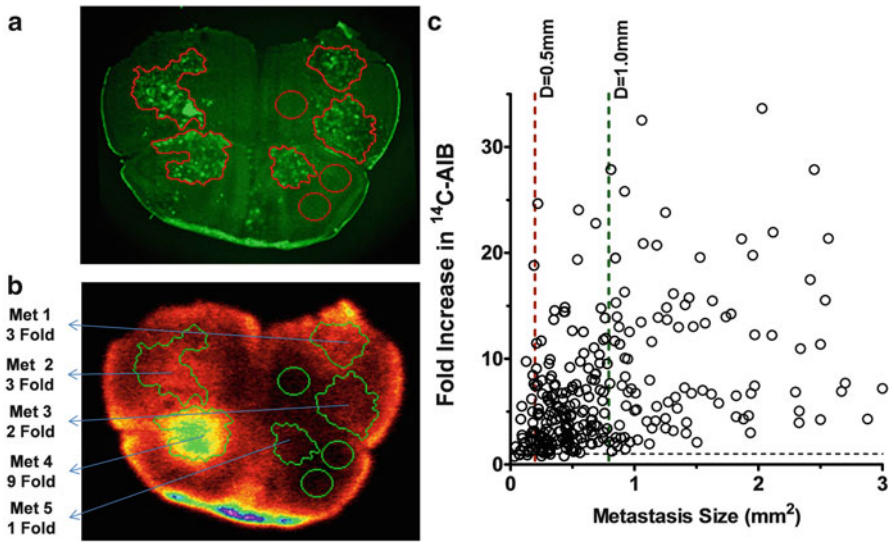

Fig. 4.2 (**a**) A representative image of a coronal brain slice from a mouse that has developed brain metastases of breast cancer. The metastatic lesions developed approximately 5 weeks after the intracardiac injection of 175,000 MDA-MB-231BR cells (brain seeking variant of the MDA-MB-231 cell line). (**b**) An representative autoradiography image showing brain and lesion accumulation (fold over normal brain) of ^{14}C-AIB (a small passive permeability marker). Note the variable permeability between lesions. (**c**) Quantitative analysis of the accumulation of ^{14}C-AIB in metastatic lesions ($n=285$) versus metastasis size (mm^2) shows there is no strong correlation ($r^2=0.11$). Diameter of the lesion is shown in *vertical lines*

junction complex is ZO-1, which acts as a scaffolding protein to anchor another tight junction protein, occludin, to the endothelial membrane [21, 35]. On the other hand, the vasculature within a primary brain tumor typically has reduced expression of tight junction proteins [36] which results in increased vascular permeability [37, 38]. While, there are numerous reasons for the decreased expression of tight junction proteins in the BTB, one primary hypothesis is that when cancer cells displace neurons and astrocytes, tight junction protein expression is reduced, or at a minimum incorrectly positioned within the cell [3]. However, there is little data on whether tight junction protein expression specifically within the vasculature of brain metastasis is decreased. In Fig. 4.3 we show evidence that the expression of ZO-1 is significantly decreased within metastatic lesions compared to the normal brain vasculature. Decreases in ZO-1 correlated to an increase in vascular permeability within preclinical models (data not shown).

A secondary issue that contributes to the increased permeability of the metastatic vasculature is the growth of new blood vessels within the lesion and the turnover of vascular endothelial cells. Within normal brain, the vascular endothelium is essentially a quiescent tissue where less than 0.01% of the cells are cycling at any one time [39]. Further, normal vascular endothelia strongly resist apoptosis, despite significant neuropathology [40–42]. Though, endothelium can replicate and repair

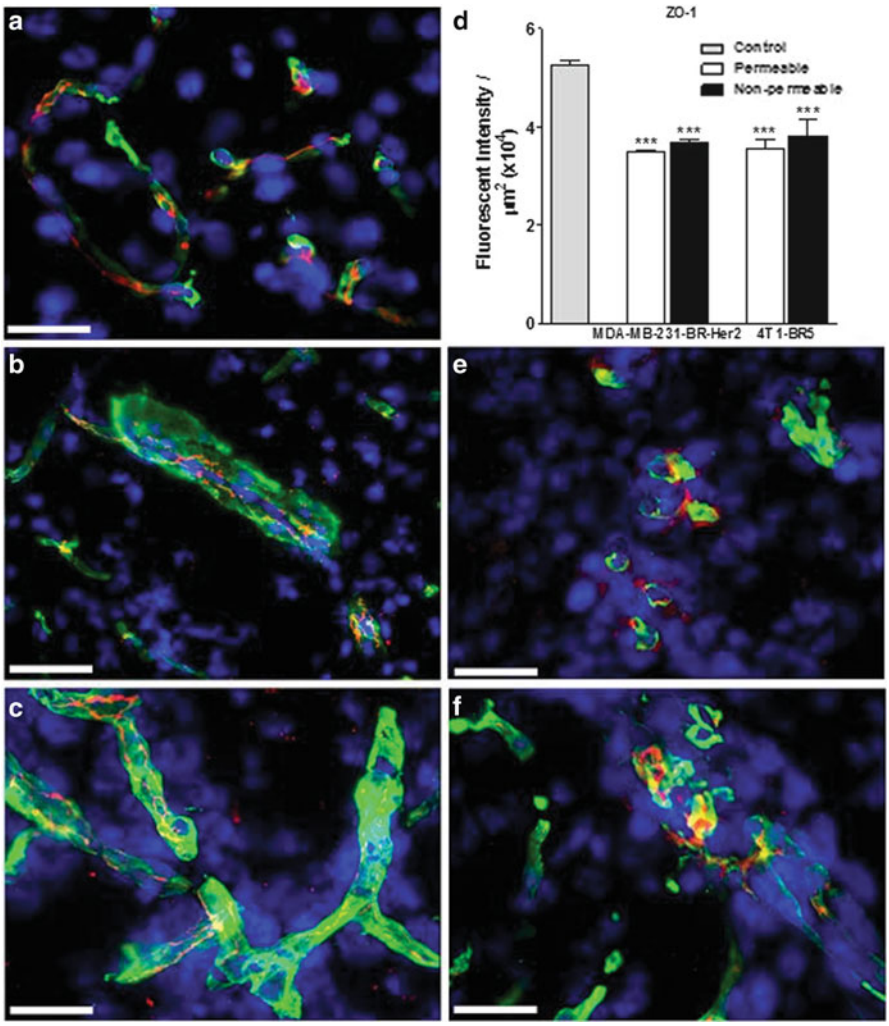

Fig. 4.3 Immunofluorescent analysis showing decreased ZO-1 expression in two metastatic models of breast cancer. ZO-1 (*red*), CD31 (*green*), and DAPI (*blue*). Vessels within normal brain (non-tumor region) are shown illustrating intense staining of ZO-1 (**a**). Representative images of non-permeable (**b** and **e**) and permeable (**c** and **f**) lesions of MDA-MB-231-BR-Her2 and 4T1-BR5 lesions, respectively. ZO-1 expression was decreased in all metastases compared to normal brain vasculature (**d**). Statistical significance was determined using ANOVA followed by Dunnett's post-test, $p < 0.05$. Scale bar = 25 μm

damaged blood vessels in the presence of vascular endothelial growth factor (VEGF; constitutively expressed in glial cells) [43]. In the presence of a developing metastasis there are areas within the lesion that become hypoxic as they grow beyond their blood supply. It is suggested [44] that the lesion will increase VEGF secretion to initiate new blood vessel formation (or elongate existing vessels) so

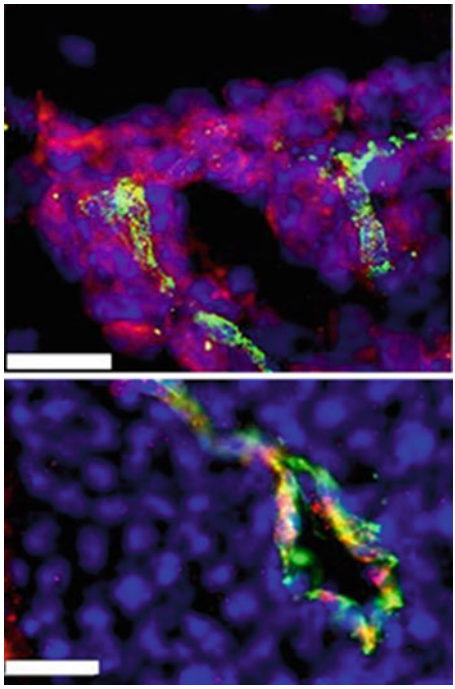

Fig. 4.4 Representative image showing the presence of VEGF (*red*) around the metastasis vasculature (*green*, CD31) in the preclinical brain metastases of breast cancer model (MDA-MB-231-BR-HER2) (*blue* is a nuclear stain; DAPI). Scale bar = 25 μm

that the lesion will obtain adequate oxygen and nutrient supplies (Fig. 4.4). The increased VEGF secretion results in the turnover of endothelial cells, the growth of new blood vessels [45] and ultimately an increase in permeability. But because VEGF secretion is so concentrated and immediate, the newly created vascular bed is often a tortuous vessel network that is largely ineffective with reduced blood flow.

Consistent with this we have observed that nestin, an intermediate filament protein that is expressed during cellular development has little expression in the mature brain vasculature [46], but is highly expressed in the newly formed vasculature in a preclinical model of brain metastases of breast cancer (Fig. 4.5). This is consistent with the up-regulated expression of nestin observed in newly formed vessels and proliferating endothelia in gliomas [47, 48].

3 Permeability Changes in Brain Metastases Compared to a Primary Tumor

A large body of literature exists for permeability studies of primary tumors within the brain, including: glioblastoma multiforme, astrocytomas, oligodendrogliomas, and meningiomas. Within these primary tumors there appear to be an approximate 200-fold difference between the permeability values across the various tumor types. For example, astrocytomas and oligodendrogliomas generally have low permeability and meningiomas and glioblastoma multiforme generally have much higher values [49].

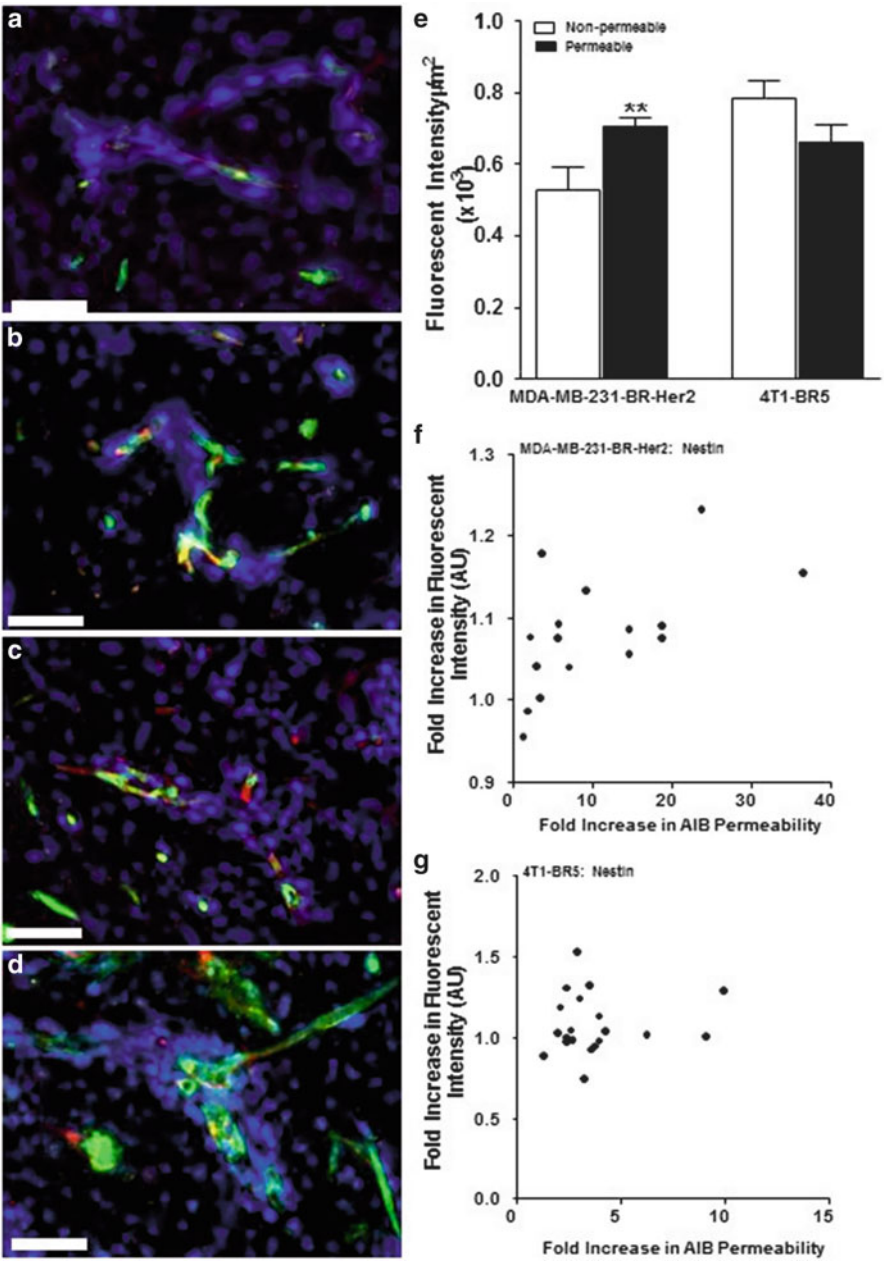

Fig. 4.5 Representative images are shown of non-permeable and permeable lesions in MDA-MB-231-BR-Her2 (**a** and **b**) and 4T1-BR5 lesions (**c** and **d**), respectively. Nestin expression (*red*) was co-localized with CD31 (*green*) within DAPI labeled lesions (*blue*). A 25% increase in nestin expression was seen in MDA-MB-231-BR-Her2 permeable lesions compared with non-permeable (**e**). No difference was seen in the 4T1-BR5 model. Plotting nestin expression versus fold increase in ^{14}C-AIB permeability revealed a correlation in the MDA-MB-231-BR-Her2 model ($r^2 = 0.33$, $p < 0.05$) (**f**) and no correlation in the 4T1-BR5 model ($r^2 = 0.011$, $p > 0.05$) (**g**). Statistical analysis was determined using student's t-test, $p < 0.05$. Scale bar = 50 μm

There are far fewer studies that directly evaluate the permeability of brain metastases compared to a primary tumor. To address this, we have begun to compare permeability values between studies of primary tumors and metastatic lesions. We admit these data are difficult to interpret and evaluate, because of the subtle and sometimes not so subtle differences in how the data was obtained. Given that caveat, we have recently evaluated two CT perfusion studies one of which appraised the permeability of a number of primary tumors (e.g., astrocytomas, glioblastoma multiforme, etc.…) and the other which calculated permeability of metastases from a number of different origins (lung, breast and melanoma). For the most part, the independent studies were identical in data acquisition and experimental parameters, with the exception of slight differences in milliamps and CT rotation speed. We observed that the permeability values (rPS_{max}) for metastases are generally 1/10th of the values that were observed in glioblastomas and anaplastic astrocytomas. However, the metastases values were very similar for those that were calculated for diffuse astrocytomas [49, 50]. A limitation should be noted, because the permeability values for all of the brain metastases were lumped into a single value, which makes dissecting out data for metastases of different origins difficult. Similarly, an MRI study which directly compared permeability values between glioblastoma multiforme and metastases, demonstrated that permeability of metastases are on average 65% of the values observed in the primary tumor. However, a limitation of this study was that there were seven different types of brain metastases evaluated (e.g., breast, lung, melanoma, etc.…), which may significantly conceal variability between the metastasis from different tissue types. Other groups have shown that a large fraction of brain metastases of breast cancer do not enhance with MRI [34].

While metastases generally exhibit reduced permeability compared to primary brain tumors, there can be considerable variation in permeability between metastatic lesions within the same brain. In an experimental brain metastases of breast cancer model, it was observed that only 20% of the lesions had significant increases in permeability (>10 fold over normal brain) and the remainder of the lesions (~75–80%) had only slight increases in permeability (~1.5 to 3-fold increases over normal brain) [33]. A perfusion CT study suggested that the variability may be related to changes in vascular endothelial proliferation (angiogenesis), where newly forming vessels in response to VEGF secretion, exhibit increased permeability compared to lesions that have less angiogenesis [51, 52]. Permeability variances can also be significant if one of the lesions has developed, or at a minimum progressed into the leptomeningial area. Lesions in this area will generally have significantly higher permeability values than lesions found solely in brain parenchymal tissue. The increased permeability may be influenced by the lesion being in contact with non-BBB vessels [53].

Lastly, there has been some controversy as to whether the size of the metastatic lesion correlates with an increased permeability. Some work has observed that larger, more compact metastases are generally more permeable than smaller and diffuse metastases [54, 55]. Similarly, a preclinical metastasis rat model using phase contrast MRI also correlated metastasis permeability to lesion size [52]. In contrast, our work using autoradiography [33] and others work using MRI [34] have shown in preclinical models, that permeability does not have a strong correlation (r^2 <0.2) to lesion size.

It is our opinion that there is a strong need for future work to directly compare the permeability changes in metastatic lesions of multiple origins (i.e., breast, melanoma, etc.) to the various primary tumors of the CNS. This work is needed to bridge the large database of permeability values for primary tumors to the much smaller database of brain metastases. This information will provide significant insight into clinical imaging studies as well as drug accumulation and effect.

4 Effect of Increased Permeability on Drug Accumulation and Effect in Brain Metastases

Unfortunately, there is only a small database which quantitatively describes correlations of vascular permeability to the extent of drug delivery and drug effect in brain metastases. It is generally assumed, and has been shown in some primary tumor models [11, 23, 45, 56], that increased BTB permeability results in increased drug distribution in the lesion, and subsequently increased chemotherapeutic effect. However, this view does not always account for other parameters, such as the magnitude of permeability changes, drug active efflux transport, protein binding, tissue binding and blood flow, all of which can significantly impact drug distribution into the lesion [23]. We [33] and others have shown standard chemotherapeutic agents (including paclitaxel and doxorubicin [57–60]) are limited from accumulating in brain metastases because the BBB remains partly intact within these lesions [11, 23, 61].

There are few reports that demonstrate whether restricted chemotherapeutic drug accumulation results in limited drug effect. To address this, we used two preclinical models of brain metastases of breast cancer [14, 33, 62] to simultaneously evaluate brain metastases in terms of permeability, drug uptake and drug effect. Among the ~1,600 lesions that we evaluated we observed that there was significant heterogeneity in terms of vascular permeability, where a good fraction (~80%) of the lesions exhibited a moderate (1.5–3.2 fold) increase in permeability over normal brain, and only a small subset (~20%) of lesions exhibited higher degrees of permeability (5–30 fold increased). Similarly, brain metastasis uptake of paclitaxel varied widely between metastases, but most lesions (80%) showed limited drug uptake of <10-fold above normal brain. When lesions exhibiting different levels of paclitaxel concentrations were assayed for drug induced cytotoxicity (cleaved caspase 3 staining), only a small subset (10%) of lesions with >50-fold drug uptake compared to normal brain showed staining for apoptosis [33]. This suggests the vasculature in brain metastases, while compromised, is intact enough to limit chemotherapeutic drug concentrations to amounts that are insufficient to induce cytotoxicity.

5 Methods to Study BBB/BTB Permeability

Historically, dyes have been integral in studying disruption of the BBB in various pathophysiology. For example, the accumulation of trypan blue in brain parenchyma after an intravenous administration, demonstrated that the BBB was disrupted by

ultrasonic damage in 1956 [63], which worsened in the presence of angiography imaging agents [64]. Dye accumulation within brain has also been seen in circulatory arrest with prolonged resuscitation [65], significant acute arterial hypertension [66], seizures [67, 68], and radiation [69].

It was recognized very early that vital dye studies were only qualitative. To overcome this, radiotracers such as ^{203}Hg were concurrently administered with dyes. This method provided an initial visualization of dye extravasation followed by quantitative measurement of BBB disruption [64, 69, 70]. It should be noted that these initial studies simultaneously injected two different tracers to demonstrate size selective openings at the BBB [64]. However, spatial resolution of dye distribution was lost.

Quantification of BBB disruption using autoradiography quickly became the gold standard [26] and has evolved into well-designed double or triple labeled studies where size dependent BBB permeability changes can be simultaneously measured [71, 72]. Though autoradiography does have limitations (two or three tracers require weeks to months of film development followed by the subtraction of multiple signals to obtain data [72]) it still can accurately quantify BBB disruption in brain or inctracranial tumor tissue at an ~25–50 μm pixel resolution [73].

5.1 *Kinetic Analysis of Permeability and/or Drug Uptake into Brain or Brain Metastases*

The gold standard in calculating BBB or BTB disruption in brain, and or lesions in the brain, is to use a mathematical model consisting of a multiple-time uptake approach [74, 75]. To accomplish this, the tracer's apparent terminal volume of distribution in brain and tumor [$V_{d(app)}$] at the time of sacrifice is calculated using the following relationship assuming negligible post-mortem tracer diffusion (brain removal and freezing in isopentane should occur in less than 60 s):

$$V_{d(app)} = \frac{C_{br}(\tau)}{C_{bl}(\tau)} \tag{4.1}$$

Where C_{br} is concentration of tracer in brain, C_{bl} is concentration of tracer in blood and t is sampling time. To measure the change of tracer concentration in brain over time in terms of uptake, and since C_{bl} is not constant with time, you use the following relationship with the assumption uptake is unidirectional over the time period sampled:

$$C_{br}(\tau) = K_{in}\left(\int_o^t C_{bl}(\tau)\, d\tau\right) \tag{4.2}$$

Where K_{in} is the unidirectional brain uptake coefficient of the tracer. You then solve for the integral of tracer plasma concentrations over time by sampling the concentration in blood in experimental animals and calculating the integral according to the equation:

$$\int_0^t C_{bl}(\tau)\, d\tau = \sum_{i-o}^{n-1} \frac{t_{i+1} - t_i}{2}(C_{bli} + C_{bli+1}) \tag{4.3}$$

Where C_{bl} is concentration of tracer in blood, n is the number of blood concentrations sampled in each experiment, and t is time.

Lastly, multiple-time uptake analysis allows the tracer to serve simultaneously as the permeability and vascular marker and therefore Eq. 4.4 is divided by the terminal blood concentration as previously described [26]:

$$\frac{C_{br}(\tau)}{C_{bl}(\tau)} = K_{in}\frac{\int_o^t C_{bl}(\tau)\,d\tau}{C_{bl}(\tau)} + V_i \tag{4.4}$$

Where V_i is the total vascular space or initial equilibrating space of the tracer in the brain vasculature (or bound to vascular endothelium) at the time of sacrifice.

However, given the heterogeneity in which is observed in metastatic lesions [33, 34, 62, 76], a single-time uptake may be used to measure K_{in} in individual animals, using the following equation [77, 78]:

$$K_{in} = \frac{C_{br}(\tau)}{\int_0^t C_{bl}(\tau)\,dt} \tag{4.5}$$

Where C_{br} is the amount of the compound in brain or tumor per unit mass of the tissue at the time t, and C_{bl} is the blood concentration of the compound.

6 Summary

The BBB serves a protective role in regulating the brain accumulation of numerous molecules, including many (if not most all) standard chemotherapeutics. One mechanism that limits drug accumulation at the BBB is the sealing of luminal endothelial cells together by tight junction proteins. However, tight junction protein expression is decreased in the vasculature of a metastatic lesion, which contributes to increased vascular permeability. While the vascular permeability of a metastasis is significantly higher than normal brain, it is on the lower end of permeability values for most primary tumors of the central nervous system. Unfortunately, the increased passive permeability of the vasculature of a metastasis is on average, well below what is needed to allow efficacious concentrations of chemotherapeutics to accumulate into the metastatic lesion.

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Chapter 5
Imaging Experimental Brain Metastases

Amanda M. Hamilton and Paula J. Foster

Abstract Studies of the metastatic process and potential cancer therapies have been advanced by the use of imaging technology that enables the noninvasive assessment of tumor development over time. Several imaging modalities have been used to examine brain metastases in preclinical cancer models. Magnetic resonance imaging (MRI) is the clinical gold standard for anatomical evaluation of brain metastases. New advances in MRI and MR spectroscopy (MRS) have now enabled physiological characteristics of tumors to be investigated including tumor permeability, vascularity, cellularity and metabolism as well as cerebral blood flow and blood volume. MRI can also be used to detect single iron-labeled cancer cells after their initial arrest in mouse brain and subsequent tumor development. Nuclear imaging techniques including positron emission tomography (PET) and single photon emission computed tomography (SPECT) are popular tools for classifying tumors and monitoring their treatment. Brain tumors can be assessed for biochemical alterations such as glucose use, DNA synthesis, amino acid transport and oxygenation state. Optical imaging techniques based on the use of fluorescent or bioluminescent reporters have been found advantageous for monitoring metastatic tumor burden in experimental animals. Fluorescent entities have further been used in intravital microscopy to track and monitor the relationship between tumor cells and brain vasculature, including cancer cell arrest, early extravasation, perpetuation of a perivascular position and either angiogenesis or vessel co-option. Finally, imaging studies of brain metastases are often improved by using multiple imaging techniques concurrently, thereby exploiting the best features of separate modalities to acquire multilayered information and provide further insights into the evolution of metastases.

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1 Introduction

Clinically, brain metastases are associated with poor prognosis and occur late in the progression of multiple common malignancies including lung cancer, breast cancer and melanoma [1]. Preclinical models of metastatic disease that epitomize the formation of tumors found in patients are important tools in the effort to find new detection, targeted treatment and prevention strategies. Studies of the metastatic process and potential therapies have been advanced by the use of imaging modalities that enable the noninvasive assessment of tumor development over time [2–5]. Imaging technology is ever advancing but techniques exist today that allow for the detection of individual cancer cells in the brain tissues and for the monitoring of brain metastases as they develop and change over time. A number of imaging modalities have been used to examine brain metastases in preclinical cancer models. These include optical techniques such as bioluminescence imaging [6] and fluorescence-based *in vivo* microscopy [5], nuclear imaging techniques such as positron emission tomography (PET) [2] and single photon emission computed tomography (SPECT) [7, 8] as well as magnetic resonance imaging (MRI) [4, 9–11]. Each of these modalities has advantages and limitations for *in vivo* imaging of experimental brain metastases. The choice of which imaging technology to use relies mainly on the stage of metastasis being studied, the spatial resolution and sensitivity required, the depth of the imaging target and the prospective for clinical translation. Imaging studies of brain metastases are often improved by utilizing multiple imaging techniques, thereby obtaining both anatomical and functional or metabolic information. This multimodality approach is already improving decision-making in clinical oncology [12].

2 Magnetic Resonance Imaging

For the clinical evaluation of brain metastases, MRI is currently the gold standard due to its ability to provide excellent anatomical detail, sensitivity for the determination of tumor size and location, as well as indications of edema, hemorrhage, necrosis and increased cranial pressure [13]. Current micro-MRI technology can achieve three-dimensional spatial resolutions on the order of tens of microns. MRI uses no ionizing radiation and is considered safe and noninvasive; subjects can be imaged repeatedly with no harm.

MRI relies on the properties of hydrogen atoms (protons) to generate an image. In MRI, protons within a subject are exposed to a strong magnetic field that causes them to align. A radiofrequency (RF) transmitter is temporarily turned on to energize the aligned protons. Once the RF is turned off the protons relax to their equilibrium state, emitting energy that produces a signal that can be detected and translated into an image by advanced computer processing. Protons in different tissues and biological states will relax at different rates and image contrast can be generated by exploiting these differences. Common image contrasts are known as T1-, T2-

and T2*-*weighted* images. Metastases may appear as either hypo- or hyper-intense regions relative to normal brain parenchyma [14].

Most brain MRI employs contrast agents to improve the signal differences between normal and diseased tissues. The most commonly used contrast agents are gadolinium (Gd) chelates. Typically T1-weighted images are acquired before and after the intravenous (iv) administration of Gd agents. Normally, Gd cannot cross an intact blood brain barrier (BBB). In the case where the BBB is damaged the presence of the Gd agent causes signal enhancement. Tumor-associated neovascularization is generally leaky and therefore brain metastases, for example, often appear bright in images acquired after iv Gd.

Several groups have used Gd enhanced MRI to evaluate the permeability of brain metastases in experimental rodent models [10, 15–18]. Percy and colleagues used contrast enhanced MRI to track the development of brain metastases due to breast cancer in nude mice [18]. They reported substantial heterogeneity in the permeability of these brain metastases. Many of the metastases became permeable with time, suggesting that over time they cause changes to the tumor vasculature that compromises the integrity of the BBB. At the last imaging timepoint there were approximately four times as many Gd permeable metastases as non-permeable. Gd-permeable metastases were significantly larger than non-permeable tumors, however, size alone was not sufficient to predict permeability (Fig. 5.1). The impermeability of the BBB hinders the delivery of chemotherapeutic agents to the brain, limiting the success of pharmacological approaches to treat brain metastases. The ability to use MRI to noninvasively assess the permeability status of brain metastases will be important for understanding the process of brain metastasis formation and for evaluating the development of BBB-permeable chemotherapeutic drugs.

Conventional contrast-enhanced MRI displays a single snapshot of tumor enhancement after contrast administration, although the anatomical information derived from such images is valuable, it lacks functional information. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), which relies on fast T1-weighted MRI sequences obtained before, during and after the rapid iv administration of a Gd based contrast agent is an imaging method to assess vascular permeability.

DCE-MRI has been used experimentally to investigate the vascularity of developing brain metastases [10, 16, 17]. Budde *et al.* used DCE-MRI to examine the vascular permeability in a rat model of metastatic breast cancer [6]. They showed that brain metastases had limited permeability of the BBB as assessed with DCE, whereas meningeal and bone metastases had high vascular permeability. Microscopically, brain metastases were highly infiltrative and grew through vessel co-option. By comparison tumors in the bone and meninges were solid masses with distinct tumor margins (Fig. 5.2). These results demonstrate that the microenvironment influences the growth patterns of metastases, and that these differences can be detected and measured by MRI. DCE-MRI could also be used to measure changes in vascular permeability that are induced by successful anti-angiogenic therapy.

Gd-enhanced MRI can also be used to measure regional cerebral blood flow and blood volume [19–21]. This is known as perfusion MRI and involves the iv administration of Gd and measurement of the T2*-weighted signal as it perfuses through

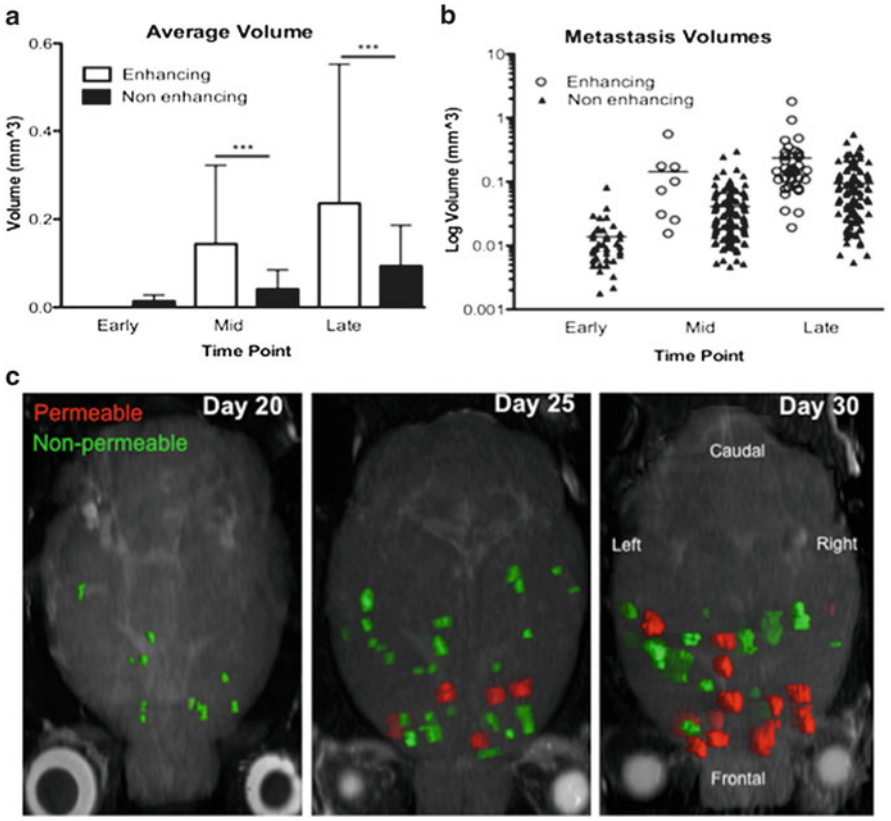

Fig. 5.1 Volume measurements of enhancing and nonenhancing metastases. (**a**). At both mid and late time points, the average volume of enhancing metastases was significantly larger than nonenhancing metastases ($P < 0.05$). However, there was a wide range of volumes for both enhancing and nonenhancing metastases (**b**). There also appeared to be a minimum volume threshold of enhancing metastases, although being larger than this did not guarantee enhancement. (**c**) 3D volume rendering of a mouse brain in the coronal plane, from the same mouse at each time point. Gadolinium-enhancing metastases are rendered in red and nonenhancing metastases are shown in green. Neither volume nor position in the brain appear to have an influence on whether a metastasis enhanced or not (Modified from Percy et al. 2011)

the brain tissue over a short period of time. Changes in blood flow over time after a single injection can be measured to generate a perfusion map that reflects local microvasculature [21]. High-grade gliomas and brain metastases can be differentiated by the peritumoral blood volume values. The higher relative cerebral blood volume measured for primary gliomas reflects the presence of infiltrating cells in the peritumoral edema of gliomas and the absence of these cells in the edema of metastatic lesions [19, 20].

Another class of MRI contrast agents that have been used to image experimental brain metastases is superparamagnetic iron oxide (SPIO) nanoparticles [15, 22].

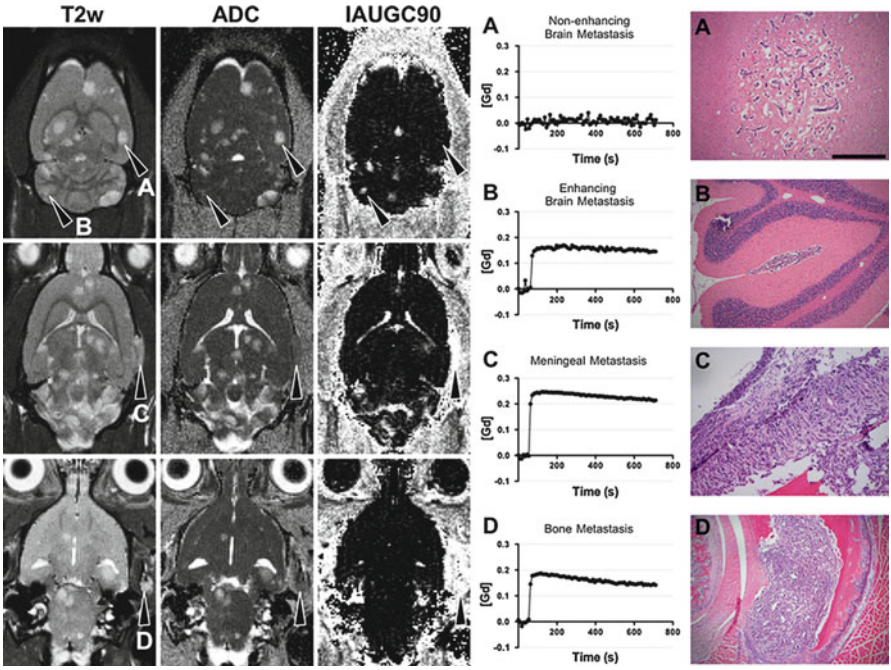

Fig. 5.2 Metastatic site determines the growth pattern and differential apparent diffusion coefficient (*ADC*) and dynamic contrast-enhancement characteristics of 231BR metastases. (**a**) 231BR metastases developing in the brain parenchyma had extensive edema detected as increases in T2-weighted signal intensity and ADC, but the BBB was largely impermeable to Gadolinium-Diethylenetriamine Penta-Acetic Acid (Gd-DTPA) in most of the brain metastases. Brain metastases displayed extensive increases in the extracellular space surrounding the co-opted metastatic foci. (**b**) In comparison, metastases situated in the ventricles or sulci (**b**) developed as solid masses and were isointense with the surrounding brain on T2-weighted and ADC maps, but these tumors were highly permeable to Gd-DTPA as shown on the IAUGC90 maps. (**c** and **d**) Likewise, metastatic sites in the meninges (c) and bone (**d**) promoted the growth of solid tumors with highly permeable vasculature. Scale bars indicate 200 mm (Modified from Budde MD et al. 2012)

SPIO generates negative contrast by altering the local magnetic field homogeneity [23]. SPIO particles are available in a range of sizes (approx. 5 nm to 1 μm in diameter). The smallest SPIO (ultrasmall or USPIO) agents are referred to as blood pool agents and imaging performed before and after the iv administration of USPIO allows for characterization of tumor vasculature and assessment of vascular volume [9]. Metastases that do not enhance after Gd administration have been shown to be visualized with iv USPIO [9, 15, 22].

Gambarota et al. compared the visualization of three different orthotopic mouse models for human brain tumors (angiogenic melanoma metastases and E34 and U87 human glioma xenografts) after both Gd (BBB permeability) and USPIO (blood volume) administration [9]. The delineation of tumors was best assessed on post-USPIO images. The melanoma brain metastases were characterized by

a blood volume and vessel leakage higher than both glioma xenografts. The U87 glioblastoma xenografts displayed higher permeability and blood volume in the rim than in the core. The E34 glioma xenografts were characterized by a relatively high blood volume and a moderate disruption of the BBB. Histological findings showed that regions where the blood volume was high contained dilated blood vessels. Since vascular permeability and angiogenesis are not strictly related, the use of these two complementary contrast-enhanced MRI techniques may be very useful for detecting irregular vasculature and for monitoring antiangiogenic therapies.

SPIO nanoparticles have also been used to pre-label cancer cells prior to their injection in experimental models of brain metastases. This approach is known as cellular MRI or MRI cell tracking. A variety of cell types can be easily loaded with iron nanoparticles by simple co-incubation [24]. Areas containing iron labeled cells appear as regions of low signal intensity, creating negative contrast. The large magnetic susceptibility of these particles affects an area much larger than the actual particle size. This effect is known as a 'blooming artifact', and leads to an exaggeration of the region occupied by iron oxide [23]. Heyn and colleagues were the first to use cellular MRI to study breast cancer brain metastasis [4]. They demonstrated that MRI could be used to detect single iron-labeled cancer cells after their initial arrest in the mouse brain and to monitor the development of brain metastases over time in the whole brain. In addition, they identified a reservoir of nonproliferative (possibly dormant) cancer cells by virtue of their long-term retention of iron particles (Fig. 5.3).

Other advanced MRI techniques can be applied to accentuate features of growing tumors without the addition of exogenous contrast agents. Diffusion weighted imaging (DWI) is a functional MRI technique that measures the mobility of water molecules in a tissue of interest [25]. Changes in the ratio of extracellular and intracellular water volumes affect the overall mobility of water within a tissue. DWI can detect these changes and use the resulting information to generate apparent diffusion coefficient (ADC) maps, which reflect physiological features not evident in conventional MRI. The initial application of this technique for brain tumors was for the detection of early tumor treatment response in primary brain tumor pre-clinical models [25, 26]. Here ADC served as a marker for tumor cellularity and an indicator of apoptosis and necrosis following cytotoxic therapy. In these studies a tumor response to chemotherapy was evident days to weeks before a change in volume [25].

ADC mapping has been applied differently to brain metastasis. Co-opted growth of brain metastases causes extensive edema of the invaded brain tissue resulting in enlarged extracellular spaces [10]. As a consequence of the additional water content, ADC measurements are elevated in metastases compared to the surrounding normal parenchyma. Due to this complication, DWI is not useful in the assessment of therapeutic tumor response for edema-prone brain metastases. However, high ADC values have been used to differentiate edema from metastases in animal models of brain metastases and this technique still holds value in the evaluation of the physiological features of metastatic tumors prior to treatment [10, 17].

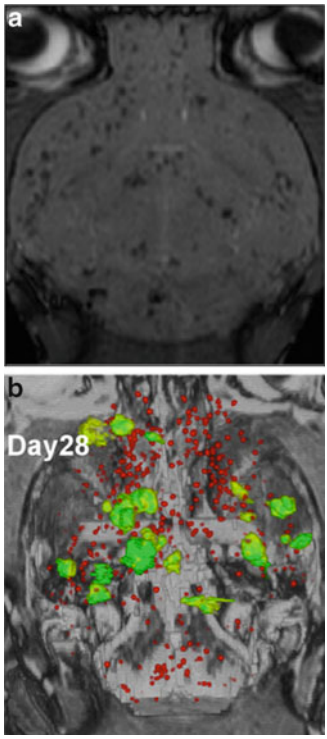

Fig. 5.3 MRI of a mouse brain containing 231BR breast cancer cells. (**a**) One day after the intracardiac injection of 100,000 cells numerous discrete regions of signal void which represent iron-labeled breast cancer cells are visible. (**b**) 3D volume rendering of MRI of the same mouse brain at 28 days post injection shows metastases that have developed (*green*) and persistent signal voids (*red*), which represent non-proliferative cancer cells

3 Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) is another nuclear magnetic resonance technique that allows the noninvasive evaluation of brain biochemistry [21]. This method examines the proton spectra in one or several imaging voxels, within a specified area of healthy or diseased tissue. Individual metabolites correspond to different peaks in the spectra and alterations in the levels of these compounds can be used to detect and monitor metabolic changes during metastasis development and response to therapy [21]. In addition, different malignancies often display different alterations in spectra, which makes MRS a potential tool for differentiating between various types of brain tumors.

Many compounds can be detected by proton MRS but several are more often used in research and clinical practice. Creatine (resonates at 3.02 ppm) is a measure of energy metabolism and is relatively constant in the brain so it is commonly used as a reference compound [21]. Choline (at 3.2 ppm) reflects the degree of membrane turnover and is often increased in disorders that cause accelerated cell membrane turnover and hypercellularity. N-acetylaspartate (NAA, at 2.02 ppm) is an indicator of neuronal viability and is reduced in conditions that destroy or replace neurons. Lactic acid (at 1.33 ppm) measures anaerobic metabolism and is elevated in tumors

with growth that exceeds their blood supply and must rely on anaerobic glycolysis to meet energy requirements. Elevated mobile lipid (at 0.8 and 1.5 ppm) is a marker of necrosis and an indicator of both high-grade primary brain tumors and metastases. In general, ratios of these metabolites are measured and comparisons are made of diseased versus normal tissue.

Simões and colleagues used MRI and MRS to develop and characterize a mouse model of breast cancer brain metastases [17]. The first indication of metastatic growth was a decreased level of NAA. As metastases increased in size the spectral pattern changed to reflect an increase in choline containing compounds, a decrease in creatine, an increase in mobile lipids and elevated lactate. Comparing the mobile lipid resonance at both short and long echo times enabled investigators to determine that lipids were mostly located in small intracellular lipid droplets rather than large extracellular lipid droplets generally found in necrotic regions. This finding indicated that metastasis progression in this model occurred without major necrosis [17].

Clinically, the spectral pattern that nonspecifically indicates brain cancer is low NAA and high choline levels with elevated lactate if the tumor is hypoxic, or elevated lipid if the tumor is advanced [21]. Brain metastases typically exhibit high lipid and lactate resonance without any other visible brain metabolites [27, 28]. However, if the examined voxel is contaminated with even a small volume of brain tissue, the tumor may be misclassified because of small peaks of choline, creatine and NAA [29]. The intratumoral spectral pattern for different types of primary brain tumors and metastases often exhibit significant overlap [30], making the clinical differentiation of tumor types difficult.

4 Positron Emission Tomography

Positron emission tomography (PET) is a nuclear imaging technique that can also be used to monitor changes in tissue metabolism. PET can detect trace amounts of positron-emitting radionucleotides with high sensitivity and excellent depth penetration [2]. Natural biological molecules can be labeled with positron-producing isotopes without alteration of their normal function. Labeled tracers can then be introduced into animal or human subjects and PET used to follow their distribution and concentration in the body. Frequently used isotopes include ^{14}O (oxygen), ^{13}N (nitrogen), ^{11}C (carbon), ^{64}Cu (copper) and ^{18}F (fluorine). PET can identify cancers based on altered tissue metabolism and can serve as a tool for monitoring the effects of pharmacological or radiation therapy before structural alterations occur. *In vivo* biochemical assessment of tumors, specifically glycolysis, DNA synthesis, amino acid transport and oxygenation state, is becoming an increasingly popular tool for classifying tumors and monitoring their treatment [2, 31]. Although many PET applications have already moved into the clinical realm, feasibility studies in animal models have served a key role in radiolabeled tracer development [32]. These studies have demonstrated variable tumor uptake dependent on such parameters

as cancer type, organ of origin, host species and radioligand chemical structure. With continuing advances in molecular biology, small animal studies will continue to be useful in the development of newly identified cancer targets and tracers.

To develop suitable tracers for imaging cancers, metabolic processes must be identified that differ from the natural state of surrounding tissues or organs [31]. Many malignant tumors have accelerated glycolysis compared to surrounding tissues [32]. 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) is a glucose analog that can be used to measure regional glucose utilization and was the first PET agent used to investigate the malignancy of cerebral tumors [33, 34]. FDG PET has become a key imaging modality in oncology for diagnosing, staging and predicting prognosis in systemic tumors, however its use in the evaluation of brain metastasis has been limited [35]. Normal brain tissue has a high rate of physiologic glucose metabolism and shows high FDG accumulation [36, 37]. Consequently, FDG PET images show hypermetabolism in the brain cortex, making it difficult to differentiate a lesion from the normal tissue. In addition, while most systemic metastatic tumors are hypermetabolic, not all brain metastases show FDG accumulation [36, 37]. For example decreased uptake of FDG has been noted in brain metastases from both non-small cell and small cell lung carcinomas [36, 38, 39].

Another important characteristic of cancerous tissue is the increased rate of proliferation and consequent DNA replication. Thymidine transport and thymidine kinase (TK-1) activity is upregulated by malignant cells because thymidine is needed for DNA synthesis [40]. 3′-deoxy-3′-[18F]fluorothymidine (FLT) is a thymidine analog and proliferation tracer for PET. Like thymidine, it follows the salvage pathway of DNA synthesis and undergoes phosphorylation by TK-1 [41]. Studies of brain malignancies have indicated FLT uptake correlates with Ki-67 expression, a proliferation index commonly used *ex vivo* [13]. In general FLT tumor uptake is lower in comparison to FDG, however, FLT has low uptake in normal brain because of a lack of significant neuronal cell division [42]. This discrepancy provides better contrast between brain tumor and surrounding normal tissue compared to FDG [2, 37].

Amino acid tracers such as ^{11}C-methionine and 3,4-dihydroxyl-6-[^{18}F]-fluoro-L-phenylalanine (FDOPA) have been used to investigate altered amino acid transport associated with malignant transformation [13]. Amino acid transport is increased in tumor cells regardless of the phase of the cell cycle. These tracers have been very attractive for brain tumor imaging as they show selective uptake in tumor cells and low uptake in normal brain, thereby creating high tumor-to-normal brain contrast [35]. In fact studies comparing FLT with ^{11}C-methionine PET showed ^{11}C-methionine had greater sensitivity especially for low-grade tumors [43, 44]. In animal models, upregulation of the amino acid transporter in the supporting vasculature of brain tumors was shown to be responsible for facilitating amino acid transport into the tumor cell [45].

Hypoxia in tumors is a consequence of diminished oxygen diffusion though the tissue due to high proliferation and functionally disrupted angiogenesis [13]. ^{18}F-Fluoromisonidazole is a nitroimidazole derivative that has been developed as a PET tracer to image hypoxia [46]. Metabolites of the agent are trapped exclusively

in hypoxic cells. Hypoxia is a key factor as it has been associated with tumor progression and resistance to radiotherapy [47].

A large area of growth in the field of PET imaging is the development of antibody-based tracers that target specific tumor antigens such as upregulated cell surface receptors. This class of PET tracer is largely comprised of radiolabeled humanized versions of engineered antibody fragments such as minibodies and diabodies [2, 48, 49]. Clinical trials have begun with this type of tracers but small animal studies will continue to be useful in the development of newly identified cancer targets and tracers. Due to the larger size of these probes and the necessity to cross the BBB, brain imaging with tumor antigen-specific tracers remains limited.

5 Single Photon Emission Computed Tomography

Single photon emission computed tomography (SPECT) is another nuclear imaging technique that can be applied to study metastasis. For this technique gamma-emitting isotope-labeled tracer is injected and a gamma camera is rotated around the subject to generate tomographic images [50]. Commonly used isotopes include ^{99m}Tc (technetium), ^{111}In (indium), ^{123}I (iodine), and ^{201}Tl (thallium). These isotopes are not naturally occurring and their incorporation into radiolabelled tracers must be done in a manner that minimally perturbs the biochemical behavior of the molecule [2]. Alternatively, positron-emitting isotopes used for PET can be substituted for naturally occurring atoms. PET is tenfold more sensitive than SPECT and it is for these reasons that PET is more commonly used for imaging molecular events.

SPECT tumor screening agents have been used to visualize tumors [7, 8, 51]. One agent that has been used for detecting brain tumors is ^{201}Tl, a potassium analogue that reflects regional blood flow, destruction of the blood brain barrier and Na + −K + ATPase activity [51]. An intact BBB has been suggested as partially responsible for the minimal ^{201}Tl uptake in normal brain [52]. The agent is more rapidly incorporated into tumor cells and its retention in cells has been observed as altered in different cancer types. A preliminary study performed by Kojima and colleagues used superdelayed ^{201}Tl SPECT imaging to differentiate between malignant gliomas and cerebral metastases [51]. They hypothesized that slow washout in gliomas may be due to reduced Na + −K + ATPase activity compared to metastatic brain tumors.

6 Whole-Body Optical Imaging

Optical imaging techniques are based on the detection of light emitted from either fluorescent (i.e. green fluorescent protein, GFP) or bioluminescent (i.e. luciferase) reporters [3, 6]. There are several advantages in the use of optical imaging for experimental animal studies. These methods are minimally or non-invasive, inexpensive, have high sensitivity and allow for high throughput imaging. The main disadvantage

of these techniques is the limitation of penetration depth due to the absorption and scattering of light through tissue [53].

Fluorescent imaging (FI) is based on the bright inherent fluorescence of fluorophores such as GFP and red fluorescent protein (RFP). These fluorophores can be imaged using fluorescence dissecting microscopy that first provides a filtered excitation light source to excite the fluorophore (for example ~490 nm for GFP) and then collects the resulting fluorescence emission from the fluorophore through a long-pass filter (520 nm for GFP) [54]. Fluorophores can be stably expressed in cells or even whole animals to enable the use of *in vivo* whole-body fluorescent imaging for the detection of a variety of biological conditions including primary tumor growth and metastases [3]. In the mouse, external imaging can be done through relatively transparent body walls including the skull.

Bioluminescence imaging (BLI) is based on light produced by an enzyme-substrate reaction. When luciferin in cleaved by the reporter enzyme, luciferase, bioluminescence photons are released and can be detected using a charge-coupled imaging device [6]. Like FI, the reporter must be stably transfected into cells prior to their injection in a disease model. To localize the luciferase reporter, animals must be anaesthetized, injected with the luciferin substrate and imaged in a light-free environment [3].

Both FI and BLI have been used for real-time measurement of primary and metastatic tumor growth in rodent models [3, 53, 55–57]. Chung *et al.* engineered breast cancer cells (231BR-HER2) to express Gaussia luciferase and investigated its use as a biomarker for monitoring metastasis and treatment responses using BLI [57]. They detected numerous brain metastases as well as systemic metastases in the spine and lungs. In addition, they monitored the total metastatic burden during the course of treatment with lapatinib, a dual tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2), and observed that treated mice had many fewer metastases and survived much longer than control animals (Fig. 5.4).

Optical imaging has become a popular method for monitoring tumor burden in animals over time largely due to the inherent advantages of the techniques discussed above but also due to the quantitative nature of each method. The relative amount of fluorescent or bioluminescent light detected can be correlated to the progression or regression of a tumor over time or in response to therapy [3]. Limited research has been conducted specifically investigating mechanisms of brain metastasis using whole-body optical imaging. These techniques are more often used in concert with other imaging modalities to provide a convenient means to monitor intracranial tumors *in vivo* [16, 58].

Optical imaging is also used to examine whole mouse brains immediately after necropsy. In a study examining the effect of HER-2 overexpression on breast cancer metastasis in the brain, Palmieri and colleagues used *ex vivo* GFP imaging to identify mice with brain metastases [59]. They were able to clearly image foci of GFP-expressing brain-metastatic breast cancer cells using a spectral imaging system, however, quantification of these images was not possible because of low resolution, autofluorescence and overlap of the fluorescent signal from nearby metastases.

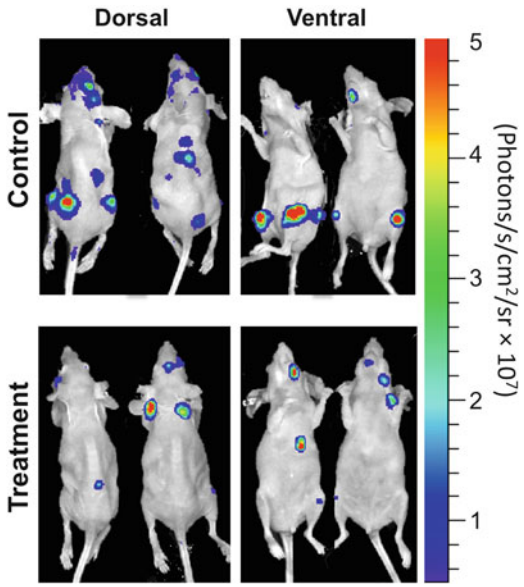

Fig. 5.4 Representative Bioluminescent images (BLI) (*dorsal and ventral view*) of lapatinib treated and untreated mice 28 days after intracardiac 231BR-HER2-G cell injection. Blood Gaussia luciferase (Gluc) and BLI were assessed weekly (n = 16 per group), when blood Gluc value reached at 1 RLU/s, mice were treated with lapatinib. Mice were sacrificed 28 days after treatment for sample collection. Imaging was done individually (Modified from Chung E et al. 2009)

Similarly, Rozniecki and colleagues used a luciferase-tagged mouse breast cancer cell line to investigate the effect of stress on brain metastasis [60]. Tumor-bearing mice were injected with luciferin immediately prior to sacrifice and brains were imaged *ex vivo* to reveal an increased number of brain metastases in mice exposed to restraint stress. Investigators speculated that the observed increase in metastasis might have been due to stress-induced increases in BBB permeability [61].

7 Intravital Microscopy

The use of fluorescent and bioluminescent proteins in live animals has provided new insights into the real-time growth and metastatic behavior of cancer [3]. Using fluorescent proteins to color-code cancer cells as well as elements of the tumor microenvironment either through genetic manipulation or the administration of fluorescently-tagged exogenous dyes has allowed the assessment of tumor/stromal interactions using intravital microscopy [62]. Essentially all aspects of the cancer process can be visualized including tumor growth, tumor cell motility, invasion and colonization as well as interactions between the tumor and its microenvironment. Individual, dormant cells as well as micro- and macrometastases can be clearly visualized and quantified [5, 63].

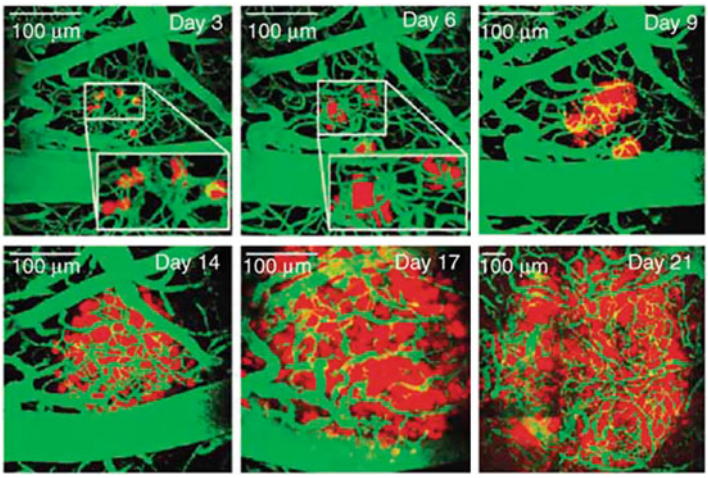

Fig. 5.5 *In vivo* multiphoton laser scanning microscopy images of PC14-PE6 lung carcinoma cell macrometastasis formation in the brain of a GFP-expressing transgenic mouse. Five foci of extravasated lung carcinoma cells in close proximity to each other on day 3 merge into one growing macrometastasis overtime (depth: 50–450 µm) (Modified from Kienast et al. 2010)

Work investigating metastasis in the brain has been performed using intravital multiphoton laser scanning microscopy (MPLSM) [5, 63]. For single-cell resolution chronic transparent windows are surgically inserting into the mouse skull thereby enabling longitudinal real-time tracking of tumor growth and metastasis in the intact animal. A key component of brain metastasis that has been imaged successfully in this fashion is the relationship between tumor cells and the vasculature of the brain [5, 63].

Carbonell and colleagues used MPLSM to serially image GFP expressing human breast cancer and melanoma cells following their intraparenchymal injection into mouse brain [63]. They found that during early stages of colony formation the majority of micrometastases were in direct contact with the vascular basement membrane of existing brain vessels. Based on their observations, they concluded that the vascular association of tumor cells in brain colonies was not due to the physical association of the tumor cell with the vessel after extravasation, but rather a preferential interaction with the vessel.

Kienast and colleagues used intravital MPLSM to track individual metastasizing lung cancer and melanoma cells in relation to blood vessels deep in the mouse brain [5]. They imaged mice minutes after the intra-arterial cell injection and continued to follow them over months. Using RFP-expressing cancer cells and fluorescein isothiocyanate (FITC)-dextran to label blood vessels they were able to identify four essential steps of successful macrometastasis formation in the brain: initial arrest at blood vessel branches, early extravasation, perpetuation of a perivascular position and either angiogenesis (lung cancer) or vessel co-option (melanoma) (Fig. 5.5). These findings provided new insights into the evolution of metastases and helped with understanding of certain clinical observations.

8 Multimodality Imaging

It has become quite common to see multiple imaging modalities used in a complementary fashion to acquire multilayered information. The goal of multimodality imaging is to combine the best features of separate modalities. For instance, high-resolution anatomical images acquired with MRI or computed tomography (CT) are often combined with functional or metabolic imaging such as with PET or SPECT.

A promising advancement in multimodality imaging has been the development of hybrid multimodal scanners. Currently PET/CT, SPECT/CT and PET/MR scanners have been developed that can provide complementary anatomical, physiological and functional information [2]. The development of these systems has incurred some challenges. PET/CT exposes patients to higher than recommended doses of radiation (as high as 25 millisieverts (mSv)) [64], while PET/MR requires complicated attenuation correction and MR compatible hardware [65, 66]. Despite the challenges, the potential benefits are great. In clinical centers where these systems are already in use, the ability to obtain data from multiple modalities is already improving clinical decision-making [2, 12].

Image co-registration is another multimodality strategy employed when integrated systems are not available. Here imaging sessions are performed independently and images are later fused. Registration methods are most accurate for the brain and fused images have been shown as more useful than each modality alone. For example, co-registration of FDG-PET images with MR images greatly improves image interpretation as anatomical information helps delineate the metabolic alterations in an area of interest [13].

Applying multiple modalities without co-registration still offers the benefit of added information and opens the possibility of using modalities that are not easily co-registered. For mouse models the most common approach is to combine an optical imaging technique with either MRI or micro-CT [16, 58, 63, 67]; although there are few examples of the use of multimodality imaging to study experimental brain metastases. Song and colleagues used MRI and BLI to non-invasively track the temporal and spatial distribution of breast cancer metastases in a rat model [58]. Brain images were acquired with MRI and the whole rat body was imaged with BLI. This approach revealed metastases in the brain, spinal cord, bone and internal organs. Each imaging modality had an important role; brain metastases detected by MRI were not always present on BLI and it is impractical to image the whole rat body with MRI. The combined use of MRI and BLI provided the tools necessary to monitor both brain and systemic metastases in the same animals, which had not been done before.

Current micro-CT systems can achieved ultra-high spatial resolutions and produce excellent quality images of bony structures in mice. Low radiation doses will allow for multiple imaging sessions to be performed. Lim and colleagues used micro-CT and BLI to monitor the distribution and development of systemic breast cancer metastases and specifically bone metastases with associated osteolytic lesions [67]. The optical and CT data sets were co-registered in 3-dimensions. Optical methods should also be

very useful for complementing MRI cell tracking studies since the use of iron-labeled cell detection by MRI is limited by the slow clearance of signal when cells die, whereas optical methods offer the ability to monitor and quantify cell viability.

9 Summary

Traditionally, methods used to identify and examine brain metastases are labor-intensive, time-consuming, invasive, and provide little information on the dynamics of cancer cells *in vivo*. The use of sophisticated experimental models of brain metastasis along with advanced imaging technologies will increase our understanding of the development, progression and treatment of brain metastases. With the ability to reliably track the metastasis and proliferation of small numbers of cancer cells, and specific subsets of cancer cells, will come new knowledge of the behavior of these cells in a relatively undisturbed environment.

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Chapter 6
Possibilities of Targeted Therapies for Brain Metastasis

Frank Winkler

Abstract In the era of therapies successfully targeting distinct molecular pathways in cancer, the incidence and relevance of brain metastases are rising. Generally, the old therapeutic nihilism with respect to brain metastasis has given way to a more pragmatic approach, aiming to optimally combine (radio)surgery, whole brain radiotherapy, and sometimes systemic chemotherapy. However, local approaches inevitably fail to address the multifocal nature of the disease, whole brain radiotherapy shows relevant neurotoxicity, and systemic chemotherapy faces the obstacle of the blood-brain/tumor-barrier. Therefore, judicious addition of targeted agents to the therapeutic armamentarium for brain metastases holds the promise to make a real difference for patients suffering from this devastating disease. Unfortunately, because of their unfavorable prognosis, patients with brain metastases have traditionally been excluded from studies with targeted therapies. This is changing now for several reasons, making it likely that we will obtain relevant clinical data in the next few years. The following chapter gives an overview of new therapies targeting molecular pathways both in the tumor stroma and in cancer cells, covering its theoretical and reported activity against brain metastases. A special emphasis will be placed on prophylaxis, i.e. prevention of macrometastasis formation.

1 Introduction

Brain metastasis (BM) therapy faces the challenge to efficiently target the cancer cell, or its supportive relationship with the brain parenchyma, without damaging the delicate organ it is colonizing. Therapeutic agents targeting distinct molecular

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pathways of cancer cells hold the promise to do just that [1]. Furthermore, the fact that the majority of BM patients suffer from multiple metastases that occur unpredictably at different sites during the course of the disease makes a systemic therapy treating macro- and also micrometastases most adequate. Optimally, a systemic therapy might even prevent brain colonization altogether, or at least arrest single cells or micrometastases in a dormant state. Even though we are far away from having such a weapon with proven clinical efficacy at hand, there is some reason to be cautiously optimistic.

First, one of the greatest challenges of systemic brain tumor therapy can be overcome: the blood-brain/blood-tumor barrier. For example, antiangiogenic agents targeting the VEGF pathway have to reach only the endothelial cell, but do not have to cross the entire blood-tumor barrier, consisting of additional layers of thickened basement membrane, irregular pericyte coverage, and occasionally astrocyte foot processes in the brain [2–4]. In contrast, this is mandatory for all chemotherapeutics or targeted drugs that have to reach the cancer cell to exert their action. Furthermore, drug penetration to the cancer cell is also hindered by the aberrant and highly heterogeneous blood flow in brain tumor vessels lacking the normal hierarchical structure of normal brain vasculature. Finally, increased interstitial fluid pressure hinders extravasation into the tumor [5]. All in all, it is a futile challenge for most drugs available today to overcome these barriers between the blood stream and the brain tumor cell, at least in meaningful concentrations. Like antiangiogenic agents, immunomodulators targeting cells responsible for anti-tumor immunity (e.g., Ipilimumab) do not need to reach the cancer cell to exert their action.

Second, targeted small molecule and even antibody inhibitors can be designed to efficiently cross the blood-brain barrier (BBB), or linked to an agent that is actively transported over it [6]. Until recently, pharmaceutical companies did not show great interest in developing such agents. However, the rising incidence of brain diseases like Alzheimer's or Parkinson's changed this, and today pharmaceutical companies start drug development programs to select and/or design agents with maximum BBB penetration capabilities, including antitumor agents.

Third, it is proven that macrometastatic outgrowth in the brain can be effectively prevented – by prophylactic whole brain irradiation which targets the whole organ. Applied during a short time frame (2–3 weeks) early in the beginning of the disease, prophylactic whole brain irradiation decreases the incidence of (macro)metastasis formation by more than 50%, an effect that continues over the next 24 months [7]. This matches well with common preclinical and clinical experience that prevention of a disease is much easier than treating it when it is fully developed. Since targeted agents can be applied over long periods of time, are active in the whole body, and do not show the neurotoxicity of whole brain radiotherapy (WBRT), they seem to be perfect future candidates for brain metastasis prevention.

In the last 10 years, targeted cancer therapy [8] has grown explosively and is now established for many tumor entities. However, like established cytotoxic therapies, its role in influencing the occurrence of metastases has rarely been systemically addressed [9, 10]. Furthermore, virtually no targets for molecular therapies have been identified in small cell lung cancer (SCLC) yet, which makes the tumor entity

with the highest incidence of BM formation still largely terra incognita. In general, clinical trials are not (yet) designed to prospectively investigate the rate of metastasis formation. Taken that the vast majority of cancer patients die of metastasis and not the primary tumor, this appears to be one of the most important issues for future cancer research. This chapter provides an overview of those targeted therapies that seem most suited for use in BM therapy, both of established macrometastases and of early metastatic events. Furthermore, the clinical data available today is provided, with the limitation that a controlled, prospective, randomized clinical trial testing the effect of targeted therapies on BM has not been completed yet. However, there are several clinical studies on the way that aim to explore the efficacy of targeted agents in BM therapy. At this time, patient data from small case series, retrospective analyses, or even anecdotal reports may teach us what pathways and agents might be the best candidates for future trials. In the following paragraphs, those pharmacologically targetable molecular pathways will be presented that are most promising with respect to BM therapy, because of existing clinical data or for conceptual reasons.

2 Antiangiogenic Therapy

Most antiangiogenic agents target the VEGF pathway. It is important to keep in mind that – in general – tyrosin kinase inhibitors show only moderate selectivity for one receptor (or even class of receptors) [11], which extends their activity to PDGFRs and others. During vessel formation, PDGF-BB is required for the recruitment and differentiation of pericytes, and preclinical data suggest that concomitant inhibition of VEGF and PDGF signaling can improve anti-tumor activity compared with VEGF alone [12]. It needs to be clarified if normalization of brain tumor vasculature during VEGF pathway inhibition [2] is preferable for every patient, or if agents that disturb the vasculature by disrupting pericyte support (such as PDGF receptor inhibitors) may sometimes have greater benefit. However, severe reduction or lack of pericyte coverage may also facilitate metastasis by disrupting the integrity of the vasculature [13]. In contrast, bevacizumab, the antiangiogenic agent most widely used today, inhibits only VEGF-A. Accordingly, there is rising evidence that different antiangiogenic agents can exert very different actions in vivo, which makes it problematic to generalize one finding with one inhibitor to all antiangiogenic agents. Furthermore, other pathways like the angiopoietin system are now coming into the focus of drug development. From a conceptual point of view, antiangiogenic agents that mainly prevent ligand binding/receptor activation at the endotheralial cell do not have to cross the BBB/blood-tumor-barrier, which could prove to be their most important advantage for brain tumor therapy. Therefore, the argument that large antibodies like bevacizumab do not cross the intact BBB and may therefore not be useful in brain tumors does not apply.

In primary brain tumors, antiangiogenic therapy with the humanized monoclonal anti-VEGF-A antibody bevacizumab has shown clinical activity [14], received an

accelerated FDA approval due to its excellent response rates and very good progression free survival data at 6 months, and is now widely used for patients suffering from malignant gliomas. Two large double-blind, placebo-controlled phase III studies are currently investigating bevacizumab as first-line therapy for glioblastoma in addition to radio/chemotherapy (www.clinicaltrials.gov). Both have completed accrual, recruited more than 700 patients each, and first results are expected for 2013. This high level of clinical study activity is limited to primary brain tumors though. With respect to BM, there is mainly preclinical evidence from multiple animal models that antiangiogenic agents can be effective: elevated VEGF expression has been linked to the development of BM in a murine model [15]. Kim et al. showed that treatment with the VEGF-receptor tyrosine kinase inhibitor PTK787/Z 222584 reduced angiogenesis and restricted the growth of brain metastases in a murine breast cancer model [16]. In another mouse model, inhibition of VEGF signaling using bevacizumab was able to efficiently inhibit angiogenesis and metastasis formation of lung cancer, but not melanoma cells [17]. In established brain metastatic disease, high-dose bevacizumab therapy could induce vascular normalization, and blood vessel and tumor cell regression [von Baumgarten L, Kienast Y, Winkler F; unpublished data], similar to what we have found in glioblastoma [18]. However, from what is known today, the growth pattern of different tumor (sub)types in the brain is highly different, with lung carcinoma being the most angiogenesis-dependent, and melanoma being the most angiogenesis-independent (due to the ability to grow co-optive along pre-existing brain microvessels). Breast cancer seems to be located in the middle of this continuum, but considerable variability within tumor entities is likely. It is plausible that this has great impact on the efficacy of antiangiogenic therapies [17]. Conclusively, antiangiogenic therapy has not shown efficacy in melanoma patients yet. All in all, these preclinical results argue for a serious clinical evaluation of antiangiogenic agents in BM therapy and prophylaxis. As with other tumor sites, a clinical parameter (laboratory, imaging, or histological) that predicts response to antiangiogenic therapy would be extremely helpful – but is lacking. Until then, the preclinical results strengthen the point that brain metastases from different tumor entities should be investigated separately in clinical studies.

There is limited data about the clinical activity of antiangiogenic agents in BM patients yet. This is mainly due to exclusion of patients with BM from clinical trials with antiangiogenic agents since a single patient with brain metastatic hepatocellular carcinoma (a disease with high incidence of intracranial bleedings [19]) developed a cerebral hemorrhage 2 weeks after a single dose of bevacizumab in a phase I trial [20]. Since then, large meta-analyses, retrospective case studies and a prospective phase II trial have shown that bevacizumab therapy does not increase the incidence of clinically relevant intracranial bleedings in patients with central nervous system (CNS) metastases [21–23]. This seems to be also true for tyrosine kinase inhibitors [24]. Consequently, the contraindication for BM has been removed from the bevacizumab label in Europe and most likely will be removed also in the US in due time. Several phase I and II trials evaluating bevacizumab alone or in combination with cytotoxic compounds in BM patients have been initiated and are ongoing (Table 6.1). Other drugs with antiangiogenic properties that are investigated

Table 6.1 Overview of targeted agents that are currently being investigated in ongoing clinical studies (http://clinicaltrials.gov)

Type of treatment	Investigational agent	Tumor type per trial	Trial phases
Anti-angiogenic agents	Bevacizumab	All, NSCLC, breast cancer, melanoma	I, II
	Cilengitide	Lung cancer	I
	Sorafenib	All, kidney cancer	I, II
	Sunitinib	All, NSCLC, kidney cancer, melanoma, breast cancer	I, II
	Thalidomide	All, melanoma	I, II, III
BRAF inhibitors	GSK2118436	Melanoma	II
	Vemurafenib	Melanoma	II
EGFR inhibitors	Afatinib	All	II
	Erlotinib	NSCLC	I, II, III
	Gefitinib	NSCLC, lungadenoc arcinoma	II
	Lapatinib	Breastcancer, lungcancer	I, II
	Trastuzumab	Breastcancer	II
	Nimotuzumab	NSCLC	II
Gamma-secretase/ notch inhibitor	RO4929097	Breastcancer	I/II
HDAC inhibitors	Panobinostat	All	I
	Vorinostat	All, NSCLC	I
Immunomodulatory agents	Ipilimumab	Melanoma	II
	Interferon alfa-2a	Breastcancer	II
mTor inhibitors	Everolimus	Breastcancer, NSCLC	I, II
PARP inhibitors	ABT-888	All	I
	Iniparib	Breastcancer	II
Protein kinase C beta inhibitor	Enzastaurin	SCLC	II
Radiation sensitizers	Cytochlorandtetrahy drouridine	All	I
	Efaproxiral	All, breastcancer	III

From [1]

in clinical trials enrolling BM patients include sunitinib, sorafenib, and cilengitide. Older trials evaluated non-specific antiangiogenic agents such as thalidomide, in combination with WBRT, without demonstration of improved efficacy, but high numbers of dropouts due to severe side effects [25]. Hopefully, the newer studies with more specific antiangiogenic agents will provide us with data on the efficacy of antiangiogenic drugs in established brain metastases.

The experience with antiangiogenic agents in primary brain tumors highlights several issues that may require special attention also in brain metastases [26]. VEGF-targeting drugs like bevacizumab have a BBB-stabilizing effect which leads to a reduction of brain edema and radiological contrast media uptake. This effect, which has also been shown in brain metastases [27], may lead to

overestimation of tumor shrinkage and requires stringent application of adequate response criteria and clinical trial endpoints [28]. Interestingly, treatment of mice with glioblastoma with cediranib prolonged survival despite persistent brain tumor growth in mice by reducing brain edema [29]. It remains to be clarified whether a potential tumor growth-inhibitory or an anti-edematous effect is responsible for the clinical benefit in humans.

Prophylactic administration of VEGF antagonists seems also feasible and is an attractive approach that can be tested in patients at high risk for developing BM [17, 30]. In a novel preclinical animal model we used in vivo multiphoton microscopy for real-time imaging, and tested the prophylactic effect of VEGF-A blockade on the outgrowth of individual metastasizing lung cancer cells in the mouse brain [17] (Fig. 6.1). One experimental group received the anti-VEGF-A antibody bevacizumab just after tumor cell inoculation into the internal carotid artery. Bevacizumab completely prevented early angiogenic events in micrometastases, and thereby induced prolonged dormancy of micrometastatic tumors (maximum ten cells). We did not observe any effects on any other essential steps of the metastatic cascade (initial arrest at vascular branch points; early extravasation; perivascular position with close physical contact to a brain microvessel). Bevacizumab had no effect on the metastatic colonization of melanoma cells in the brain, which showed a non-angiogenic growth pattern under normal conditions. Further preclinical studies are required to determine how discontinued versus prolonged inhibition of VEGF, and combination with other treatment modalities, influences the establishment and growth of micrometastatic disease. An interesting retrospective analysis from the clinic has shown that patients with renal cell carcinoma who received sorafenib had lower incidence of brain metastases than those patients who did not receive sorafenib (3% vs. 12%). This effect stayed statistically significant over 2 years [31]. Even though both groups consisted of considerably low numbers of patients, the prophylactic properties of antiangiogenic agents is an area of important future clinical research.

It is also important to mention several caveats regarding antiangiogenic therapy for brain tumors. In 2009, anti-VEGF monotherapy became controversial with respect to tumor metastasis: accelerated tumor invasiveness and metastasis was observed in mice after pharmacological blockade of the VEGF pathway [13, 32]. However, this did not translate into impaired animal survival (partly to the contrary), and – as stated above – is not in accordance with current signals from the clinic. Furthermore, in glioblastoma, bevacizumab treatment has been suggested to increase the rate of intracerebral distant and diffuse tumor progression by increasing the tendency of glioma cells to invade the brain parenchyma along pre-existing vasculature [33, 34]. However, this view has been challenged lately in better controlled clinical studies which failed to demonstrate a different pattern of relapse in bevacizumab-treated glioblastomas [35]. Increased vascular co-option has been shown for bevacizumab-challenged brain metastatic lung cancer [17] and melanoma cells [36] in the experimental setting. Like in glioblastoma, we have to closely monitor potential pro-invasive effects of antiangiogenic therapies in controlled clinical trials of BM. Finally, the vasculature of brain metastases differs significantly

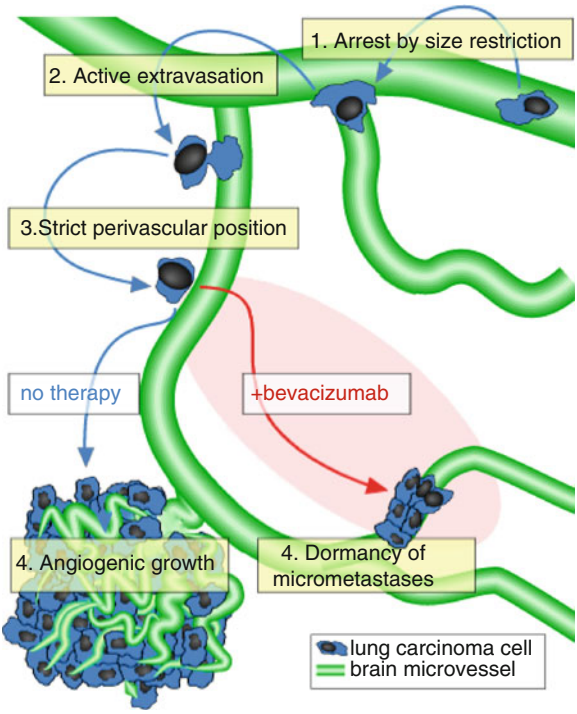

Fig. 6.1 Prophylaxis of brain metastasis formation, as demonstrated in a novel preclinical animal model [17]. Continuous antiangiogenic therapy with the anti-VEGF-A antibody bevacizumab has the potential to interrupt the metastatic cascade by forcing micrometastases into a state of chronic dormancy. This is due to interruption of an early angiogenic switch that is crucial for successful macrometastasis growth of angiogenesis-dependent cancer cells

from that of the primary tumor [37]. This strengthens the point that results from clinical trials investigating the systemic effects of antiangiogenic therapy cannot be transferred to the CNS setting one-to-one.

3 HER2 in Breast Cancer

HER2 amplification or overexpression is found in around 20% of primary breast tumors and is associated with poor prognosis and with the development of BM [38–41]. The incidence of BM in patients with HER2 amplified breast cancer is 25–40%. The reasons for the increased incidence of BM are unclear and are likely multifactorial: First, there is ample data that HER 2 overexpression increases the outgrowth of metastatic tumor cells in the brain by a direct biological effect [42–44]. The exact mechanism of how HER2 modulates BM formation is not known yet; it might involve HER2-induced activation of the angiogenic VEGF pathway [45–47]. Compared to HER2 amplified primary breast tumors, HER2 mRNA levels were increased fivefold in breast cancer BM [48], which supports an important role of HER2 for breast cancer metastasis growth in the brain microenvironment. In support of this, MDA-MB-231 human breast carcinoma cells transfected with HER2 produced threefold larger brain metastases than control transfected cells [43].

3.1 Trastuzumab

Another cause of the increased incidence of BM in HER2 overexpressing breast cancer could be that trastuzumab, a recombinant humanized monoclonal antibody against HER2 that is significantly improving the survival of women with HER2 amplified systemic breast cancer, is not active against breast cancer cells in the brain. Trastuzumab does not penetrate the BBB, which makes the brain a "sanctuary site" for metastatic cells [10]. Poor cerebrospinal fluid (CSF) penetration of trastuzumab was found even after WBRT and in the presence of leptomeningial carcinomatosis [49]. In line with this, several studies showed that more than two thirds of trastuzumab-treated patients present with BM at a time of systemic disease control [38, 50]. The systemic disease control with trastuzumab seems to endure even after diagnosis of BM [51]. The CNS delivery problems of systemic trastuzumab therapy have lead to attempts to bypass the BBB: trastuzumab has been injected directly into the CSF of patients that suffer from leptomeningeal carcinomatosis, with casuistic evidence of impressive and prolonged clinical activity [52, 53]. Since the HER2 status is largely (87%) consistent between matched primary tumors and cerebral metastases [44], it appears promising to investigate smaller HER2 inhibitors that have the chance to cross the BBB in sufficient concentrations for HER2-positive breast cancer patients with BM.

3.2 Lapatinib

Lapatinib is an orally available inhibitor that binds reversibly to the cytoplasmatic ATP-binding site of the HER2 and EGFR tyrosine kinases and is primarily used for treatment of trastuzumab-resistant advanced breast cancer. Its brain penetration might be compromised by drug efflux transporter activity in the BBB [54]. In fact, a recent preclinical study has found highly heterogenous lapatinib concentrations in brain metastases that depended on local BBB permeability; generally, only 10–20% of the drug concentration in peripheral metastases was reached [55]. Accordingly, two phase II trials investigating lapatinib in breast cancer patients with BM have been completed and have shown no certain [56] or only modest [57] single agent activity. In a recent study, lapatinib plus capecitabine achieved a good objective response rate of 38%, but no signs of response were found for lapatinib plus topotecan, again questioning the role of lapatinib [58]. Trials investigating lapatinib in combination with other antineoplastic agents are ongoing. The Radiation Therapy Oncology Group (RTOG) is in the process of initiating a clinical trial for women with HER2-positive breast cancer and BM; the two treatment arms will test WBRT with or without lapatinib, in the context of a randomized phase II trial. These trials should provide a better idea whether lapatinib has relevant CNS activity or not.

It is noteworthy that there might be a decreased incidence of CNS relapses in patients treated with lapatinib in Phase III trials [59, 60], even though this was not

the primary study objective , and the low patient numbers resulted in borderline significance. In a mouse model, Gril et al. tested the efficacy of early onset lapatinib treatment in breast cancer cells with HER2 overexpression, and showed an inhibition of the formation of large brain metastases by approximately 50% [61]. Taken together, lapatinib might not have a great therapeutic effect if large metastases have formed, but might very well be of preventive ("prophylactic") benefit with respect to brain metastasis formation. Remarkably, a large ongoing phase III study can illuminate the prophylactic potential of lapatinib in brain metastasis formation. Patients with recurrent systemic HER2 positive breast carcinoma are randomized to receive lapatinib plus capecitabine vs. trastuzumab plus capecitabine, and the primary outcome measure is the incidence of CNS metastases as the site of first relapse (www.clinicaltrials.gov; NCT00820222). This is one of the very few phase III clinical trial addressing the role of targeted therapies in BM, in this case the prevention of it.

3.3 Other HER2 Targeting Agents

Afatinib is an orally available next generation tyrosine kinase inhibitor that irreversibly inhibits HER2 and EGFR tyrosine kinases. In higher doses of 40 mg/day, clinical responses of brain metastases have been observed [62]. A phase II randomized multicenter trial is now enrolling patients with HER2 positive breast carcinoma with recurrent or progressive brain metastases after trastuzumab or lapatinib treatment into three treatment arms: afatinib 40 mg/day; afatinib plus vinorelbine; investigator's choice of treatment (www.clinicaltrials.gov; NCT01441596).

4 EGFR in Non-small Cell Lung Cancer

Ten percent (US) to 25% (Asia) of non-small cell lung cancer (NSCLC) cases (mainly adenocarcinomas) carry EGFR activating mutations; these numbers might be higher in BM [63, 64]. A recent study has shown that EGFR mutations are found in 44% of BM from NSCLC, and are associated with a doubled median survival of patients. This was due to better intracranial and also extracranial disease control; 78% received EGFR inhibitor therapy after diagnosis of BM [63]. The oral EGFR tyrosine kinase inhibitors gefitinib and erlotinib are approved and routinely used for the treatment of NSCLC: gefitinib for NSCLC with mutations of EGFR and erlotinib for locally advanced or metastatic NSCLC that has failed at least one prior chemotherapy regimen. A number of case reports, small retrospective and prospective case series and non-randomized phase II trials indicate that EGFR inhibitors may be active in NSCLC BM (Table 6.2), particularly in cases with activating EGFR mutations [65–76]. Erlotinib seems to produce higher CSF concentrations than

Table 6.2 Overview of clinical study results showing that EGFR tyrosine kinase inhibitors may have clinical activity in NSCLC brain metastases, although adequately powered and designed studies are missing[a]

Drug (dose)	n patients	Disease	Study type	RR	PFS[b] (months)	OS (months)	Reference
Gefitinib (250 mg)	76	NSCLC	Prospective	33.3%	5	9.9	73
Gefitinib (250 mg)	41	NSCLC	Prospective	27%	3	5	72
Gefitinib (250 mg)	40	NSCLC-adenocarcinoma	Phase II	32%	9	15	70
Gefitinib (250 mg) or erlotinib (150 mg)	23	NSCLC-adenocarcinoma	Prospective	73.9%	7.1	18.8	69
Gefitinib (250 mg)	15	NSCLC	Retrospective	60%	8.7	8.3	68
Gefitinib (250 mg) + WBRT	21	NSCLC	Phase II	81%	10	13	71
Erlotinib (150 mg)	17	NSCLC with EGFR mutations	Retrospective	82.4%	11.7	12.9	66
Gefitinib (250 mg)	14	NSCLC	Retrospective	86%	7.7	9.1	67

[a]Only studies fulfilling the following criteria were included in this compilation: results reported for >10 patients with brain metastases of NSCLC, drug monotherapy with erlotinib or gefitinib (From [1])

[b]Abbreviations (alphabetical order): *EGFR* epidermal growth factor receptor, *mg* milligram, *NSCLC* non-small cell lung cancer, *OS* overall survival, *PFS* progression-free survival, *RR* response rate

gefitinib and therefore may be preferable [77]. Unfortunately, definite results from randomized and adequately powered trials are not available [78]. Case reports suggest that dose escalation strategies should be considered, especially for patient who develop BM under standard dose EGFR inhibitor therapy [64]. This has also been shown for leptomeningeal carcinomatosis [79]. Interestingly, a recent retrospective study demonstrated a potential prophylactic role of EGFR tyrosine kinase inhibitors in patients with advanced NSCLC and somatic EGFR mutations. The cumulative risk of CNS progression at 1 and 2 years was 5% and 21% in patients receiving erlotinib or gefitinib vs. 24% and 31% in the chemotherapy group, indicating a potential prophylactic role of EGFR inhibitors [80].

5 BRAF in Melanoma and Beyond

Activating mutations of the serine threonine kinase v-RAF murine sarcoma viral oncogene homolog B1 (BRAF) are found in a wide range of human cancers and are frequently found in melanoma (60% of cases). More than 95% of BRAF mutations are of the V600E type, which leads to the substitution of valine by glutamic acid in the activating segment of the kinase domain of BRAF. This aberration leads to constitutive kinase activity of BRAF, thereby enhancing the proliferative and metastatic tumor potential through downstream activation of the mitogen-activated protein kinase (MAPK) signal transduction pathway. BRAF mutations seem to be associated with an increased risk for BM formation in patients [81], which makes this mutation overrepresented in BM and the BRAF pathway an interesting therapeutic target. Furthermore, it matches well with preclinical experience that the small proportion of melanoma cell lines that forms parenchymal BM in animals have mutated BRAF.

Several specific inhibitors of BRAF V600E mutated protein are under preclinical and clinical development and have shown favorable clinical activity in metastatic melanoma. Vemurafenib (PLX4032) produced compelling response rates of up to 70% and improved overall and progression-free survival times in BRAF V600E mutated metastatic melanoma patients [82]. Unfortunately, patients with active brain metastases have been excluded from current vemurafenib trials. However, there are favorable preliminary efficacy data on GSK2118436, another inhibitor of mutant BRAF, in patients with brain metastatic melanoma. In a phase I/II study enrolling patients with metastatic melanoma, GSK2118436 lead to shrinkage and even some complete responses of previously untreated asymptomatic brain metastases in a subpopulation of ten patients [83]. Based on these preliminary observations, a large non-randomized phase II study exploring the effect of GSK2118436 on the radiological response rate in patients with BRAF V600 mutated melanoma brain metastases was launched and almost completed (NCT0166967). Also, a phase II trial evaluating efficacy and safety of vemurafenib in patients with brain metastatic melanoma has been initiated (NCT01378975). Such systemic approaches are very promising, as expression of the therapeutic target (BRAF V600E-mutant protein) has

been shown to be homogenous throughout the tumor tissue and to be consistent between different tumor manifestations in individual patients [84]. However, although most patients with BRAF V600E mutated melanomas initially show response to BRAF inhibitors, a significant number of patients develop secondary resistance and experience disease relapse. Treatment resistance may be explained by mechanisms like platelet derived growth factor (PDGFR)-beta upregulation or acquisition of N-RAS mutations or MET mutations [85, 86].

6 Cytotoxic T Lymphocyte Antigen 4 Immunomodulators in Melanoma

Ipilimumab, a human IgG1 monoclonal antibody to cytotoxic T-lymphocyte Antigen 4 (CTLA-4), activates T-cells by blocking the inhibitory action of CTLA-4. CTLA-4 ligation down-regulates T-cell responses and its clinical effects. Overall survival of patients with advanced malignant melanoma was prolonged in two randomized, double-blind multi-national phase 3 trials of ipilimumab as monotherapy [87] and in combination with dacarbazine chemotherapy [88]. Furthermore, anecdotal data and subgroup analyses imply that ipilimumab can show clinical activity against melanoma BM [89–90]. These studies demonstrated the activity of ipilimumab as a monotherapy with responses measured as tumor reduction (objective tumor response). Partial responses were noted in about 25% of patients not on corticosteroids and 5% of those on corticosteroids. Importantly, the current data implies an acceptable safety profile, including patients who previously received CNS radiation. This point has to be followed closely, since previous effective immunotherapies against targets in the CNS showed meningitis and encephalitis including serious brain swelling [91].

7 WNT Pathway

The WNT pathway has been strongly implicated in cancer including cancer stem cell maintenance [92], with 80% of colorectal cancers harboring WNT pathway mutations. Nguyen et al. identified activation of the canonical WNT/TCF pathway as a major factor for metastatic spread to the brain and the bones in NSCLC [93]. Remarkably, WNT signaling was also strongly associated with BM in breast carcinoma patients [94]. In a preclinical study, it was found that microglia promotes brain tissue colonization by breast cancer cells in a WNT-dependent manner [95]. Since the WNT pathway is critical for tissue regeneration and for the ability of stem cells in the bone marrow and gut to self-renew, there is concern that WNT pathway inhibitors could have serious side effects. Accordingly, gastrointestinal and wound healing defects were seen in animals, although these were reversible after drug removal [96]. Therefore, several researchers and pharmacological companies are

moving steadily forward with WNT pathway inhibitors. At this time, a handful of WNT inhibitors are already being investigated in Phase I clinical trials, although none of them in the context of BM. Taken the strong evidence for WNT pathway involvement in BM formation, this is one of the most promising future targets for clinical trials.

8 Predictive Markers

There is currently no validated predictive marker that tells a clinician which BM will respond to a specific targeted therapy. However, it is plausible to assume that the laws of general oncology can be transferred to the brain metastatic setting. Furthermore, there seems to be a high consistency (generally around 90%) for molecular alterations in the primary tumor and the BM. This makes it reasonable to take the genetic or gene expression information from the primary tumor as stratification for BM therapy, when (a) the molecular marker is validated to be predictive for the extracranial disease, and (b) the molecular marker has been demonstrated to be consistent between primary tumor and BM. At the moment, those requirements are fulfilled for HER2 status in breast carcinoma and BRAF status in melanoma. However, it is preferable to note that the tissue from the brain metastatic lesion itself is lacking. One very promising potential predictive marker in brain metastasis is BRAF V600E in brain metastatic melanoma. Correct identification of candidate patients for BRAF inhibitors requires reliable identification of BRAF V600E mutated tumors. So far, DNA-based methods have been primarily used and a real-time PCR test kit has been approved by the FDA for diagnostic purposes. However, the feasibility of DNA-based methods in the routine diagnostic setting is limited. The mutation-specific monoclonal antibody VE1, which allows immunohistochemical detection of BRAF V600E protein in formalin-fixed, paraffin-embedded tissue samples including brain metastases, has recently been generated (Fig. 6.2) [84, 97]. Immunohistochemistry using VE1 seems to be an attractive tool for the diagnostic setting and facilitates mutation screening in large tumor series, even in entities with low mutation frequencies. Finally, one ongoing area of research is the identification of predictive markers for antiangiogenic therapy. Despite intensive research in this area, no biomarker could be validated yet; candidates for brain tumors include changes in distinct MRI sequences, circulating endothelial cells, and plasma levels of cytokines, receptors, and components of the vascular basement membrane [98]. The most straightforward approach, measurement of VEGF-A and/or its receptors, did not prove successful yet. However, new retrospective analyses from large phase III trials now point towards a potential predictive role for plasma-VEGF-A in extracranial tumors; this needs to be evaluated in a prospective setting. In general, it is likely that the advent of effective targeted therapeutics will further increase the necessity of molecular analysis from BM, which might increase the future role of surgical procedures (resection, or biopsy).

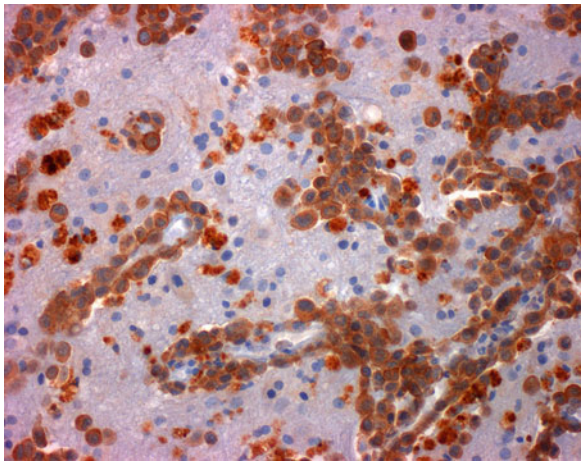

Fig. 6.2 BRAF V600E mutated protein visualized by immunohistochemistry in a melanoma brain metastasis (VE1 immuno-staining, original magnification × 200). There is homogenous expression of the aberrant protein in all tumor cells. Note the perivascular growth pattern of the tumor cells (vascular co-option). (From [1])

9 Outlook

The advent of targeted therapies will hopefully facilitate the shift from the current practice of treating BM according to a rather crude algorithm, in many cases not even considering the histological tumor type, to rational treatment based on individual tumor characteristics. Established BM may be amenable to targeted inhibition of signaling pathways, at least in a proportion of cases. Patients with BM have long been systematically excluded from clinical trials, although there is a growing recognition in the international community that there is no rationale to continue to do so [99]. Hopefully, this will result in the realization of more high-quality trials for BM. Such studies need to take into account the large diversity of cancer entities producing brain metastases and should implement molecular stratification factors whenever possible. Basic and translational investigations are needed to identify novel molecular targets and also to understand secondary resistance mechanisms that are expected to limit lasting effects of many targeted drugs. The use of Response Evaluation Criteria in Solid Tumors or RECIST criteria to measure tumor response of molecular targeted agents might underestimate their effectiveness, as prolonged tumor stabilization should also be considered as a common mode of action. Furthermore, clinical trials should routinely include neurocognitive status and quality-of-life metrics, as both parameters are important to inform decisions regarding the individualized, therapeutic strategies in patients with BM.

A particularly interesting approach is the development of prophylactic systemic therapy to decrease the incidence of BM in high-risk patients. We see advantages, in recent years, to identify these patient subgroups by molecular and/or histological subtype. There are several approaches one can think of: After prevention of intravasation in the primary tumor, the next approach would be to interfere with tumor cell migration through the BBB with drugs targeting selectins, integrins or other adhesion

molecules. Another possibility could be to inhibit growth of micrometastases by blocking ECM-degrading substances (e.g. heparanase, MMP) or early angiogenesis, as successfully exemplified with bevacizumab in experimental NSCLC [17] (Fig. 6.1). The latter seems most promising, since tumor metastasis is regarded as an early event today, which would make it likely that disseminated tumor cells or even micrometastases are already residing in the brain at the time of diagnosis of cancer. For clinical metastasis prevention studies, optimized trial designs are mandatory. Only those patients with a high risk of future BM formation should be included: when one to three brain metastases received successful local treatment, and/or when the tumor type has a known high propensity to metastasize to the brain, including SCLC, NSCLC, and breast carcinoma of the basal-like, triple-negative, and/or HER2 overexpressing subtype. Further molecular stratification approaches (e.g., WNT pathway, chemokine receptor status, BRAF) are on the horizon. The primary end point should be time to progression measured by development of new brain metastases, and secondary end points should include new BM formation thereafter, next to brain metastasis-related morbidity and mortality. Finally, drugs that are normally developed and tested in vivo with respect to their growth inhibitory effect on established tumors are not necessarily effective in terms of metastasis prevention, or might even promote metastasis formation. Therefore, a careful preclinical evaluation of candidate agents is needed before moving to clinical trials of metastasis prevention. In this regard, prophylactic WBRT could at best be displaced by systemic treatment options that are less neurotoxic and have additional effects on systemic metastasis prevention. It is reasonable to assume that this might be a targeted therapy, maybe in a low-dose regimen.

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Chapter 7
Surgery for Brain Metastasis

Douglas L. Stofko, Robert J. Weil, and Steven A. Toms

Abstract Brain metastases (BM) are by far the most common intracranial adult tumor, diagnosed in approximately 150,000–170,000 cancer patients annually in the United States. Due to recent advances in the management of systemic cancers patient survival has increased, with a consequent increase in the incidence of BM. It is estimated that 20–40% of all patients with systemic malignancies harbor cerebral metastases during their life. With the increased incidence due to prolonged patient survival, more patients are being considered for surgical resection. Although surgical management of BM has been performed since the turn of the twentieth century, early results were discouraging and viewed with much doubt. Therefore, treatments for BM were limited to corticosteroids and whole brain radiotherapy until the last few decades. With recent advances in neurosurgical technique, neuroanesthesia and improved localization techniques, more lesions are surgically accessible and there has been a corresponding decrease in surgical morbidity and mortality. Surgical resection of brain metastases continues to evolve but has already demonstrated quality of life benefits as well as increased survival. Currently, surgical resection is considered a key component to the management of BM.

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The goal of this chapter is to review: (1) the current variables used to determine which patients with brain metastases (BM) are candidates for surgical treatment, specifically patient selection and histological criteria for both single and multiple brain lesions; (2) the surgical methods and approaches currently used to resect BM; (3) surgical adjuncts useful in planning and performing resection; (4) whole brain radiotherapy as a postoperative adjunct; (5) postoperative management and complications and, (6) the survival data for patients after surgical resection of BM.

1 History

Surgical excision of BM has traditionally been viewed as a significant cause of neurological morbidity and mortality, since the first case reported by Bucholz in 1898 [1]. In 1926, Grant postulated that surgical excision of cerebral metastases was not justified secondary to extensive operative morbidity and mortality [2]. It was not until 1933 when Oldberg concluded that surgical resection of cerebral metastases could increase patient survival, although this was not a widely accepted belief [3]. In 1954, Chao et al. first reported the results of whole brain radiotherapy (WBRT), which quickly became the favored approach due to its non-operative nature and general improvements in overall patient survival [4]. Concomitantly, Kofman et al. found that while corticosteroids did not significantly extend survival, they did reduce peritumoral edema, with transient but overt improvement in the signs and symptoms of mass effect due to BM. [5]. Due to the work of Chao and Kofman, WBRT and corticosteroids became the mainstays of treatment for the next several decades. While a number of retrospective studies in the 1980s alluded to increased survival for surgically-resected single BM, these studies were viewed with skepticism secondary to questionable selection bias [6–10]. It was not until the 1990s that two prospective, randomized controlled trials showed the efficacy of surgical resection [11, 12]. The trials established that resection of a single cerebral metastasis followed by postoperative WBRT was superior to WBRT alone, demonstrating a survival benefit and validating the role of surgical resection in the management of BM. In 1990, Patchell et al. randomly assigned 48 patients with single brain metastases to either surgical removal of the brain tumor followed by radiotherapy (surgical group) or needle biopsy and radiotherapy (radiation group) [11]. Twenty-five patients were assigned to the surgical group and 23 to the radiation group. Recurrence at the site of the original metastasis was less frequent in the surgical group than in the radiation group (5 of 25 [20%] vs. 12 of 23 [52%]; $p<0.02$). Overall survival was longer in the surgical group (median, 40 weeks vs. 15 weeks in the radiation group; $p<0.01$), and the patients treated with surgery remained functionally independent longer (median, 38 weeks vs. 8 weeks in the radiation group; $p<0.005$). In 1993, Vecht et al. confirmed Patchell's work in a similar, prospective, randomized trial [12]. Sixty-three patients with systemic cancer and a radiological diagnosis of a single brain metastasis were enrolled to either surgery plus radiotherapy or to radiotherapy alone. Thirty-two patients were assigned to the surgical group and 31

patients to the radiation group. The surgical group survived 10 months compared to 6 months for the patients receiving radiation ($p=0.04$) and had improved functionally independent survival (FIS) ($p=0.06$). Furthermore, this study determined that patients with progressive extracranial disease had poorer outcomes than those with stable disease. Those with progressive systemic disease were found to have a median overall survival of 5 months and a FIS of 2.5 months irrespective of treatment for the cranial disease. However, patients with stable extracranial disease had a median survival of 12 months vs. 7 months (surgery vs. radiotherapy, respectively) and a median FIS of 9 months vs. 4 months. Improvement in functional status occurred more rapidly and for longer durations of time after neurosurgical excision and radiotherapy than after radiotherapy alone. Both studies demonstrated conclusively that patients with cancer and a single brain metastasis treated with surgical resection plus radiotherapy live longer, have fewer recurrences of cerebral metastases (local and distant) and have a better quality of life than similar patients treated with radiotherapy alone.

A subsequent study by Patchell et al. in 1998 evaluated the use of WBRT and surgery versus surgery alone [13]. Ninety-five patients were randomized to treatment with postoperative WBRT (radiotherapy group) or no further treatment (observation group) for BM. Forty-nine patients were assigned to the radiotherapy group and 46 patients to the observation group. Although there was no difference in survival observed between the two treatment arms, patients treated with surgery plus WBRT had fewer recurrences at the original site of metastases (5 of 49 [10%] vs. 21 of 46 [46%]; $p<.0.001$) and at other sites in the brain (7 of 49 [14%] vs. 17 of 46 [37%]; $p<0.01$) and fewer neurological deaths than surgery alone (6 of 43 deaths [14%] vs. 17 of 39 [44%]; $p=0.003$). This study supported WBRT with surgery vs. surgery alone, although the role of WBRT or more localized adjuvant irradiation remains controversial.

2 Role of Surgery

Currently, surgery should be considered the most definitive treatment for cerebral metastases, with several advantages over other treatment modalities. Surgery is the only modality that provides a histological diagnosis. This can be important in some patients, since 5–11% of patients with known systemic cancers and a single cerebral lesion have lesions that are not metastatic cancer, such as primary tumors or brain abscess [11, 14]. Furthermore, surgery is necessary in patients with cerebral metastases where there is no identifiable primary tumor on staging evaluation. Histological diagnosis allows oncologists to infer potential sensitivities to chemotherapy and radiotherapy, which may influence treatment strategies for metastatic tumors from different primary cancers. For example, small cell lung cancer is far more responsive to WBRT than melanoma, renal cell carcinoma, and sarcomas; the sensitivities of breast, GI, and non-small lung cancers lie between these two extremes [15–18]. For other tumors, such as germ cell tumors and choriocarcinoma,

chemotherapy is viewed as the primary treatment modality [19]. Histologic tissue diagnosis provides tissue samples for receptor studies, such as estrogen, progesterone or thyroid hormone and HER2, and other tissue markers that assist in further development of more tumor directed treatment modalities. Furthermore, surgical resection is the modality that most rapidly alleviates the symptoms of increased intracranial pressure by eliminating local compression and direct irritation, which are also causes of peritumoral edema and potential seizure. Relieving the source of edema attenuates the need for prolonged high dose steroids, which can result in hyperglycemia, hypertension and impaired wound healing. More extreme cases of chronic high dose corticosteroid administration can result in Cushing's syndrome, steroid myopathy and peripheral neuropathies. Large tumors resulting in mass affect and midline shift require urgent excision. Furthermore, surgery provides additional benefit in tumors >4 cm, for which stereotactic radiosurgery (SRS) is not indicated [20].

The underlying goal of surgical excision is complete cure. This possibility exists if all tumor cells can be removed. Unfortunately, the reality is that surgery often leaves behind microscopic deposits of tumor cells. This combined with the burden of extracranial disease keeps the prognosis for brain metastases poor for many patients. Surgical resection of single cerebral metastases followed by WBRT carries median survivals from 6 to 16.4 months with local recurrence rates of 7–15% [21]. Three retrospective analyses of 3,131 patients, with varying metastatic brain tumors, were evaluated to compare supportive care to surgery alone and to radiation therapy alone [22]. Two studies included patients with suspected melanoma totaling 2,946 patients and a third study consisting of 1,292 patients with primary tumors from lung, breast and melanoma [23–25]. Regardless of tumor type, patients treated with supportive care alone had median survival of 1-2 months, while patients treated with radiation therapy alone had median survivals of 3-4 months. Surgery alone resulted in median survivals of 6-9 months, with median survival time increased to 9 months with surgery plus radiotherapy. However, in non-eloquent areas of the brain, it may be feasible to remove the entire metastatic lesion and a small margin of surrounding edematous brain, which may obviate the need for post-operative WBRT or other therapy. This strategy may be particularly useful for BM that are less sensitive to radiation, such as renal cell cancer, melanoma or sarcoma [26].

As previously stated, modern advances in microsurgery, a better understanding of surgical approaches, functional neuronavigation, intraoperative ultrasound, cortical mapping and awake craniotomies have allowed previously inaccessible lesions to be resected with lower morbidity and mortality. Currently, neurological morbidity is less than 10% [8, 27, 28], non-neurological morbidity less than 8% [27, 28] and mortality less than 3% [29–31]. While there are no current firm surgical criteria for inaccessible or unresectable lesions, most agree that with the limited survival of patients with systemic cancers and the availability of numerous non-invasive treatment modalities, surgical resection should not cause neurological deficits that may require rehabilitation or prolonged hospital stays. This tends to prohibit surgery for lesions within the brainstem, although successful resection of lesions

within this area has been reported [32]. Other lesions historically deemed inaccessible are those located in the basal ganglia, thalamus and internal capsule, although with the advent of neuronavigation and intraoperative ultrasound more of these lesions are being resected [28, 33]. Some centers employ intra-operative CT or MR imaging, although the utility and cost-effectiveness of these suites in surgery for BM remains to be demonstrated [34]. Furthermore, lesions located within motor, visual and speech cortices pose an increased risk. However, with improved localization techniques, cortical mapping and awake craniotomies these lesions can be resected with great success [21, 35, 36]. Ultimately, the amount of postoperative morbidity a patient is willing to accept is of utmost importance when assessing resectability [33].

3 Patient Selection for Surgical Treatment of Brain Metastases

When considering patients for possible surgical resection of cerebral metastases it is important to realize that not all patients will benefit from surgical resection. Multiple variables must be taken into account when developing a treatment plan, such as: (1) the status of the primary cancer; (2) the patient's functional status; (3) histology and grade of metastasis; and, (4) radiographic features such as number, size and location of BM.

3.1 Patient and Clinical Characteristics

Patient selection is largely directed by the overall health of the patient. As with other neurosurgical procedures, patients should be evaluated with a complete history and thorough physical examination. Although status of systemic disease needs to be taken into consideration when assessing patients overall general health, the patient's medical comorbidities also play an important role when assessing surgical risk. Conditions that affect general anesthesia risk need to be evaluated carefully and surgical risks need to be stratified to determine whether surgical resection is appropriate. Patients with life-threatening medical comorbidities, such as cardiac or respiratory conditions, may be better treated with less invasive modalities such as stereotactic radiosurgery. Traditionally, patient selection for surgical benefit focuses on factors such as age, preoperative neurological status based on the Karnofsky Performance Score (KPS), stable or absent extracranial disease and the interval between diagnosis of primary tumor and cerebral metastases. The KPS ranks patients on their ability to carry out activities of daily living, with scores 70 or greater having the best outcomes after surgical resection [37]. Of all the factors discussed above the KPS has repeatedly shown to be the strongest predictor of survival [24, 38, 39]. Conversely, studies have shown that older age is a strong predictor of worse prognosis for BM [10, 40].

More recently, the Radiation Therapy Oncology Group (RTOG) in the United States proposed three prognostic groups, referred to as the recursive partitioning analysis (RPA), for patients with cerebral metastases [41]. The data was based on RPA for trials of radiotherapy for cerebral metastases. The patients were ranked into one of three prognostic groups based on age, KPS and status and extent of extracranial disease. The best prognostic group, RPA Class 1 included patients less than 65 years of age, KPS score of 70 or greater, absence of extracranial metastases, and good control of primary tumor. In this group median survival was 7.1 months. Class 2 patients had a KPS of 70 or greater but were deficient in meeting one of the other criteria. For example, patients older than 65 and/or with uncontrolled systemic disease fall into Class 2. Median survival in this group was 4.2 months. Patients in RPA Class 3 were those with KPS < 70, having the poorest prognosis and median survival of 2.3 months. Class 1 patients are considered as having the best chances for favorable outcome with surgical resection of cerebral metastases, while surgical resection of Class 2 patients requires careful consideration of patient survival and operative risk. Class 3 patients are typically not considered for surgical resection. The RPA classification system has been confirmed by multiple other studies and should be taken into account, along with KPS, when evaluating patients for resection of BM [42–44]. Other classification schemes exist, such as the Graded Prognostic Assessment (GPA) system and others. The GPA considers 4 factors: patient age, KPS, presence of extracranial metastases, and number of intracranial lesions [45]. Each of the aforementioned variables is assigned a score of 0, 0.5, or 1, and the final GPA score is the sum of these values. The final GPA scores can be separated into four classes: 0-1, 1.5-2.5, 3, and 3.5-4, with greater scores having the better prognosis in terms of median survival. The GPA is as prognostic as the RPA index, as it is a compilation of the most current data from 5 randomized RTOG studies, however it is less subjective and more quantitative. Additionally, the GPA score takes into account the number of intracranial metastases, whereas the RPA classification does not include this measure. How well the GPA or the RPA apply to a strictly surgical population or allow direct comparisons between surgical and non-surgically treated populations remains to be demonstrated.

While the KPS and previously discussed classifications provide a general framework for patient selection, additional parameters provide important predictors of surgical outcome. Patients with a longer disease-free interval between first diagnosis of primary tumor and diagnosis of BM have a longer median survival. Different primary tumors metastasize to the brain at different rates: for example, patients with lung cancer have the shortest time interval from initial diagnosis to diagnosis of BM, with a median interval of 6–9 months [7, 33, 46]. On the other hand, patients with melanoma and breast cancer more often present in a delayed fashion, with a median interval of 2–3 years after primary diagnosis [33, 47]. Multiple studies have found that longer disease-free intervals correlate to prolonged survival times [11, 13, 39, 48]. Pieper et al. examined disease-free interval in breast cancer patients and found that a longer disease-free interval correlated to longer survival after craniotomy

[39]. Similarly, Galicich and coworkers demonstrated that the diagnosis of cerebral metastases within 1 year of diagnosis of a primary tumor lead to decreased survival time after craniotomy [48]. It is postulated that a shorter interval between diagnosis of a primary tumor and a brain metastasis may be a result of a more aggressive phenotype of the cancer in question. Thus, patients with shorter disease-free intervals between the diagnosis of their primary tumor and their brain metastasis may have poorer prognosis. This should be considered when selecting candidates for surgical resection.

As with any surgical procedure, the patient's clinical status must be carefully integrated to determine who may benefit from surgical resection. The degree of control of the systemic disease, defined as activity and extent of primary cancer and extra-cerebral metastases, has been shown to be the most important variable in determining overall survival in patients undergoing surgical resection of brain metastases [49–52]. All patients should undergo a thorough metastatic work up consisting of CT scans of the chest, abdomen and pelvis to assist with disease staging and prognosis unless mass affect or a primary cancer is identified. Positron emission tomography (PET) scanning, bone scanning, and serum tumor makers may also be needed to stage a patient's systemic disease [49]. If a patient's systemic disease is well controlled, the intracranial disease becomes a more important determinant of patient survival. Patchell et al. found that 71% of the patients in the surgically treated group died from progression of their systemic disease rather than from neurological causes [11]. This point was further expanded upon in 1996 by Mintz and colleagues who reported a prospective, randomized trial in which surgery plus WBRT was not shown to suggest a survival advantage over WBRT alone in patients with a single metastases [52]. However, their results were deceiving as greater than 45% of the patients in their series had uncontrolled systemic disease and 41% had a KPS of 50 or less. This is in contrast to Patchell's study where only 38% of the patients had extracranial disease and all patients had KPS of 70 or greater. Further examination of Mintz's patient cohort revealed that a great majority of the patients died from progression of their systemic (extracranial) disease. Also, Wronski and colleagues found that the presence of leptomeningeal disease is associated with poorer prognosis, and that surgery is contraindicated in these patients [17]. The current tendency is to offer surgery to patients with an expected survival of greater than 3–4 months, based on the degree and control of their systemic disease [49, 53].

Other important factors that should be assessed are gender, location of the BM, and neurological status [10, 11, 54]. In general, a worse prognosis is associated with posterior fossa lesions and the chance of leptomeningeal dissemination is higher in this location [55, 56]. A patient's preoperative neurological status is highly suggestive of their potential for neurological recovery post operatively, and as previously stated it is of critical importance to limit prolonged recovery. A final independent factor in patient survival is that patients with minimal neurological deficits survive longer than those with severe deficits [8, 57].

3.2 Primary Tumor Characteristics

Before embarking upon the surgical resection of brain metastases, it is useful to consider the chemosensitivity and radiosensitivity of the primary tumor. For example, metastases from small cell lung cancer and lymphoma tend to be highly radiosensitive and most often treated with WBRT in the United States. Conversely, renal cell carcinoma, melanoma and most sarcomas are radioresistant and are more often treated with surgery, while the chemosensitivity of germ cell tumors and choriocarcinoma lend themselves to chemotherapy as the primary treatment [53].

Tumor histology also plays a vital role as an indicator in patient survival. Median survival for treated brain metastases ranges from less than 6 months in melanoma [58], to 8 months in lung [59], nearly 12 months in breast [60] and 21.5 months in renal cell carcinoma [61]. For example, the fact that patients with BM from melanoma have poorer survival, even after surgery, when compared to patients with other types of cerebral metastases suggests that more aggressive tumors such as melanoma may be better treated with modalities other than surgery [30, 62–64]. Since melanoma has a high tendency to metastasize to the brain many patients may be sheltering undetectable lesions at the time of resection or radiosurgery that may become apparent later and lead to earlier neurologic progression.

3.3 Number of Lesions

3.3.1 Single Brain Metastases

Currently, operative resection is considered the optimal treatment for patients with surgically-accessible, single BM who have a good functional status [1, 49]. As previously discussed, multiple retrospective studies have shown a benefit in survival for patients with single brain metastases undergoing surgical resection when compared to other treatments. However, it was not until two independent randomized, prospective trials by Patchell and Vecht in the 1990s confirmed the efficacy of surgical resection [11, 12]. In a Patchell et al. study, patients treated with surgery plus WBRT, when compared to WBRT alone, had a longer median survival (9.2 and 3.4 months, respectively), better local tumor control (80% and 48%, respectively) and better KPS at distant interval from treatment, signifying better quality of life [11]. Vecht et al. reported similar results, with an increased survival in patients receiving surgery plus WBRT as compared to patients in the radiotherapy group alone (10 and 6 months, respectively) [12]. The surgical group also had a longer period of functional independence. Importantly, this benefit of increased survival may only be seen in patients with the potential for long-term survival as outlined by those with lower age, higher Karnofsky scores, and stable extracranial disease [11, 44].

3.3.2 Multiple Brain Metastases

Historically, surgical resection of multiple BM was fraught with nihilism. It was believed that the patients would likely die before any benefit, therefore surgery was not considered a good treatment option [65–67]. In 1993, Bindal and colleagues challenged this notion by retrospectively reviewing 56 consecutive patients in whom multiple brain metastases had been surgically resected [27]. Of the 56 patients, 30 patients had one or more lesions left unresected (Group A) and 26 patients had resection of all lesions, up to 3 (Group B). Groups A and B were compared to Group C, which was 26 matched controls with single surgically resected lesion. Survival was only 6 months in Group A, with unresected lesions; whereas, Groups B and C both had median survivals of 14 months. There was no difference in surgical morbidity, mortality, or complications due to craniotomy in all three groups. The authors concluded that the removal of multiple metastatic lesions (<4) is as effective as resection of single BM, when all lesions are surgically accessible and completely resected. Similarly, Wronski et al. compared 70 patients with cerebral metastases from breast cancer that were treated by surgical resection and found no significant difference in overall survival in patients with two or three lesions resected when compared to those with a single brain metastasis [17]. Similarly, Paek and coworkers retrospectively evaluated 208 patients who underwent surgical resection of brain metastases [68]. A single lesion was resected in 191 patients and two or more metastases were resected in 17 patients. Survival was nearly identical in the two groups, suggesting that in good prognostic patients with single or multiple brain metastases, surgical resection improved or stabilized neurological symptoms, conveying a survival advantage without an increase in perioperative risk. Lastly, in 2000, Iwadate and colleagues studied 61 patients who underwent surgical resection of multiple brain metastasis and they observed a median survival time of 9.2 months, which did not vary significantly from 77 patients who had resection of a single brain metastasis (8.7 months) [69].

While the benefit of surgical resection of multiple BM needs to be evaluated by a randomized study, current recommendations are that patients with multiple cerebral metastases, not greater than four, not be excluded from surgical consideration. Furthermore, each lesion should be evaluated independently and if deemed resectable then be removed through one or more craniotomies. If not all lesions are considered resectable then surgery may be considered for the symptomatic lesion as long as further therapy with whole brain or stereotactic radiation is pursued. Finally, in patients with four or more lesions in whom there is a dominant lesion with significant mass effect and neurological signs or symptoms, surgical resection of the dominant lesion may be reasonable, to diminish mass effect and permit subsequent treatment with WBRT, SRS, chemotherapy, or a combination of these modalities.

3.4 Recurrent Metastases

Recurrence of brain metastases in patients who had previously undergone surgical resection for a single brain metastasis is roughly 31–48% [1, 33, 70]. This includes both local (initial resection site) and distant (a brain lesion distant from initial resection) recurrences. Typically, local recurrences are from the growth of residual, microscopic tumor cells that may remain after gross resection at the time of initial surgery whereas distant recurrences result from the growth of dormant or newly established embolic tumor foci. Surgical resection has a significant role in recurrent brain metastases. Resection has shown to improve survival and quality of life in patients who undergo repeat craniotomy for recurrent disease [29, 70]. Bindal et al. reviewed 48 patients with recurrent brain metastases, 30 with local recurrence, 16 patients with distant recurrence and 2 with both local and distant [29]. Reoperation resulted in 75% of the patients showing neurological improvement, with no operative morbidity or mortality. Their conclusion was reoperation for recurrent brain lesions could prolong survival and increase quality of life. Furthermore, they concluded that five factors influence survival: status of systemic disease, KPS score, time to recurrence, age, and type of primary tumor. They used this data to predict which patients may benefit from repeat resection. A grading system was devised using five variables that negatively correlated with survival. Each of the following, if present, was given a value of 1; or O, if absent: preoperative KPS 70 or less; presence of active systemic disease; age greater than 40; if melanoma or breast cancer was the primary tumor; and a time to recurrence less than 4 months. The maximum score possible was 5. Each numerical total was converted to a Roman numeral grade. Bindal found that there was a correlation between grade and survival. Grade I patients had a 57% 5-year survival, while Grades II, III, and IV had median survivals of 13.4, 6.8 and 3.4 months, respectively. Typically, patients in grades I and II are considered for surgery while those in grade III are less likely candidates and Grade IV patients are rarely offered surgery. Arbit et al. also reviewed patients with non-small lung cancer harboring recurrent brain metastases and described a statistically significant survival benefit with repeat resections [71].

Other benefits of reoperation are to confirm tumor histology and discern between radiation necrosis and recurrent tumor. Determination of radiation necrosis has proved difficult when exclusively based on imaging characteristics, yet pathological determination of radiation necrosis may be important to plan adjuvant treatment. The presence of radiation necrosis may preclude radiation treatment [49]. Furthermore, it allows for resection of necrotic tissue, which may exert significant mass effect, and for those patients in whom additional radiation is contraindicated, resection may allow for the placement of intracavitary chemotherapy, which may provide prolonged local control [72], although definitive data on this modality is still lacking.

3.5 Tumor Size

The size of BM is another important variable that needs to be considered when assessing patients for possible surgical resection. Even though the size of cerebral metastases has not been shown to effect survival, with the wide availability of SRS, size has become progressively more important when deciding treatment modalities. Although the considerations regarding the use of SRS to treat a single brain metastasis will be addressed elsewhere in this volume, SRS has been shown to be effective for small BM [73–75]. The treatment paradigm tends to be clearest with lesions >4 centimeters (cm) in maximum diameter and lesions less than or equal to 1 cm. Lesions greater than 4 cm are not amenable to SRS and are typically better treated with surgical resection. On the other hand, lesions less than or equal to 1-2 cm and especially those located deep with the brain or solely in eloquent brain regions may also be treated with SRS [49]. If both treatment modalities seem feasible for a given patient then ultimately other variables need to be taken into account such as the extent of systemic disease, presence or absence of seizures, amount of peritumoral edema, and the patient's overall medical condition.

4 Surgical Methods

4.1 Principles and Goals

Brain metastases can arise in any part of the brain but tend to have a predilection for the grey-white junction, especially within the vascular distribution of the middle cerebral artery [76, 77]. This unfortunately often positions them in or near eloquent areas of brain, such as the angular gyrus or the pre- and post-central gyrus. Brain metastases typically are solid masses and displace rather than invade the surrounding brain. However, infiltration from brain metastases can occur although it typically does not extend beyond 5 mm within the brain parenchyma [33]. In larger lesions there may be areas of central necrosis. The primary goal of surgery for brain metastasis is gross total resection. This involves meticulously defining the tumor-brain interface and removing all of the tumor tissue as safely as possible. Often a gliotic pseudo-capsule that surrounds the metastasis separates it from the edematous brain, which can help aid in gross total resection [33]. Meticulous attention must be taken as to not injure any vessels that traverse or are adjacent to the tumor and that may perfuse normal brain parenchyma. Conversely, vessels supplying only tumor tissue can be appropriately coagulated and divided. In 2009, Yoo et al. reported that gross total resection along with microscopic resection of tumor cells infiltrating adjacent brain parenchyma, to a maximum depth of 5 mm circumferentially around

tumor bed, significantly reduced local recurrence when compared to gross total resection alone [26].

Surgical resection of brain metastases can be complicated by leptomeningeal dissemination (LMD). Primarily, metastatic tumors should be resected *en bloc*; however, until recently, there has been little in the neurosurgical literature to suggest benefit of *en bloc* resection over piecemeal tumor resection. In general, a piecemeal resection carries an increased risk of leaving residual tumor as well as increasing the potential risk of tumor spillage into the surrounding area [78]. Recently, Suki et al. studied 260 patients with posterior fossa brain metastases to see if there was a higher incidence of LMD in patients treated with surgery when compared to patients treated with SRS [56]. They found that piecemeal tumor resection was associated with a significantly higher risk for LMD when compared to *en bloc* resection and to SRS (123 cases, $P=0.006$). The same group presented a second study that showed an increase risk of local recurrence of brain metastases when resected via piecemeal rather than *en bloc* [49]. As helpful as *en bloc* resection may be in preventing LMD and local recurrence, there are larger tumors that may not be amenable to *en bloc* resection. These tumors may require central debulking to prevent damaging eloquent cortex.

Improved understanding of brain anatomy and surgical approaches, along with technological advances in imaging, microsurgery, neuronavigation and intraoperative surgical adjuncts aid surgeons in performing safer surgery with increased likelihood of gross total resection.

4.2 Surgical Approaches

Surgically, supratentorial metastases can be described based on their relationship to adjacent sulci and gyri while cerebellar metastases are characterized by hemispheric (lateral or medial) or deep locations [28, 79]. Supratentorially, metastases can occur superficially just below the cortex, filling a gyrus (subcortically), deep within a sulcus (subsulcal), or deep within a gyrus adjacent to a sulcus (subgyral), deep within white matter, or lobar, which is independent of a single sulci and gyrus. Less common, BM can occur in the ventricles (intraventricular) [53].

When planning for surgical resection, the approach is determined by the anatomical location of the metastasis. Lang et al. thoroughly explain multiple surgical approaches, based on anatomical location, as follows [53]. Supratentorial subcortical lesions are best approached making an incision at the apex of the sulcus with circumferential removal of the lesion. By removing cortical tissue above the lesion this will aid in removal of the tumor. If the lesion lies within eloquent cortex, a longitudinal incision planned via local functional mapping; with direct brain stimulation can suffice in tumor resection. Subgyral and subsulcal metastases are best approached via splitting the fissure leading to the lesion, with the only difference being for subgyral lesions an incision is made in the side of the sulcus where as for subsulcal lesions an incision is made at the base of the sulcus. Tumors located deep within the white matter can be approached either by transsulcal or transcortical approaches. Splitting of the sylvian

fissure allows access to tumors in the subinsular cortex while the interhemispheric approach is used for lesions located in the midline. Intraventricular tumors can be approached either by the transcortical or transcallosal routes.

Surgical planning for cerebellar lesions is best approached using the shortest transparenchymal route to the tumor. Superior hemispheric lesions are best resected through the supracerebellar cistern, while lateral hemispheric lesions are approached directly via a posterior approach. Resection of inferior cerebellar tumors often requires removal of the bone of the midline aspect of the posterior rim of the foramen magnum, with opening of the cisterna magna to decompress the cerebellum.

5 Surgical Adjuncts

Due to the technological advances in tumor localization and ability to identify eloquent brain, safe and effective tumor resection is plausible for lesions previously considered unresectable. With the advent of computer-assisted, image-guided stereotaxis, intraoperative ultrasonography and increasing availability of intraoperative CT and MR imaging, the ability to localize the lesion is significantly improved [80]. Our ability to identify the central sulcus is enhanced by somatosensory evoked potentials. Awake craniotomy can also be a useful adjunct in the resection of tumors in or near eloquent cortex [35]. These tools allow for more precise identification of the lesion or lesions resulting in more accurate and smaller operative corridors through which the lesion can be resected. They also allow for resection of small, deep tumors or tumors located within functional brain with fewer complications and decreased length of stay, while enhancing functional outcomes (KPS) and quality of life [35].

5.1 Ultrasound

Intraoperative ultrasound has been used in neurosurgery since the 1980s and was a major surgical adjunct until the introduction of newer localizing techniques, such as frameless stereotactic neuronavigation [81, 82]. Portable, two-dimensional intraoperative ultrasound is able to determine real-time information such as tumor location, size, and morphology (cystic or solid) as well as evaluate the extent of tumor resection and outline a tumor's relationship to adjacent anatomic structures, like ventricles and sulci [83]. The majority of metastatic lesions are highly echogenic and well demarcated, when compared to normal or edematous brain. On the other hand, cystic metastases may appear inhomogeneous with only a small echogenic rim surrounding the anechoic cyst [84]. The major added benefit of intraoperative ultrasound is its ability to overcome the brain shift that inevitably occurs during surgery and the resultant inaccuracy that arises in other forms of localizing techniques that rely on preoperative data [85]. Ultrasound is also portable and

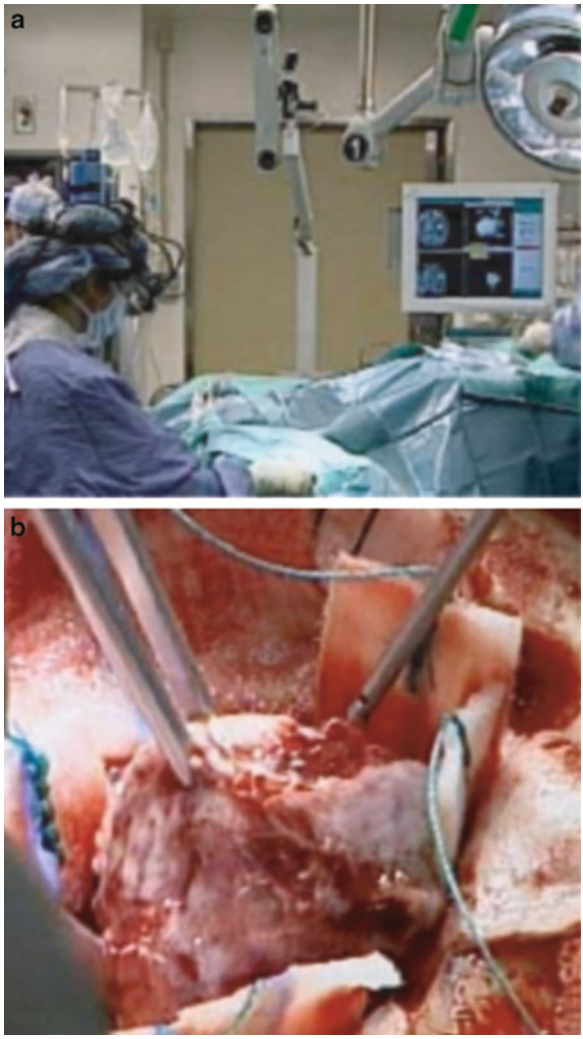

Fig. 7.1 In surgical excision of brain metastases, the surgical team relies upon stereotactic navigation using preoperative images of the patient to identify the location of the tumor deep to the skull (**a**). This allows precise localization of the lesion and *en bloc* resection (**b**)

inexpensive. One limitation of ultrasound is that since it cannot penetrate bone, it cannot be used for pre-operative surgical planning; which may be obviated by using it in combination with stereotactic navigation systems.

5.2 Stereotaxis

The invention of computer-assisted image-guided stereotaxis has allowed for more accurate surgical planning and smaller, more direct corridors for surgical resection of brain tumors (Fig. 7.1). Frameless stereotaxy is an essential tool in the surgical

management of deep, small cerebral metastases. A virtual projection of the patient's brain is constructed from the pre-operative CT or MRI imaging studies. Fiducial markers, or anatomic landmarks, are matched directly to the pre-operative imaging, re-constructing a virtual map which becomes the stereotactic space of the operative field [28, 86]. This advanced localization technique is useful for planning the skin incision, the boundaries of the craniotomy and the initial surgical route. However, as eluded to previously, this technique does not account for the intraoperative changes that occur, such as brain shift [85]. Currently available systems are able to combine diffusion tensor imaging (DTI) or functional MRI and integrate this data with anatomical stereotaxic images [87, 88]. Intra-operative CT or MR imaging suites have also been developed, although they as previously stated their utility and cost effectiveness remains to be determined.

5.3 Functional Mapping

When BM are located within eloquent regions of the brain, neurophysiologic brain mapping is useful in preserving function and decreasing neurological morbidity. While DTI can help identify important white matter tracts and functional MRI can help identify motor, sensory and language, these modalities remain imprecise, as a rough localization based on pre-operative studies. When precise intraoperative localization is crucial to preserve neurological function, one may use either phase reversal techniques or direct cortical or subcortical stimulation.

5.3.1 Phase Reversal

Somatosensory evoked potentials (SSEPs) can be used to define the central sulcus and thus the motor and sensory cortices (Fig. 7.2). After exposure of the cortical surface a strip electrode is placed perpendicular to the long axis of the motor and sensory gyrus. An SSEP is produced via stimulation of the median, ulnar or tibial nerves on the limb contralateral to the exposed hemisphere. After electrical stimulation, the signal is transmitted by the dorsal columns of the spinal cord to the medial lemniscus, thalamus and ultimately the contralateral somatosensory cortex [36]. This results in a recordable potential via the strip electrode. A phase reversal is seen when the positive potentials of the motor cortex are simultaneously seen with negative deflections from the sensory cortex. The corresponding number on the strip electrode where the reversal of positive and negative deflection occurs corresponds to the central sulcus. Visual inspection then will allow for identification of the motor and sensory cortices. It should be noted that the vector of the tibial waveforms is often difficult to localize on the cortical surface and may lead to inaccurate localization of the central sulcus [89].

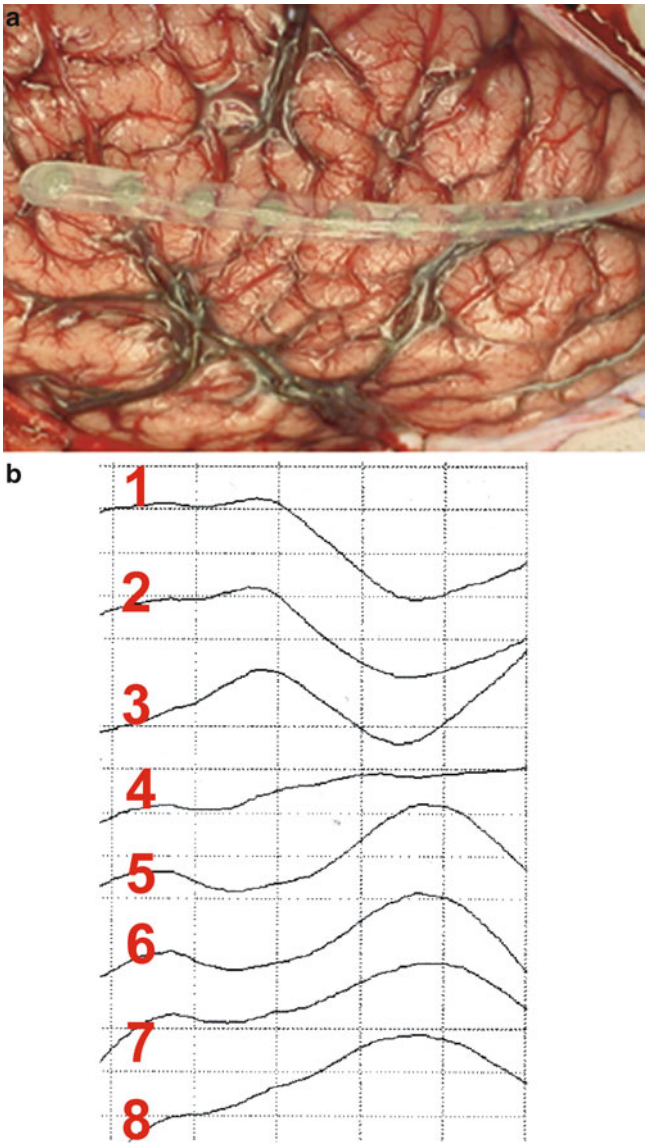

Fig. 7.2 In central sulcus localization for tumors in or near the motor strip, a surface electrode is placed upon the brain (**a**) in order to identify the somatosensory evoked potential impulses from the stimulation of the contralateral median nerve. In this patient, the impulses show a phase reversal between electrodes 3 and 5 (**b**), suggesting that the central sulcus is immediately beneath electrode 4

5.4 Direct Cortical Stimulation

Direct cortical stimulation can be used alone or in conjunction with phase reversal, to identify motor cortex but tends to play an especially crucial role when used with awake craniotomies to localize language areas. The procedure consists of stimulating the cortical surface with constant current biphasic, square wave pulses and a current incrementally raised from 1-15 mA until the desired affect is observed [90–92]. Direct cortical stimulation of the motor cortex will result in a direct response from the patient, for example, movement of the contralateral face, arm or leg, or speech arrest. Direct cortical stimulation reveals eloquent cortex to be avoided in attempting resection of cortical and subcortical lesions.

6 Role of Whole-Brain Radiation Therapy After Resection of Metastatic Brain Tumors

WBRT has been a mainstay in the treatment of brain metastases for many decades. It is used as an adjunct after surgical resection of a brain metastasis in an attempt to eliminate local residual tumor cells as well as distant tumor deposits, if present. Multiple retrospective studies have examined the efficacy of WBRT, with most showing benefit [8, 64, 93, 94]. However, WBRT does have known side effects, such as dementia, in long-term survivors. The neurocognitive side affects tend to occur 6-12 months post radiation and may outweigh the intended benefit of WBRT [95]. Therefore, several authors have advocated that WBRT be deferred, especially for radioresistant tumors and only employed if local treatment fails. Multiple randomized trials have been conducted in recent years evaluating the outcome of withholding WBRT [13, 96, 97]. Patchell and coworkers conducted a prospective, randomized trial comparing the effectiveness of adjunct WBRT in patients, with single brain metastases, treated by surgery [13]. Following surgery, patients were randomly assigned either to an observation group or a treatment group (received 50.4 Gy over 5.5 weeks). The patients who received WBRT had a reduction of tumor recurrence when compared to the observational group (18% vs. 70%, respectively) and 46% and 10% local recurrence rates in the surgery alone group and surgery plus WBRT, respectively. Unfortunately, the study did not show any increase in functional independence or survival, suggesting that the long-term neurotoxicity of WBRT offsets its potential benefits. Opponents of this study suggested that the deleterious effects in neurocognition were potentially attributable to the higher than standard radiation doses (50.4 Gy vs. more conventional 30 Gy). However, a randomized control trial in 2006 by Aoyama and colleagues using 30 Gy in 10 fractions reported that omitting WBRT in patients after either surgery or SRS results in worse local and distant control but it does not increase functional independence or survival [96]. More recently, Kocher et al. showed that after stereotactic radiosurgery or surgery the addition of WBRT (30 Gy in 10 equal fractions) reduces

intracranial recurrence and neurological death, but fails to improve the duration of functional independence or overall survival [97]. Although becoming increasingly more popular, withholding adjuvant WBRT until local treatment failure will need more study in an attempt to avoid the deleterious neurocognitive side effects of WBRT.

7 Post-Operative Management and Potential Complications

Post-operatively most patients undergo an MRI within 24 h of surgery to determine the completeness of resection. This study also serves as the baseline scan to aid in determining recurrent tumor at follow-up imaging.

Two immediate concerns perioperatively in the care of brain metastasis patients are post-operative peritumoral edema and seizures. The use of post-operative steroids is largely determined by the edema on post-operative imaging as well as the patient's clinical exam. If steroids are used, the clinician should strive to administer the lowest effective dose and taper rapidly. A number of studies have tried to answer the question of whether or not to administer prophylactic anticonvulsants in the setting of brain tumors, unfortunately they were unable to achieve consensus [64, 98]. The American Academy of Neurology has since released practice guidelines, these guidelines recommend that anticonvulsants need not be given unless seizures have been documented [99].

Surgical complications must be considered when weighing the risks and benefits of resection of BM. Non-neurologic complications that can arise are similar to complications that can arise from other neurosurgical procedures, such as venous thromboembolic disease, pulmonary embolism, postoperative hematoma, wound infection, pneumonia and others. Non-neurological complications range from 3–6%, while neurologic complications (hemiparesis, speech dysfunction) are less well documented, with rates ranging from 3–6% [8, 27, 100, 101].

Surgical mortality is most often defined as death within 30 days of operation, although historically some studies used different intervals [102]. In the early twentieth century, Harvey Cushing found that surgical mortality after resection of brain metastases was 38% [103]. Today, with the introduction of modern surgical techniques, mortality rates of less than 3% are expected [29–31].

8 Survival

Currently, surgery for BM shows a 1 year survival of 44% (range of 22–68%) and a median survival of 10 months (range of 6–16 months), when not segregated by histological type [21]. The shortest survival is found in patients harboring metastatic melanoma, while patients with metastatic lung, breast or renal cell carcinomas have the longest survival [53].

9 Conclusions

As oncologists develop improved treatments for systemic cancers, patients with metastatic disease are surviving longer and more patients are being considered for surgical resection of brain metastases. Improvements in neurosurgical and neuroanesthetic techniques, along with advances in computer-assisted stereotactic navigation, intraoperative ultrasound and functional mapping has led to safer, more complete resections for BM. Furthermore, these advances have led to marked improvements in both length and quality of life in patients with BM. Thus, surgery continues to have an important role in the treatment of patients with BM. Further refinements in the surgical treatment of BM will depend upon critical analysis of data related to specific histologic types of metastatic tumors in general and specific molecular subgroups in particular (for example, in breast cancer, women with "triple negative" status versus those that have HER2 amplification) [104]; and assess the role of limited field irradiation (for example, SRS to the operative bed and a small margin or intra-operative radiotherapy to the resection bed) as well as the role for chemotherapy and small molecule inhibitors to enhance the efficacy of treatments for patients with brain metastatic disease.

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Chapter 8
Is There a Role for Systemic Chemotherapy in the Treatment of Brain Metastases?

Marc C. Chamberlain

Abstract Brain metastases (BM) are the most common metastatic complication of systemic cancer to the central nervous system (CNS). Treatment is most often with radiotherapy (whole brain radiotherapy (WBRT), stereotactic radiotherapy (SRT) or a combination) and in selected patients (for example solitary metastasis) resective surgery. The role for chemotherapy in the treatment of BM is difficult to define due to a paucity of clinical trials the majority of which are nonrandomized, retrospective studies and case reports. Two factors influence the efficacy of chemotherapy in BM; the intrinsic chemosensitivity of the tumor and chemotherapy drug delivery. Several generalizations can be made regarding chemotherapy of BM based on the limited literature. Response to chemotherapy reflects inherent chemosensitivity of the primary tumor with best responses seen with small cell lung cancer, intermediate responses seen with non-small cell lung cancer and breast cancer and low response rates with melanoma. Response to chemotherapy is in addition determined by prior chemotherapy exposure as front-line chemotherapy has higher response rates than second- or third-line chemotherapy. Response to chemotherapy as compared to WBRT or SRT is inferior and less durable. The use of chemotherapy for the treatment of BM is most often limited to patients having failed radiotherapy (often both WBRT and SRT) and with multiple lesions. Emerging data suggests that targeted therapies may play an increasing role in the treatment of BM.

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1 Introduction

Brain metastasis (BM) like other metastatic complications of cancer is a multistep process characterized as a sequence of distinctive steps that have been termed the invasion-metastases cascade [1]. The cascade entails a successive series of biologic processes commencing with local invasion at the primary cancer site of origination, then intravasation of cancer cells into neighboring lymphatics and blood vessels, transit of cancer cells to the parenchyma of distant tissues (site of metastasis), extravasation of cancer cells into the site of metastasis with formation of micrometastases followed by macrometastases, a process termed colonization [2]. However unlike other sites of metastasis, BM is characterized by colonization in the brain, an organ that in part is both an immune and pharmacological sanctuary that has consequences with respect to delivery of systemic therapies [3–5].

Malignant cells contributing to the development of central nervous system (CNS) metastases may localize to the brain parenchyma, pachymeninges (dura), or leptomeninges (pia, arachnoid and cerebrospinal fluid (CSF)), compartments within the CNS [6]. About one third of all CNS metastases occur within multiple compartments, resulting in a combination of parenchymal, dural and/or leptomeningeal disease [6]. However, in the majority of cases, CNS metastases are isolated to a single compartment [6]. Post-mortem evaluations indicate that about 39% of all CNS metastases are restricted to the parenchyma, 18% are isolated to the dura, and 12% are isolated to the leptomeninges [6]. Intraparenchymal BM are the most common neurological complication related to cancer, and represent the most common brain cancer exceeding gliomas in prevalence by nearly ten times and occur in 20–25% of all patients with systemic cancer [3–11].

More than 170,000 new adult cases of BM occur annually in the United States with lung cancer accounting for the majority [5, 9–11]. Lung cancer accounts for 60% of all BM and 25–30% of patients with lung cancer will develop BM. The incidence of brain as the first site of relapse is 15–30% in non-small cell lung cancer (NSCLC) and in 33% of patients the brain is the only site of recurrent disease. In an analysis of Southwest Oncology Group (SWOG) trials, Gaspar et al. reported on 422 patients with NSCLC amongst whom 64% progressed [12]. Amongst the progressing patients, 26% progressed in brain (20% brain only and 6% brain + other site). Median time to BM was approximately 6.5 months, with nearly one quarter manifesting BM during treatment. Greater than 40% of patients dying of NSCLC are discovered at autopsy to have evidence of BM. These rates of failure of NSCLC in the brain have provided the rationale for trials utilizing prophylactic whole brain irradiation in stage 3a NSCLC [13]. Even higher rates of brain failure are seen in small cell lung cancer (SCLC) and based on randomized trials, prophylactic cranial irradiation is recommended for both limited and extensive SCLC responding to adjuvant chemotherapy [14–16]. Though prophylactic cranial irradiation reduces rates of BM and purportedly without significant neurocognitive consequences, no difference in overall survival is seen when comparing patients treated with or without prophylactic cranial irradiation.

Breast cancer represents the second most common etiology of BM (approximately 25% of all patients with BM) [3–11, 17]. It is estimated that 6–16% of all breast cancer patients ultimately develop BM. A further increased incidence of BM is seen in patients with hormone receptor negative and HER2 negative (triple negative breast cancers) as well as HER2 positive breast cancers (estimated at >30%) [18, 19]. Autopsy studies suggest a further 15–30% of all patients with metastatic breast cancer harbor BM that were asymptomatic in life [20]. Unlike NSCLC, breast cancer related BM develops later on average 19 months after initial diagnosis. HER2 positive breast cancer endows tumor cells with increased metastatic aggressiveness to specific sites. The chemokine receptor CXCR4 and its ligand stromal cell derived factor 1-alpha (SDF-1α) are expressed in organs that represent sites of breast cancer metastases [21]. CXCR4 expression is associated with HER2 amplification and overexpression [22]. SDF-1α is selectively expressed in the CNS, increases vascular permeability and penetration of HER2 positive metastatic breast cancer through brain endothelium [23]. This emerging data suggests a role for chemokine-mediated movement of malignant cells to specific organs that is likely a general etiopathogenic theme for BM as well. The increased incidence of BM in breast cancer reflects limitations of drug delivery imposed by an intact blood brain barrier (BBB) in early breast cancer treatment (as well as other solid cancers), trends for improved systemic disease control and overall survival in metastatic breast cancer (not yet realized in other solid cancers) and the above mentioned role of chemokine-mediated chemotaxic breast cancer with tropism for brain relapse (organotropism) [24].

Brain metastases are common in patients with metastatic melanoma (clinically recognized in >30% of all patients) and is the third most common cause of BM (approximately 10% of all BM) [25]. Approximately 60% of patients with BM and melanoma have 1–3 metastases (50% solitary, 50% 2–3 BM) and 40% manifest with >3 BM. Similar to breast cancer, presentation of BM in patients with melanoma averages >2.5 years after initial diagnosis and >65% of patients are symptomatic [25, 26]. Hemorrhagic BM are common in patients with melanoma (as well as in NSCLC, renal cell cancer and choriocarcinoma) and is seen radiographically in approximately one third of all patients. Postmortem evidence of BM is seen in 50–75% of all patients dying of melanoma [6, 25]. It is estimated that 20–50% all melanoma deaths are secondary to BM. The incidence of BM both as a site of metastases and isolated disease is likely to increase with new and more effective systemic cancer treatment (BRAF inhibitors and ipilimumab) as has been demonstrated with HER2 positive breast cancer treated with trastuzumab [27].

2 Treatment: Medical

The treatment of BM entails symptomatic and definitive therapy [3–11, 28–30]. Symptomatic therapy is defined as the administration of steroids and anticonvulsants, whereas definitive therapy is defined as systemic chemotherapy in selected instances, surgery or radiotherapy.

Vasogenic edema is commonly seen with BM, contributes to intracranial mass effect and often can be ameliorated with administration of oral steroids. Dexamethasone is most often utilized for symptomatic and first-line treatment of BM for several reasons including the fact that it is the most potent steroid, has the best CNS penetration, the least mineralocorticoid side effects, the least protein bound steroid and has a long biologic half-life (24–36 h) [31]. Dexamethasone dose response data have never been established and therefore an empiric dose of 4–16 milligrams (mg) of dexamethasone is administered daily. How often to administer dexamethasone varies but based on the biologic half-life once or twice per day is sufficient, though more often dexamethasone is administered four times per day without a clear rationale. As the clinical situation permits, the lowest dose of dexamethasone that controls symptoms should be utilized. Asymptomatic patients with BM, for example patients discovered incidentally to have BM by cranial imaging, do not require dexamethasone and may be therefore spared of potential steroid-related toxicity. Prolonged use of dexamethasone (defined as greater than 3 weeks) is associated with the emergence of steroid-related side effects (for example proximal myopathy, weight gain, skin fragility) that may seriously compromise patient quality of life [31, 32]. How much and how rapid to taper dexamethasone is again not evidence based but rather is empiric and determined by patient symptoms with steroid withdrawal. There is very little data to commend the concurrent use of gastric acid inhibitors however their use with dexamethasone is frequent and pervasive.

The use of antiepileptic drugs (AED) in patients with BM should be reserved for patients with seizures (seen in 15–25% of patients at presentation, 10–20% after diagnosis and 25–45% overall) and for seizure prophylaxis immediately following surgical resection. Based on the recommendations of the American Academy of Neurology guidelines regarding AED use in patients with brain tumors, AED prophylaxis does not prevent first seizures, AED may manifest novel and increased risks in patients with cancer and the practice of AED prophylaxis in patients with primary and metastatic brain tumors should be abandoned [33]. If AED are indicated, emerging data recommends the use of non-enzyme inducing AED to minimize drug interactions that may confound the treatment of patients with cancer [34].

3 Treatment: Chemotherapy

3.1 Overview

Several issues are pertinent to a discussion of chemotherapy for BM (Table 8.1) [4, 5, 11, 17, 28–30]. First and most important, there is a paucity of clinical trials with very few randomized trials. The limited evidence supporting the use of chemotherapy for BM comes primarily from nonrandomized, retrospective studies and case reports. Second, survival in BM is often limited by death from systemic disease (approximately 30% of patients with BM die as a direct result of CNS disease)

Table 8.1 Issues regarding the treatment of brain metastases with chemotherapy

Blood–brain-barrier
Prior treatment with acquisition of acquired drug resistance
Few effective chemotherapy agents
Concurrent systemic disease
Heterogeneity of patient population
Heterogeneity of tumor types enrolled
Measurement of efficacy
Interpretation of the literature

Table 8.2 Outcome measures in brain metastases

Survival
Overall
6-months
12-months
Brain-specific
Time to tumor progression
Control rate
Local
Distant
Response rate
Functional status
Karnofsky performance status
FACT-Brain

[3, 6, 17, 28–30, 35, 36]. Patients with BM are heterogeneous and the importance of stratification for prognostic factors for example by way of the Radiation Therapy Oncology Group (RTOG) recursive portioning analysis is often overlooked [37, 38]. Third, how to measure efficacy has proven challenging as many studies report overall survival as a primary outcome (Table 8.2). Survival is most often used as an outcome measure of chemotherapeutic response. However, in patients with BM this is unlikely to reflect chemotherapy efficacy [35, 37, 39–41]. As mentioned above, the majority of patients with BM die of systemic disease progression. More relevant is radiographic response, duration of response, maintenance or improvement in neurologic function and quality of life (Table 8.2). Fourth, the majority of patients with BM have in general been treated with at least one and often two or more prior chemotherapy regimens. Consequently, the systemic cancer has developed acquired chemotherapy resistance such that few active chemotherapy agents remain available for treatment. Lastly, the majority of BM-chemotherapy trials have evaluated a single chemotherapy regimen directed at multiple tumor histology's making determinations of responsiveness against specific tumor histology problematic.

Two factors influence the efficacy of chemotherapy in BM; the intrinsic chemosensitivity of the tumor and chemotherapy drug delivery [28–30, 42]. Parenchymal brain drug delivery is determined by drug properties such as lipophilicity, ionization state and molecular weight and by the BBB (Table 8.3) [43]. The BBB protects the

Table 8.3 Chemotherapy and BBB passage (Adapted [43])

Very good	Good	Poor	No penetration
ACNU	DTIC	VP-16	Taxanes
BCNU	MTX	Cisplatin	Gemcitabine
CCNU	Temozolomide	Carboplatin	CPT-11
Procarbazine	Ara-C	Vincristine	Cytokines
Hydroxyurea	Capecitabine	Fluorouracil	_
Topotecan	_	_	_

brain from exposure to toxins and prevents many traditional and novel drugs from crossing the systemic circulation into the CSF and brain parenchyma. The BBB consists of a network of closely opposed endothelial cells in the brain's capillaries characterized by the presence of continuous tight junctions, a lack of fenestrations, and very low levels of pinocytic activity compared with endothelial cells in the periphery [44]. Impermeability of the BBB is further mediated by the presence of an enhanced extracellular matrix, pericyctes, astrocyte foot processes, and a high electrical resistance that excludes polar and ionic substrates. There are also high levels of proteins that pump foreign molecules away from the brain (efflux protein pumps) but allow others necessary for brain function, such as glucose and insulin, to cross the barrier. Drugs and other substances can enter the brain by either passive transcellular diffusion, which is restricted to lipid-soluble agents, or by receptor-mediated transcytosis of molecules such as insulin, glucose, amino acids, and other substances necessary for brain function. Substances can exit the brain via CSF absorption through the arachnoid granulations, diffusion into the extracellular fluid and surrounding cells (cell/extracellular fluid partitioning), diffusion across brain capillaries (transcapillary uptake), and biotransformation [44]. Because the majority of chemotherapy agents with activity against systemic cancer are non-lipophilic i.e. water soluble and of large molecular weight, parenchymal drug delivery is limited. Consequently, the optimal treatment for systemic disease often does not cross the BBB. As a result, optimal chemotherapy treatment for BM is often different than that used to treat systemic disease. The BBB normally is a barrier to xenobiotic drug brain entrance, however it is disrupted in patients with BM as evidenced by radiographic contrast enhancement. Consequently, the BM is permeable to chemotherapy agents that otherwise would not penetrate the BBB. However, brain adjacent to tumor (usually contaminated with tumor) and micrometastases within the brain (tumors 1–3 mm in size) maintain an intact BBB and therefore are regions physically inaccessible to non-lipophilic and large molecular weight chemotherapy. Furthermore, the concomitant use of corticosteroids (most often dexamethasone) in patients with BM re-establishes the BBB and thereby limits chemotherapy access into brain/tumor. Lastly, up to 40% of patients with BM develop tumor-related seizures and accordingly are often treated with hepatic cytochrome P450 inducing anticonvulsant drugs such as phenytoin that alter the metabolism of systemic chemotherapy [34].

Several generalizations can be made regarding chemotherapy of BM based on the limited literature [28–30]. Response to chemotherapy reflects inherent chemosensitivity of the primary tumor with best responses seen with SCLC, and intermediate

Table 8.4 Single agent temozolomide for brain metastases

Author, reference	Number of patients (primary)	Time to tumor progression (months)	Response (%)		
			Complete	Partial	Stable
Abrey [45]	41 (various)	2	0	5	37
Agarwala [46][a]	117 (melanoma)	1	1	5	29
Christodoulou [47]	27 (various)	3	0	4	17
Dzidziuszko [48]	25 (NSCLC)	Not reported	0	0	25
Friedman [49]	52 (various)	Not reported	0	6	63
Giannitto [50]	9 (NSCLC)	Not reported	3	0	3
Siena[51][a]	21 (NSCLC)	Not reported	0	8	24
Siena[51][a]	21 (melanoma)	Not reported	0	8	40
Siena[51][a], Arena [52], Christodoulou [47], Friedman [49], Abrey [45]	72 (breast)	Not reported	–	7	–
Schadendorf [53][a]	45 (melanoma)	<2 months	0	4.4	11.1
Boogerd [54]	52 (melanoma)	7 months	6	4	12

[a]No prior radiotherapy, TMZ used as first-line therapy

Table 8.5 Single agent topotecan for brain metastases

Author, reference	Number of patients (primary)	Time to tumor progression (months)	Response (%)		
			Complete	Partial	Stable
Larruso [55]	19 (various)	2	0	5	37
Oberhoff [56]	16 (breast)	Not reported	6	31	31
Manegold [57][a]	16 (SCLC)	Not reported	25	38	31
Ardizzoni [58]	7 (SCLC)	1	43	14	0
Depierre [59]	9 (SCLC)	Not reported	11	44	33
Schutte [60]	24 (2 NSCLC; 22 SCLC)	Not reported	17	33	25
Korfel [61]	30 (SCLC)	Not reported	10	23	27

[a]No prior radiotherapy, TMZ used as first-line therapy

responses seen with NSCLC and breast cancer and then low response rates with melanoma. Response to chemotherapy is in addition determined by prior chemotherapy exposure as front-line chemotherapy has higher response rates than second- or third-line chemotherapy. Response to chemotherapy as compared to whole brain radiotherapy (WBRT) or stereotactic radiotherapy (SRT) is inferior and less durable in patients with breast cancer, SCLC, NSCLC and melanoma [3–5, 28–30]. The use of chemotherapy for the treatment of BM is most often limited to patients having failed radiotherapy (often both WBRT and SRT), with multiple lesions and in selected instances, for example, solitary BM surgically resected and previously treated with intracavitary chemotherapy. The majority of chemotherapy trials for BM have utilized either single agent, for example, temozolomide or histology-specific multi-agent chemotherapy (Tables 8.4, 8.5, 8.6) [45–66]. A less common

Table 8.6 Single agent for breast cancer brain metastases

Author, reference	Number of patients	Agent	Time to tumor progression (months)	Response (%)		
				Complete	Partial	Stable
Zulkowski [62]	–	Bendamustine	2	0	5	37
Wang [62]	–	Capecitabine	Not reported	6	31	31
Pons [64][a]	16	Tamoxifen	Not reported	25	38	31
Stewart [65]	9	Megestrol acetate	Not reported	11	44	33

[a]No prior radiotherapy

Table 8.7 Carmustine wafer implants in patients with brain metastases

Author, reference	Ewend [67]	Golden [68]	Brem [69]
Number of patients	25	36	42
Local recurrence	0	0	0
Distant recurrence	4/25	7/36	3/42
Median survival	14.2 months	Not reported	16.8 months

Table 8.8 Epidermal growth factor receptor inhibitors as single agent therapy for NSCLC brain metastases

Author, reference	Number of patients	Concurrent WBRT	Intracranial response (%)			Median survival (months)
			Complete	Partial	Stable	
Cappuzzo [70]	4	3	25	75	0	6
Ceresoli [71]	41	18	0	10	17	3
Hotta [72]	14	0	7	36	57	9
Namba [73]	15	1	7	53	13	8.3
Shimato [74]	8	8	0	37.5	0	9.5

chemotherapy approach has been the placement of carmustine wafers (Gliadel) in the bed of a resected and most often solitary metastasis as mentioned above (Table 8.7) [67–69]. More recently, targeted therapies, for example, tyrosine kinase inhibitors such as erlotinib (Tarceva) have been used in patients with NSCLC and BM with modest success (Table 8.8) [70–74]. In patients with asymptomatic and small volume BM, primary chemotherapy and deferred WBRT is reasonable however careful assessment of intracranial response is required. Often, the intracranial response is discordant with and less than the systemic response. In the later instance in which no response to primary chemotherapy is seen, WBRT would be administered. As the majority of patients with BM are treated with WBRT, the question of whether concurrent chemotherapy adds benefit remains uncertain [28–30]. A synergetic effect may be seen with respect to intracranial response, though less certain is whether meaningful benefit is realized as overall survival appears similar in patients treated with or without chemotherapy and WBRT. The major utility of systemic chemotherapy in the treatment of BM is in a patients' refractory response to radiotherapy and in which no other treatment options remain. In this limited context,

chemotherapy may offer limited benefit though whether an advantage is seen with single vs. multi-agent chemotherapy is uncertain. The utility of targeted therapy and in particular small molecule inhibitors continues to evolve in oncology and hopefully will offer new therapies for patients with BM.

3.2 Single Agent Chemotherapy

Temozolomide (TMZ) has been the chemotherapy agent studied most and not surprisingly, used most often in patients with refractory BM (Table 8.4) [45–54]. TMZ crosses the BBB (approximate serum to CSF ratio 0.33), has a favorable toxicity profile and has emerged as the chemotherapy agent of first choice for patients with gliomas. However, the data regarding the efficacy in extraneural tumors is quite limited aside from melanoma and consequently TMZ is rarely used as a primary therapy for either lung or breast cancer. Several TMZ drug schedules have been used to treat BM (42/56; 75 mg/m^2/day for 42 days with 14 day break in therapy: 21/28; 75–100 mg/m^2/day for 21 days with 7 day break: and 5/28; 150–200 mg/m^2/day for 5 days with a 23 day break) though most commonly the 5/28 schedule has been utilized. As can be seen in Table 8.4, TMZ for BM results in neuroradiographic responses in approximately 5% (all partial responses) and 25% disease stabilization. However, median time to tumor progression is only 1–3 months. All but the trials by Sienna and Argawala administered TMZ as salvage therapy after evidence of disease progression following WBRT [46, 51]. In the trial by Schadendorf et al., a dose intensive TMZ schedule (7/14) was utilized for asymptomatic melanoma BM without prior application of WBRT [53]. Response rate was 4% and median survival was 4 months. The best response data regarding single agent TMZ (5/28 schedule) was reported by Boogerd [54]. Amongst 52 patients (29 treated with TMZ only; 23 with TMZ and immunotherapy) with melanoma and small mostly asymptomatic (73%) BM, there were 5 responders (11%) with a median duration of response (including stable disease) of 7 months. These data suggest that TMZ has limited efficacy as a single agent in patients with BM though may provide palliation for a brief period of time.

Single agent fotemustine, a nitrosourea available in Europe, results in similar response rates and duration of response as TMZ in patients with melanoma and BM. In a trial by Jacquillat et al. of 153 patients with metastatic melanoma of whom 36 (23%) had BM, fotemustine resulted in a 25% partial response rate with a median duration of response of 4 months [75].

Single agent topotecan has been investigated in several studies for the treatment of BM primarily due to its well-established activity and the fact that it freely penetrates the BBB (Table 8.5) [55–61]. Lorusso et al. report on 19 patients with a variety of systemic cancers and BM treated with topotecan (1.5 mg/m^2/day for 5-consecutive days every 3-weeks) [55]. Two responses were seen (both small cell lung cancer) however the trial was stopped for failing to meet pre-specified efficacy criteria. In a phase 2 study of 92 patients with SCLC treated with topotecan (same schedule as above) and 7 patients with BM, Ardizzoni et al. reported that 3 patients

achieved a complete response and one a partial response [58]. Similar response data is seen in Table 8.5 suggesting that topotecan is an active agent in patients with either breast cancer or small cell lung cancer. There is limited data to suggest that patients with NSCLC and BM not previously treated with pemetrexed (Alimta) may respond to single agent therapy in part due to use of a tumor active agent with good CNS penetration [76–78]. Similarly, there is limited data to suggest efficacy and safety of bevacizumab in the treatment of bevacizumab naïve patients with NSCLC and BM [79].

Experience with targeted agents in the treatment of BM is limited and best characterized in NSCLC treated with gefitinib or erlotinib (Table 8.7) [70–74]. Intracranial response is predominantly seen in patients with responding concurrent systemic disease (usually Asian female nonsmokers with adenocarcinoma), presence of epidermal growth factor receptor (EGFR) mutations (EGFRmut) and manifesting treatment- related rash. An increased radiographic response and survival is seen in patients with EGFRmut NSCLC BM compared to EGFR wild type patients. It has been suggested that EGFRmut NSCLC represents a radiosensitive phenotype [80, 81]. An additional advantage of EGFR inhibitors is the potential of both systemic and CNS control in patients with EGFRmut NSCLC. EGFR inhibitors when used alone illicit response in 70% or more in EGFR inhibitor naïve NSCLC patients. EGFR inhibitors are appropriate therapy for EGFRmut NCSLC patients with asymptomatic BM permitting deferred WBRT. As is true for other tumor specific chemo- and targeted therapies for the treatment of BM, response to therapy is dependent upon prior therapy. Previous treatment with an EGFR inhibitor in a patient with NSCLC rarely results in control of BM when an EGFR inhibitor is reintroduced. At present there is no data regarding crizotinib (an ALK inhibitor) in the treatment of patients with BM and EMLA-ALK mutant NSCLC, but very likely the response will be similar to that seen with EGFR inhibitors in patients with NSCLC and EGFRmut. Two new targeted agents have been introduced in the treatment of metastatic melanoma: ipilimumab, an immune checkpoint inhibitor (CTLA-4 antagonist that sustains T-cell activation) and vermurafenib (PLX4032), a BRAF inhibitor (50% of all melanoma with mutations in BRAF, the V600E mutant) [82–86]. Both agents have shown significant activity in recurrent systemic disease and there is limited evidence these targeted agents may as well be active for melanoma related BM. A prospective trial of vermurafenib in patients with V600E BRAF mutations, melanoma and BM is presently on-going to specifically address the utility of this targeted agent for this indication. Lapatinib monotherapy was evaluated in a study of 242 women with BM from HER2 positive breast cancer prior trastuzumab therapy and cranial radiotherapy [87]. CNS antitumor activity of lapatinib monotherapy was modest; 8% of the patients treated with lapatinib alone experienced a 50% reduction in CNS lesion volume and 21% had a 20% reduction in CNS lesion volume. The median survival duration was 6.4 months. Patients who experienced CNS progression with lapatinib monotherapy were given the option to receive lapatinib in combination with capecitabine. Of these patients ($n=50$), 22% experienced a $\geq 50\%$ reduction and 40% experienced a $\geq 20\%$ reduction in the CNS lesion volume. Thus, response rates were substantially higher when lapatinib was administered in combination with capecitabine than when given as monotherapy.

Although a single agent effect of capecitabine cannot be excluded due to the design of this particular study, a growing body of evidence suggests that lapatinib may have a synergistic effect with capecitabine within the CNS [87–89]. Lapatinib is additionally associated with a decreased risk of relapse within the CNS in patients with HER2 positive advanced breast cancer who have progressed on trastuzumab [90]. Specifically, 2% (4/198) of patients treated with lapatinib and capecitabine and 6% (13/201; $p=0.045$) of patients treated with capecitabine alone had their first progression in the CNS [90].

3.3 Multi-Agent Chemotherapy

A number of nonrandomized trials have evaluated combination chemotherapy in patients with BM [91–115]. Notwithstanding higher response rates in SCLC, median survival is similar when comparing NSCLC to SCLC (approximately 7 months). In a recent study of SCLC and BM, Seute et al. evaluated 181 consecutive patients with newly diagnosed SCLC by cranial MRI [112]. Twenty-four (13%) had asymptomatic BM compared to 38 patients (21%) with symptomatic BM. All patients were treated in a similar manner with respect to systemic chemotherapy (cytoxan, etoposide and doxorubicin). In patients with asymptomatic BM, the intracranial response rate was one third that of the systemic response rate (27% vs. 73%) suggesting that poor brain drug delivery limits response of BM to active systemic therapy. These results are similar to those reported by Kristensen in a review of BM response to chemotherapy in patients with SCLC (overall response 40%) [99]. The largest series of patients with breast cancer and BM treated with chemotherapy was reported by Rosner et al. [113]. In this study, 100 women were treated with multiagent chemotherapy using a variety of regimens and 50% response rate was seen with a median duration of response of 7 months. Boogerd et al. using a similar chemotherapy regimen reported a response rate of 59% in women with BM and breast cancer [115]. However both studies treated women with breast cancer and BM not previously treated with chemotherapy, suggesting chemotherapy naïve patients with BM and breast cancer have high response rates. More problematic however is the fact the majority of women with BM and breast cancer have seen prior therapy and often multiple regimens. The combination of cisplatin and etoposide was studied in 107 patients who had newly diagnosed brain metastases, 56 of whom had breast cancer (all not previously treated with WBRT) [94]. A total of 38% of breast cancer patients achieved either complete or partial response, more so than any other histology (non–small cell lung cancer was second with a 30% response rate). Median survival for breast cancer patients was nearly 8 months, again comparable to WBRT alone historically suggesting a subgroup of patients with breast cancer and BM may respond to systemic chemotherapy [94].

Multi-agent therapy when compared to single agent TMZ appears to offer no advantage with respect to response rates in the treatment of BM and melanoma. Furthermore, duration of response to TMZ plus therapy and melanoma BM is limited to 3+ months in patients previously treated with systemic chemotherapy.

3.4 Pre-Radiation Chemotherapy

Several trials demonstrate the feasibility and safety of concurrent therapy in the treatment of patients with BM [93, 101, 104, 116–120]. Robinet conducted a randomized trial in 171 patients with newly diagnosed BM and NSCLC. Patients received either upfront WBRT or deferred radiotherapy at time of intracranial disease progression [93]. Both groups were treated with systemic cisplatin and navelbine chemotherapy. Response rates (both intracranial and extracranial), progression free survival and overall survival were similar in both groups. Two thirds of patients in the deferred radiotherapy group required radiotherapy. This trial suggests that in patients with NSCLC and synchronous BM, primary chemotherapy is a reasonable approach however, patients require careful neurological follow-up. A similar finding (primary chemotherapy in patients with NSCLC and synchronous asymptomatic BM) was demonstrated in the survey evaluation by Moscetti et al. [104]. The Robinet et al. trial of NSCLC is to be contrasted with that of Seute et al. in patients with SCLC mentioned above wherein the intracranial response rate was one third that of the systemic disease response to chemotherapy [78, 106]. Consequently, a majority of patients with BM required WBRT. These studies suggest a subset of patients with either SCLC or NSCLC-related BM may respond to systemic chemotherapy permitting deferred radiotherapy.

4 Concurrent Treatment: Chemotherapy and Radiotherapy

Antonadou et al. studied 52 patients with BM and solid tumors (40 with lung cancer; 5 with breast cancer) in which patients were randomized to either WBRT with or without TMZ [116]. The radiographic response rate was 96% (38% complete; 58% partial) in the TMZ arm compared to 67% (33% complete; partial 33%) in the radiotherapy only arm ($p = 0.017$). Margolin et al., in a single arm study of 31 patients with BM secondary to melanoma, treated with TMZ and WBRT demonstrated a very modest response rate (1/31 complete; 2/31 partial) [118]. In a similar study, Hofman et al. treated 34 patients with melanoma and BM with WBRT and TMZ [119]. Observed response rate was 9% (3% complete; 6% partial) with a median progression free survival of 5 months and overall survival of 7 months. Ulrich et al. treated 12 patients with metastatic melanoma and BM with WBRT and concurrent fotemustine [120]. A 50% response (33% complete; 17% partial) and 8 months median survival was reported. Two other studies, both in patients with NSCLC, utilized either daily topotecan ($n = 80$) or once weekly paclitaxel ($n = 86$) in conjunction with WBRT reported a 10–12% response rate (all partial) and a median survival of 5–6 months.

Several novel strategies have been used to improve drug delivery to brain in patients with symptomatic BM. One strategy is by local administration using carmustine impregnated biodegradable wafers (Table 8.7) [67–69]. This therapy is performed in patients undergoing surgical resection at which time carmustine wafers are implanted following which patients are treated with WBRT. This therapy however

is for select patients (surgical candidates, solitary metastasis in whom local control is paramount), and purportedly results in improved local control rates. Problematic with interpreting these studies is WBRT is variously applied, metastatic tumors are treated either at presentation or recurrence and administration of systemic chemotherapy is usually not reported. Another strategy though less often used approach entails administration of intra-arterial chemotherapy with or without osmotic BBB disruption. Again, this therapy is for select patients and can be performed only by centers skilled at intracerebral intra-arterial drug administration [102]. At present, it is unclear as to whether intra-arterial therapy is superior to alternative approaches discussed above and furthermore has associated risks as seen with invasive intra-arterial therapies.

In aggregate, these studies suggest that chemotherapy and WBRT may be synergistic in the treatment of BM and thereby result in improved radiographic responses. However less clear is whether there is benefit with respect to either neurological function or quality of life and brain-specific survival.

5 Conclusions

Chemotherapy has a limited role in the management of patients with BM [28–30, 114]. For the majority of patients, primary therapy of symptomatic BM will be WBRT except in patients with either solitary or oligometastatic disease [22, 121]. Surgery is of benefit in good risk patients i.e. the RTOG recursive partitioning analysis (RPA) class 1 and some class 2 [4, 5, 9, 11, 39]. Whether added benefit is gained by placement of carmustine wafer implants at time of surgery is unclear [67–69]. Furthermore, whether the use of carmustine implants in patients with resected solitary BM can permit deferral of WBRT is unknown. In patients with asymptomatic BM, primary chemotherapy and deferred WBRT is reasonable however careful assessment of intracranial response is required. Often, the intracranial response is discordant with and less than the systemic response. In the later instance in which no response to primary chemotherapy is seen, WBRT would be administered. As the majority of patients with BM are treated with WBRT, the question of whether concurrent chemotherapy adds benefit remains uncertain. A synergetic effect may be seen with respect to intracranial response though less certain is whether meaningful benefit is realized as overall survival appears similar in patients treated with or without chemotherapy and WBRT. The major utility of systemic chemotherapy in the treatment of BM is in patients' refractory to radiotherapy and in which no other treatment options remain. In this limited context, chemotherapy may offer limited benefit though whether an advantage is seen with single vs. multi-agent chemotherapy is uncertain. The utility of targeted therapy and in particular small molecule inhibitors continues to evolve in oncology and hopefully will offer new therapies for patients with BM [79–90, 122]. An approach not yet realized is the use of systemic adjuvant therapies that either prevent or decrease the incidence of BM thereby resulting in a smaller fraction of patients with treatment requiring BM.

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Chapter 9
Radiation Therapy of CNS Metastases

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Abstract Radiation treatment of central nervous system (CNS) metastases, particularly brain metastasis, is changing. The role of radiation for intraaxial disease was originally limited to palliation. However, now there is an increasing expectation by both patients and physicians to integrate radiotherapy in an overall strategy for eradication of disease. Recent innovations in radiobiology and technical advances in radiotherapy have proven beneficial to many extracranial sites. Nevertheless, these advances have lagged behind in the treatment of brain and spinal metastases and have not kept pace with changing expectations. We aim to explain the scientific basis of radiotherapy for CNS metastasis, current treatment options and techniques, controversies, and future goals for potential improvement.

1 Molecular Basis of Radiation Therapy

Radiation therapy is used as a localized treatment modality for a wide variety of malignant and benign diseases, and is utilized in both definitive therapy and for palliation of symptoms. The total dose of radiation delivered and the number of treatments in which the total dose is delivered vary depending on the indication. Ionizing radiation is employed because it can be absorbed in all tissues and produces disruptions in atomic structure, which in turn, produces chemical and biological damage on the subcellular level. The mechanism of action of ionizing radiation appears to be multifold. The ability of photons from x- and γ-rays to hydrolyze water produces breakage of chemical bonds, particularly within DNA [1].

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The fixation of double stranded DNA breaks leading to mitotic catastrophe is the most supported mechanism of radiation-induced cell death in solid tumors [2]. Apoptosis in response to radiation occurs less often, mostly in cell populations that have diminished repair capacities such as lymphomas and leukemias [3]. However, in addition to effects on the nucleus, there is growing evidence to suggest that oxidation of the lipid bilayer [4], changes in microvascular permeability [5], cell-cell junctional complex rearrangements [6], and mitochondrial alterations inducing additional oxidative stress [7], are also subcellular targets for ionizing radiation. Because of these effects, radiation has the capacity to alter tumor microenvironment, cellular architecture, permeability of tumor vasculature and permeation of drugs within the tumor, and to produce biochemical alterations which allow for additive or synergistic cell killing in combination with pharmacological agents.

1.1 Fractionation Versus Single Dose

The ability of ionizing radiation to successfully treat a cancer is dependent on producing adequate cell killing within the target without destroying the normal tissues in the path of the ionizing radiation. The response of solid tumors to radiation depends primarily on three factors: (1) the intrinsic radiosensitivity of the tumor cells, (2) the oxygenation of the tumor cells, and (3) the number of tumor cells undergoing division between radiation treatments. Modification or changes in any of these factors would be expected to modify the radiation response of tumors. Therefore, an effective radiotherapy regimen has to overcome the obstacles of repopulation after a single radiation exposure, repair of sublethal damage, and reassortment within the cell cycle following treatment. Reoxygenation of hypoxic cells due to diminishing tumor volume allows for increased cell killing on subsequent radiation exposure [1]. This forms the biological basis for the use of fractionation.

The concept of fractionation involves the division of a total prescribed radiation dose over a defined period of time. *In vivo*, fractionation allows for multiple logs of tumor cell killing, while also allowing sufficient time for normal tissue repair to occur [8]. Standard daily radiation fraction doses of 1.8–2 Gray (Gy; a standard measure of absorbed dose) are used in a wide variety of regimens, including those where concurrent chemotherapy is delivered. Altering fractionation schemes to allow multiple radiation treatments per day within the same total treatment time is defined as hyperfractionation and may be used in specialized indications to minimize normal tissue toxicities, or to overcome tumor cell repopulation between radiation fractions. Alternatively, delivery of larger doses of radiation per treatment to shorten the total time required for administration of a prescribed dose is defined as hypofractionation and may be used in clinical situations to overcome increased repair capacity of a tumor, as with melanoma [9], or when it is in the patient's interest to complete treatment in a shorter time period, as in most fractionation schedules for whole brain radiation therapy (WBRT) and palliative spine treatments. Large fraction sizes (>4 Gy), such as those used for stereotactic radiosurgery (SRS)

and some stereotactic radiotherapy regimens (SRT), may also have a secondary effect on the tumor vasculature leading to vascular collapse and tumor necrosis [10], as compared to standard fractionation. However, doses >4 Gy at a time are classically reserved for cases where the extent of disease is easily defined and where the volume of disease is limited and in a location that can tolerate the treatment. This is particularly important within the CNS, where fraction size in addition to total radiation dose, and treatment volume are most closely linked to the long term toxicities of non-cancerous normal parenchyma [11]. However, regimens with non-standard fractionation in combination with sensitizing therapies remain largely untested, principally due to concerns for increased normal tissue toxicity without a defined, clear benefit.

An equally important consideration to how total radiation dose is divided is the acknowledgement that hypoxic cells require higher doses of radiation to produce the same amount of cell kill [12, 13]. The larger the volume of the metastasis, the greater the number of hypoxic, relatively radioresistant, cells. Approximately two-thirds of the biologic damage produced on double-stranded DNA by photons occurs as an indirect action mediated by free radicals generated by the hydrolysis of water. Oxygen that is present at the time of ionizing radiation exposure and during the subsequent formation of free radicals makes permanent the effect of free radicals. Thus, under hypoxic conditions when oxygen levels fall below 0.5%, the effect of radiation is diminished, since the cells have an increased ability to repair the free radical-induced damage without sufficient oxygen [1]. Larger tumors with significant numbers of hypoxic cells, therefore, require relatively larger radiation doses to produce the same biologic effect. As initial radiation doses induce lethal damage within the well-oxygenated outer cell layers of a three-dimensional tumor, the tumor volume decreases, allowing for re-oxygenation of previously hypoxic cell populations which increases efficiency of killing with subsequent radiation fractions. Attempts to sensitize hypoxic cells to the effects of radiation have focused on delivery of compounds to the tumor which mimic the chemical effects of oxygen, however, they have not been thoroughly vetted in the setting of CNS metastasis [14–16]. Thus, testing of newer generation oxygen-mimetic agents in combination with radiation for treatment of CNS metastases remains promising for future investigation, particularly for improved control of larger lesions.

Although radiation aims to maximize irreversible damage to the tumor, the total amount of radiation that can be safely delivered depends on the environment in which the tumor resides. Each normal tissue has its own endogenous radiation limits, beyond which repair to exposure is not possible and permanent damage ensues. Within the brain, the neurons, astrocytes and vascular endothelial cells all respond in slightly different ways to radiation. The brain is a late-responding tissue to radiation, due to the relatively slower rate of cellular turnover compared to most extracranial tissues, with reactions manifesting months to years after exposure. Radiation limits are defined as the dose for a specified volume that produces a defined effect in 5% of patients at 5 years ($TD_{5/5}$) and 50% of patients at 5 years ($TD_{50/5}$). Traditionally, the $TD_{5/5}$ for the whole brain occurs when doses exceed 45 Gy, and the $TD_{50/5}$ occurs when whole brain doses exceed 60 Gy. However, smaller volumes

of brain can sustain higher doses. The $TD_{5/5}$ when 1/3 the brain volume is treated with standard fractionation is thought to approximate 60 Gy, and the $TD_{50/5}$ after 70 Gy. The spine is noted to have a $TD_{5/5}$ of 50 Gy and a $TD_{50/5}$ of 70 Gy for a treated length of 5–10 cm [17]. One caveat of these dose limits is that it is assumed the doses are given in standard fractionation schedules of 2 Gy per day. Another consideration is that these limits are based on empiric evidence and older radiotherapy techniques, while newer data suggests slightly higher doses may be tolerated due to better conformality and three-dimensional modeling software [18–20].

Toxicity evaluations for radiation treatments differ based on anatomical location and are divided into discrete sets of acute and late toxicities. Effects manifesting from the onset of therapy to within 90 days following treatment are referred to as acute toxicities, whereas late toxicities typically develop after the 90 day mark. Although evaluation of acute toxicity within the 90 days surrounding radiation is usually the focus of toxicity evaluation in many clinical trials, the collection and analysis of data on late toxicity effects are essential because such data can often assist with interpretation of late events seen in the initial stages of phase III trials [21]. This is an exceedingly important concern for brain metastasis trials, as the CNS is noted to be a late-responding tissue, with effects from radiotherapy not manifesting for months to years [11]. The time course of adverse long-term toxicities varies and typically occurs gradually over a protracted period of time. When early histopathologic changes occur, they initially involve the white matter. As time progresses beyond a year, grey matter and vascular-based lesions begin to arise. Cognitive effects such as decreased attention and concentration are unpredictable and highly individualized, typically not manifesting until 1–2 years [22]. Radiation necrosis, when it occurs, typically arises from 6 months to 2–3 years following treatment and is typically accompanied by vasogenic edema adjacent to the area of necrosis. The edema, in turn, causes tissue distortion, and possible associated cognitive changes, which is why symptoms are often improved by steroid administration [23]. Vasculopathy, stroke and endocrinopathy are also other possible late side effects and depend on the area of the brain treated, as well as total dose [24].

The optimal dosage and timing schedules for CNS treatments aim to strike a balance between acute-responding tumor and late-responding normal tissue. To decipher the impact of regimens and to compare different fractionation schedules, the concept of biologically equivalent dose (BED) is utilized. The determination of BED is the calculation of a standardized numerical score that takes into account the dose per fraction, number of fractions, and the α/β ratio of the tumor or normal tissue as determined by its particular linear-quadratic radiation dose response characteristics. Depending on how the calculation is utilized, BED can be calculated for both normal tissue and/or tumor control, and equal BED values have the same theoretical probability of tumor control or normal tissue effect, respectively. What this means on a practical scale, for example, is that 20 Gy delivered over 5 fractions of 4 Gy is *not* the radiobiological equivalent of 20 Gy delivered over 4 fractions of 5 Gy. Within the CNS, fraction size is the dominant factor in determining late effects, with overall treatment time as a lesser influence [25]. Therefore, hypofractionation regimens have the potential to be particularly damaging when large volumes of normal brain and spinal cord are exposed.

Based on an increased understanding of the molecular mechanisms of radioresponse, current efforts to develop strategies for enhancing tumor radiosensitivity have focused on the use of agents that target molecules putatively involved in regulating radiation-induced cell death. However, complicating this approach, it has also become increasingly clear that cellular radiosensitivity is the sum effect of a combination of a wide variety of signaling and effector molecules, and the ability of a single molecule to affect radioresponse also varies with changes in the genetic and epigenetic background [26]. Accordingly, there are numerous examples in which targeting a selected radioresponse-associated molecule affects radiosensitivity in a cell type–dependent manner [27, 28].

Conversely, what constitutes "radiation resistance" is a matter of significant controversy. Brain metastases are often referred to as being "radioresistant" compared to extracranial tumors of the same cell type [19], most often because of the emergence of new metastases or regrowth of lesions following conventionally fractionated radiotherapy. There is little scientific evidence to support that the CNS confers a relative radiation-resistant microenvironment compared to extra-axial disease. [29], However, some tumor types are believed to be inherently more resistant to the effects of a standard dose of radiation, such as renal cell carcinoma, sarcoma and melanoma, which are noted to have increased repair capacities to single standard radiation doses, thus requiring altered fractionation and dosing to achieve improved control rates [30]. This is possibly related to the fact that these tumors are often highly vascularized with a tendency to bleed, and often form larger lesions with large regions of hypoxia and necrotic cores. Therefore, one would hypothesize that it may be more appropriate to pursue hypofractionated schedules versus single dose or standard fractionation options for long-term control of certain histologies. Indeed, improved local control rates are seen in the post-operative setting for extracranial head and neck melanomas when hypofractionation is used to overcome the increased repair capacity of the tumor [9].

The concept of radiation resistance rests on the assumption that certain types of malignant cells are infinitely able to repair themselves from damage after absorption of ionizing radiation. Accordingly, it may also be incorrect to assume that just because a lesion grows following a definitive radiation treatment that the lesion is somehow unsusceptible to the effects of additional radiotherapy [31]. Radiation damage is a stochastic event that randomly affects some tumor cells versus others [1], and delivers lethal damage to only a certain number of cells per fraction. Curative regimens are designed with the aim to deliver enough treatment doses to exceed the number of cells that require exposure to lethal damage. A lack of responsiveness to radiation most likely comes from the limitations of dose and fractionation employed due to the necessity to respect normal tissue tolerances. Simply because a tumor has demonstrated the ability to overcome one type of radiation dose and fractionation schedule, does not necessarily mean that another would not be more effective. The purpose of the chosen radiation regimen must also be taken into account. If the regimen is designed with the goal of palliation of symptoms, it is therefore not likely it will also be adequate for tumor eradication. It is no surprise that some lesions will begin to grow following a non-ablative regimen, but it does not necessarily define a tumor as being radioresistant.

1.2 Radiation Modifiers

A radiation sensitizer is an agent that increases the sensitivity of cells to radiation [32]. An ideal radiosensitizer would not have any cytotoxic effects on its own, being inert to both normal and tumor cells. However, most agents have a measureable amount of cytotoxicity which is separate from their effects in altering the cellular response to radiation damage. Thus, agents that have inherent cytotoxicity which additionally produce increased sensitivity to a dose of radiation are often instead referred to as radiation modifiers.

Combined chemoradiation approaches have proven most successful for clinical situations in which the amount of radiation alone that would be required to destroy a tumor would greatly exceed normal tissue tolerance, otherwise rendering radiation therapy as a single modality ineffective and highly toxic [33]. This is indeed the situation with the majority of CNS metastases. The potential benefits of a chemoradiation approach include: (1) providing a combination of systemic treatment for both CNS and non-CNS gross tumor along with simultaneous micrometastatic control of subclinical disease (potentially outside the radiation field), and (2) augmenting the localized effectiveness of radiation therapy. While combined chemoradiation approaches have demonstrated success in improving outcomes in many extracranial disease sites, chemoradiation trials to date have not demonstrated a significant benefit to patients with brain metastases [34]. This is believed to be due in large part to a lack of full penetration leading to sub-therapeutic concentrations of most chemotherapeutic agents within intracranial lesions [35]. Nevertheless, the potential exists to develop or identify a blood-CNS barrier permeable agent that would be specifically cytotoxic for tumor, protective for normal brain and spine, and would synergistically augment the cellular damage induced by localized radiotherapy.

Traditional "radiosensitizers" for extracranial diseases, cytotoxic chemotherapeutic agents such as 5-fluorouracil and methotrexate, cisplatin and taxanes, are administered on a regimented schedule to optimize the interaction between the agent and radiation [36–39], and were devised on an empirical approach where chemotherapy is administered prior to scheduled delivery of radiotherapy. Although often highly effective in experimental models, the results obtained when these combinations are applied in a clinical setting have been generally less than expected, primarily due to concomitant increases in radiation-induced normal tissue injury. In the setting of CNS disease, methotrexate, cisplatin, and taxanes given concurrently with radiotherapy have been noted to adversely affect normal tissue to a greater degree than the metastases which they were intended to treat [40–42].

In any situation, an effective radiation modifier must show a differential effect between tumor cells and normal tissue. As previously mentioned, when the differential effect is to enhance radiation-induced tumor cell damage at the time radiation is being delivered, the agent is identified as a radiosensitizer. However, when the differential effect is to reduce the damage of ionizing radiation on normal tissue at the time radiation is being delivered, the agent is identified as a radioprotector. When the agent lessens or reverses the effect of radiation-induced damage after the exposure has occurred, the agent is identified as a radiation mitigator. Effective

agents in any of these categories are developed by exploiting biological differences between normal tissue and tumor. For example, cisplatin, an empiric radiosensitizer, induces cell death by crosslinking DNA, thereby taking advantage of the fact that most cancer cells have a higher proliferation rate than the surrounding normal tissue. Conversely, amifostine, a classic radiation protector which functions as a sulfhydryl donor, distributes preferentially in salivary gland tissue compared to tumor tissue, which makes it useful in reducing the toxicity of xerostomia in radiation treatment of head and neck cancers [43]. However, both of these agents have their own set of toxicities independent of the side effects produced from radiotherapy, and produce poor penetration into CNS metastases or normal CNS parenchyma, respectively, which has limited their usefulness in the setting of brain and spine metastases [44]. To date, unfortunately, no such radiation modifiers have proven to improve the therapeutic ratio in the setting of WBRT, SRS, or spinal irradiation to the point where widescale use is recommended [45].

The recent explosion in targeted therapies development has made it possible to allow radiosensitization with less toxicity to normal tissues, more effective augmentation of radiation-induced tumor cell death, and more flexible administration routes and regimens compared to traditional cytotoxic chemotherapies [46]. However, given that a single molecule's influence on regulating cellular radioresponse is dependent on a variety of genetic/epigenetic circumstances, the possibility exists that the effectiveness of target-based radiation sensitizers against solid neoplasms could be significantly limited by intertumor and intratumor heterogeneity. As a means of reducing the consequences of cell type specificity, targeting more than one of the potential molecular determinants of radiosensitivity has been suggested as a strategy for increasing the probability and/or degree of radiosensitization. Overcoming such a limitation would involve identifying markers that indicate which tumors may be susceptible to a given target-based radiosensitizer [47], and then using a multipharmacologic approach to improve clinical results. Naturally, the effect would also be dependent of the level of penetration into the metastasis.

However, there are novel radiation modifiers being discovered and developed which may prove a future benefit for CNS metastases. Histone acetylation, controlled by histone acetylases and histone deacetylases (HDAC), modifies nucleosome and chromatin structures and regulates gene expression. The aberrant HDAC activity leading to transcriptional repression of tumor suppressor genes is considered to be a common event contributing to tumor formation. Accordingly, molecules that can inhibit histone deacetylases and reverse the aberrant epigenetic changes associated with various cancers are being investigated. HDAC inhibitors have been shown to induce tumor cell differentiation, apoptosis, and/or growth arrest in several *in vitro* and *in vivo* experimental models. Multiple HDAC inhibitors have also been shown to affect radiosensitivity in preclinical models [48, 49]. Clinical trials are currently being conducted using these novel radiation sensitizers to determine their clinical safety and efficacy. Additionally, the use of antiangiogenic agents and radiosensitizers used in primary brain tumors, such as temozolomide, are being investigated to augment the effectiveness of established radiotherapy options in the setting of brain metastases, and represent additional paradigms to affect radiosensitization [50, 51].

1.2.1 Considerations of Radiation Sensitizers in Clinical Trials

The consideration of a radiosensitizing agent should be limited to a disease site or process where an indication exists for curative or palliative radiation therapy alone as standard of care, making CNS metastases prime targets for evaluation. Clinical trials with radiosensitizers typically seek to determine the dose of the modifier that is to be administered concurrently with radiotherapy, although radiation regimens may differ greatly based on the tumor type and clinical scenario. The trials are designed so that the agents are administered exclusively concurrently with radiation. When agents are administered neoadjuvantly or adjuvantly along with concurrent chemoradiotherapy, it can be an extremely difficult task to attribute the outcome to a radiation modifier effect, particularly if the agent exhibits significant cytotoxicity. Because of the potential for confounding effects, direct anticancer properties need to be examined prior to a combination of sequential chemotherapy with a chemoradiation regimen. Endpoints such as complete response rates, local control rates, locoregional time to progression, and survival are generally preferable to overall response rates and are determined by the primary tumor being studied. As an added consideration, dose-limiting toxicities for clinical evaluation of radiosensitizers are often defined by the organ and site, as determined by the body areas targeted with radiotherapy, and therefore, initial clinical investigations are often performed in a curative as opposed to a palliative setting. This presents a conundrum for CNS metastasis trials: highly restrictive patient selection and development of algorithms for "definitive" radiotherapy would be required for what is usually considered to be an incurable condition.

Novel serum biomarkers are currently under investigation which may one day provide a reliable early marker of clinical response to radiation therapy and may provide a means to evaluate the clinical effect of radiation sensitizers as part of an individualized cancer treatment strategy. Instead of categorical radiation dosing techniques, serum proteomic tests may allow us to better quantify the biological effect of serial exposures, making it easier to avoid toxicity while maximizing therapeutic efficacy [52].

With current advances in molecular radiobiology, strategies for enhancing radiosensitivity now focus on targeting the molecules and processes that regulate cellular radioresponse on a localized and systemic level. A wide variety of pharmacologic agents have been shown to influence radiosensitivity affecting such fundamental processes as cell cycle checkpoints, DNA repair, gene expression, and apoptosis. However, to be clinically relevant, a molecular target must not only serve as a determinant of radiosensitivity, but should also be susceptible to pharmacologic manipulation, and importantly, be selective for tumor cells over normal tissue.

1.3 Radiation as Immunomodulator (Abscopal Effect)

One of the more exciting possibilities is the use of radiation in stimulating immune responsiveness. Local radiation therapy that produces systemic effects on distant

tumors has become known as the abscopal effect [53] and has suggested a potential use as an adjunct to tumor immunotherapy [54]. Experiments in animal models have suggested that the biological mechanisms which result in the abscopal effect may be multifactorial [55], and are most likely dependent on CD4+ and CD8+ T cells and NK cells. The combination of radiation and interleukin-2 (IL-2) treatment results in increased antigen presentation and lymphocyte invasion in tissue at the site of irradiation, along with initiation of a systemic immunosensitization. For example, targeted radiation improves systemic responses to IL-2, and is associated with increased tumor cell surface expression of MHC Class I [56]. In contrast, irradiated tumor demonstrates an influx of Mac-1^{+} cells [57]. Because irradiated tumor results in changes in cell surface antigen presentation which leads to targeted immune-mediated cytotoxicity [58], the abscopal effect may present an opportunity to allow targeted radiotherapy to enhance the efficacy of immuotherapeutic agents such as sirolimus and rapamycin as well as the development of effective tumor vaccines. The combination of radiation and vaccine-based immunotherapy has resulted in improved response rates versus radiotherapy alone in cervical cancer, localized and metastatic prostate cancer, hepatoma, and metastatic renal cell carcinoma, providing the ground work for consideration for trials in other disease sites [59–64]. This is an area of radiobiology which has remained largely unexplored for CNS metastases. There is existing evidence that for melanoma brain metastasis, antibodies that block the interaction of cytotoxic T-lymphocyte-associated antigen (CTLA) with its ligands B7.1 and B7.2 and thus enhanced antitumor immune responses have shown clinical benefit in patients with metastatic melanoma, including durable control of brain metastases [65]. However, the added effect of radiotherapy in this setting remains unknown.

1.4 Radiation Effects on the Blood–Brain Barrier (BBB)

The effect of radiation therapy on brain microvascular permeability has been recognized for more than 80 years. In the 1920s, Beclere [66] discussed the treatment of craniospinal tumors and cautioned against the dangers of acute vasodilation, hyperemia, transudation of serous fluid, and edematous swelling. Later, it was noted that chlorides and sugar increased in the cerebrospinal fluid relative to blood between 4.5 and 6.5 weeks in patients following head irradiation at high, supratherapeutic doses [67]. These observations gave way to the hypothesis that cranial irradiation enhances the toxicity of systemically administered drugs.

The reverse can also be true. Prior administration of certain chemotherapy agents can alter the BBB, potentiating the effect of radiation, such as demonstrated in studies of the effect of cranial irradiation following intrathecal methotrexate in patients with primary CNS lymphoma [40]. In this study, patients began sequential WBRT (45 Gy delivered in 1.8 Gy fractions) 1 week after intrathecal methotrexate administration. With only a 7 day interval between methotrexate and WBRT, there was a 15% (if age <60) to 20% (if age >60) chance that late severe neurotoxicity would occur at a median follow-up time of 504 days. This implies that the effect of

radiotherapy is magnified when neurotoxic chemotherapy is delivered in close proximity to radiotherapy. Further, it suggests the hypothesis that BBB alterations produced by the combination of intrathecal chemotherapy and cranial irradiation are responsible for the observed encephalopathy subsequent to the prior effect of chemotherapy on increased BBB permeability. The study also demonstrates that age is a major factor when considering how much neurologic reserve one has to neurotoxic insult, be it from chemotherapy, radiation, or both.

Although the mechanism of this radiation effect has not been elucidated, selective biophysical damage to endothelial cell membranes or opening of interendothelial tight junctions would provide an explanation for the observed phenomena [68]. Corticosteroids protect against or moderate the acute complications of WBRT in the short-term, when patients undergoing WBRT take dexamethasone at doses of 4-16 mg/day. A positron emission tomography study using 82Rb as a tracer, failed to demonstrate an increase in blood-to-brain or blood-to-tumor transport of 82Rb following WBRT on patients taking high-dose corticosteroids, believed to reflect the stabilizing effect of corticosteroids on the blood–brain and blood-tumor barriers [69].

The response of the BBB to ionizing radiation is dependent both on the dose to which the brain is exposed and on specific properties of the tracer. Either an increase or a decrease of BBB permeability, or both, occurring in a certain time sequence, can be observed. The mechanism of hyperpermeability after irradiation may be related to the activation of vesicular transport. However, the response of the BBB to ionizing radiation may also be nonspecific and its responses to other physical or chemical noxious factors [70]. Whether induced by specific or non-specific pathways, the ultrastructural changes to both standard and hypofractionated radiation in humans remain to be elucidated in sufficient detail and in a standardized fashion that would allow for a reliable time-dependent prediction of behavior following radiation exposure.

2 Radiation Techniques

Fundamentally, radiation is a local treatment employed as an integrated component of multimodality therapy. Radiotherapy treats what is localized within a defined field, and the field is determined on what can be visualized, either with computerized tomography (CT), magnetic resonance imaging (MRI), and/or positron emission tomography. All of these imaging modalities have limitations in resolution in being able to image micrometastatic disease, as well as in determining in geometric space the true extent of tumor. Single brain metastases are typically easily visualized and well defined relative to normal tissue, rendering them easily treated by a technique which can provide high dose radiation with rapid falloff to minimize adjacent normal tissue damage. Multiple brain metastases require treatment of the entire brain for local control due to the presence of micrometastases that cannot be visualized by current techniques. Treatment of limited brain disease, such as 1–3

metastases, is an area of significant controversy, with some practitioners preferring localized SRS first, followed by WBRT at the time of relapse, or WBRT first followed by SRS to treat relapsed disease [71].

The optimal technique for radiation treatment of CNS metastases depends on the location, size and number of lesions, the extracranial tumor control, the patient's neurologic and general medical conditions, and the natural history of the primary tumor site. All forms of radiotherapy have a basic requirement that the patient be cooperative and able to follow commands, since the treatment is delivered with the patient alone in the treatment room. A treatment planning session, or simulation, is required, as every radiation plan is uniquely constructed for each patient based on differences in anatomy and in tumor characteristics. For WBRT, the simulation is performed with the patient supine with arms at the side, and head in neutral position on a headrest. Immobilization of the head is typically achieved with a custom-made mask to prevent movement during treatment and in order to reproduce the position exactly between daily treatments. If stereotactic techniques are used, a headframe is attached to the patient (Fig. 9.1).

In the case of emergency WBRT, the simulation may be done on the treatment table. Otherwise, fluoroscopic imaging or CT simulation may be used to visualize the anatomy. The anatomic limits of the brain are defined on portal films with the linear accelerator gantry at the 90° and 270° positions to give opposed-lateral field arrangements. Custom blocks are then prepared to shield the lens and facial structures. The inferior border is most commonly set at the bottom of the C1 vertebral body. The bottom of the C2 may be used if the patient has a higher risk of drop metastases, such as in medulloblastoma, leukemia, and posterior fossa disease. The other field borders extend to 2 cm beyond the bony limits of the skull in the anterior, superior, and posterior positions (Fig. 9.2). In instances where lymphoma or leukemia is the origin of the intracranial disease, the field is modified to ensure coverage of the cribriform plate, retina, and the upper cervical spine. These modifications are not typically necessary in instances of metastases from solid extracranial tumors. Sophisticated software packages allow reconstruction of planning images and fusion with diagnostic imaging so that custom radiation plans can be devised based on the unique anatomy and tumor characteristics of each patient, taking into account both the target and surrounding normal tissues. The planning software is able to provide a "topographical map" of radiation dose distributions within a three-dimensional model of the patient.

X-rays and γ-rays enter a tissue for a distance, then begin to slow down and deposit dose once they encounter dense tissue, a process known as attenuation. The energy of the beam dictates the characteristics of how attenuation occurs, represented as a depth-dose distribution. Physical characteristics of 6 megavoltage (MV) photons, most commonly used for cranial radiation, have a maximum dose (Dmax) at 1.5 cm and a therapeutic range of approximately 3–4 cm at 90% depth dose.

Linear accelerators (linacs) are the workhorses of the radiation therapy universe. They are the most widely used type of unit on which radiation patients are treated and have replaced older cobalt teletherapy units. They are comprised of a microwave power source, a linear accelerator guide, a bending magnet, an X-ray target

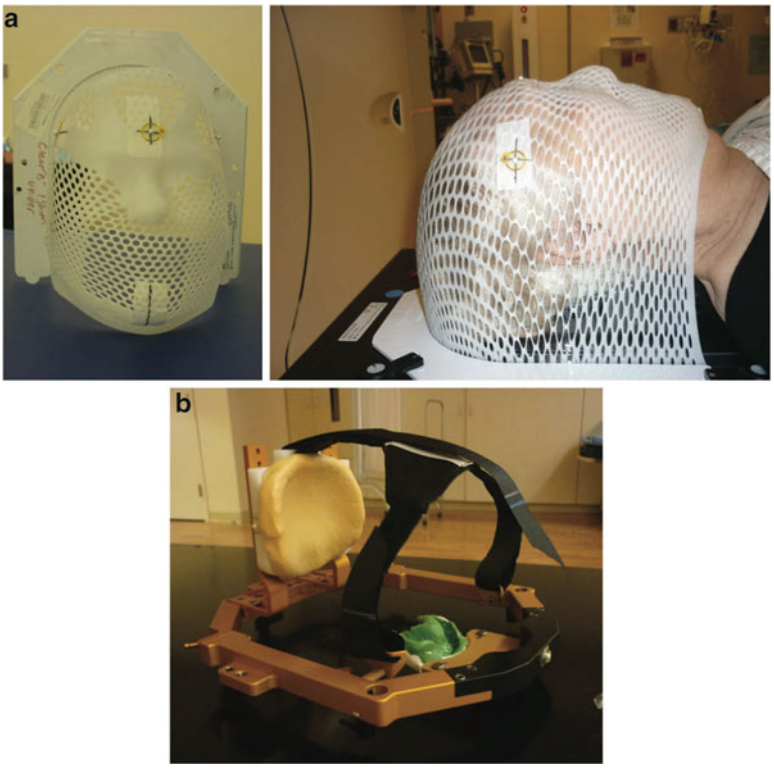

Fig. 9.1 Immobilization devices for the head commonly used in radiotherapy of brain metastases. (**a**) Aquaplast immobilization mask that has been custom fitted for the patient. (**b**) Removable headframe used for external coordinate system in stereotactic radiation delivery. The beige cup fits along the occiput of the patient's head. The *green mold* represents a bite block, which inserts into the patient's mouth and secures onto the upper dentition. The *black straps* are used to secure the frame to the patient's crown. There are multiple variations of this type of headframe, some with pins that percutaneously attach the frame directly to the skull, as in a Brown-Robert-Wells headframe commonly used for SRS

usually made of tungsten, a flattening filter, a monitor ionization chamber, and a collimator that is used to shape the beam as it exits the head of the machine. When electrons created by the microwave power source are accelerated against the tungsten target, brehmstrahlung radiation provides a spectrum of X-ray energies in the megavoltage range (as compared to kilovoltage X-ray energies required for diagnostic purposes). The head is located on a gantry which can rotate 360°, which may be parked in pre-defined positions to deliver a prescribed amount of radiation, or can deliver radiation while moving so that the dose is spread out into an arc formation. Linear accelerators can be fitted with beam modifiers and shapers such as multileaf collimators, as well as specialized collimators which allow pencil-type beams to treat SRS cases (Fig. 9.3). Many newer linear accelerators are often equipped with special imaging equipment, so that image-guided therapy may be

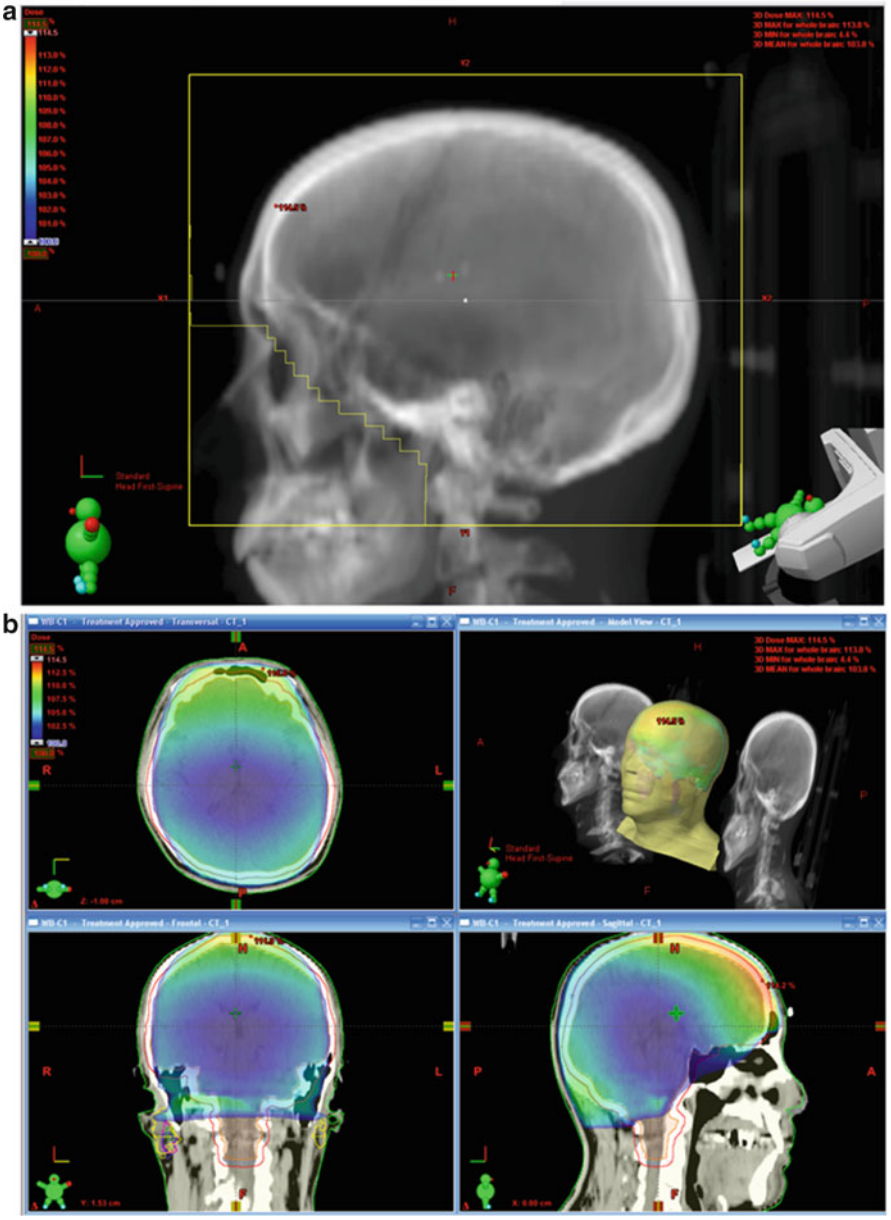

Fig. 9.2 An example of a whole brain radiotherapy plan in a patient with metastatic lung cancer treated with opposed lateral fields, 6 MV photons, to a dose of 30 Gy in 10 fractions of 3 Gy, prescribed to the 100% isodose line. Dosimetry was calculated on Eclipse 8.6 software (Varian Systems, Palo Alto, CA). (**a**) DRR (digitally reconstructed radiograph) of the left lateral treatment field. (**b**) Dose distribution is modeled to demonstrate entire coverage of the brain parenchyma

Fig. 9.3 Modern linear accelerator (linac) (Varian Systems, Palo Alto, CA)

possible. Special adaptations to linear accelarators, such as placing a compact linear accelerator on a continuously rotating gantry along with a diagnostic x-ray tube forms the basis for helical tomotherapy (Fig. 9.4). Linear accelerators that are mounted onto a robotic arm and employ image-guided software are the basis of robotic radiosurgery units (e.g. Cyberknife, Accuray, Sunnyvale, CA). However, at their root, the radiation that is delivered is derived with each of these technologies is derived from a linear accelerator.

In contrast, Gamma Knife units were engineered in the 1950s and 1960s to treat isolated intracranial lesions before the advent of modern linear accelerators. Gamma Knife units (Elekta, Stockholm, Sweden) utilize gamma rays produced as part of the natural decay of radioactive Cobalt-60 sources located in the housing of the machine. Cobalt-60 is made as a by-product of neutron bombardment in nuclear reactors and has a half-life of 5.26 years with energies of 1.17–1.33 MV and a Dmax at 0.5 cm. Both gamma rays from Cobalt-60 and photons from x-rays produce entrance and exit dose. Where the dose fields overlap onto a target, or isocenter, the dose is additive. Therefore multiple beam positions are used to spread a low radiation dose over a wide area, so that a focused, higher dose may be delivered to a smaller region.

Protons are a relatively new particle used in selected CNS treatments, and have the theoretical advantage of eliminating the exit dose produced by photon and gamma radiation treatments. However, since the availability and cost is currently prohibitive to be used on a large scale for CNS metastasis, data on comparing protons to photons in the setting of CNS metastasis is extremely limited, remains largely explorative, and is currently advised only for selected clinical situations [72].

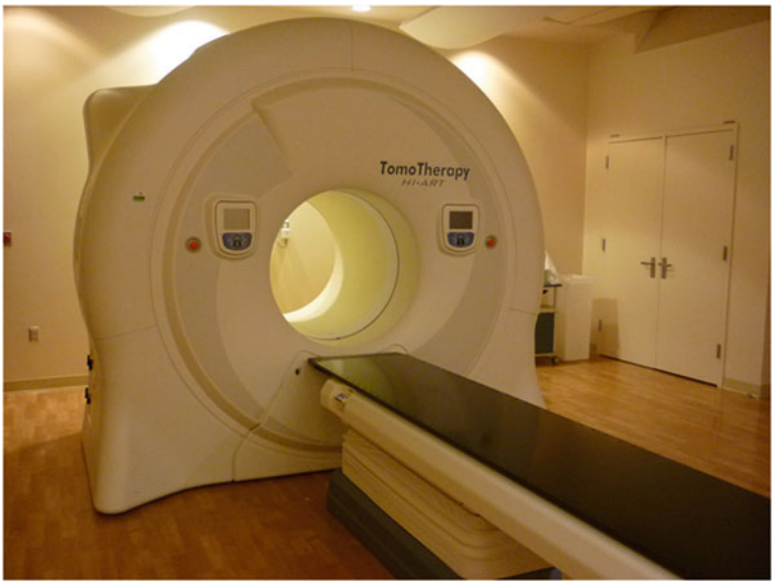

Fig. 9.4 Helical tomotherapy unit (TomoTherapy HiArt, Accuray, Sunnyvale, CA)

2.1 Whole Brain Radiotherapy (WBRT)

In August, 1973, a landmark Radiation Therapy Oncology (RTOG) trial enrolled its final patient on what would set the standard of care for the treatment of multiple brain metastases. That standard of WBRT has remained unchanged in the nearly 40 years since [73]. In those days, intracranial imaging with CT scans or MRIs were non-existant, and chemotherapy treatments for cancer were in their infancy. The study treated patients with symptomatic brain lesions with WBRT and randomized subjects to multiple fractionation schemes. The results demonstrated that patients who were treated with a large single fraction size of 10 Gy had a much poorer outcome, but otherwise there was no statistically significant difference between fractionation schemes that took between 1 and 4 weeks of treatment. Given the very limited lifespan of patients with brain metastases at the time, the investigators concluded that the most efficacious regimen in terms of economic cost, inconvenience to the patient, and benefit of therapy was a fractionation scheme of 3 Gy × 10 fractions. The addition of corticosteroids to WBRT was found to help improve short-term symptomatic control. Although long-term symptomatic control was achieved by WBRT, overall survival was not improved.

A follow up trial to evaluate the efficacy of still shorter time-dose fractionation schemes was initiated in November 1973 and closed in February 1976 [74]. The methods of diagnosis, randomization and follow-up assessment were essentially the same as for the first study. Three treatment options (arms) were utilized with 902 evaluable patients. The initial neurologic function status, general performance

status and ambulatory status were implicated as prognosticators of response. This study demonstrated that WBRT improved overall neurologic function in approximately 50% of patients and improvement of specific neurologic symptoms was as high as 90%. Patients who presented with initial higher neurologic functional status and who were ambulatory at the time of WBRT had higher response rates and more rapid improvements. Treatment schedule and primary site of disease had no influence on response in these studies. Administration of steroids during irradiation resulted in slightly faster improvement for patients with neurologic deficit, however, after 3-4 weeks of steroid treatment, response to WBRT was no longer dependent on steroid administration. In terms of survival, ambulatory patients survived longer (21 weeks) than did non-ambulatory patients, and breast cancer patients as a group survived longer than did lung cancer patients. For all schedules, 75-80% of remaining life was spent in either an improved or stable neurologic state, thus, shorter time-dose fractionation schedules than 50 Gy delivered in 4 weeks were preferred. Importantly, the intent of these studies was to establish guidelines for whole brain radiation as palliative therapy, since at the time, there was no expectation of cure. With the advent of modern improved systemic therapies, the brain increasingly may serve as a sanctuary site in a patient with controlled extracranial disease. Subsequently, selection of fraction size and total dose for WBRT has depended mostly on patient comorbidities and prognosis [75].

Patients who receive WBRT usually experience mild acute toxicities, such as transient worsening of neurologic symptoms prior to resolution, otitis, alopecia, skin reaction, headache, mild fatigue, and possibly slight nausea or vomiting. Late-term side effects such as decreased concentration and short-term memory loss are not expected to appear in the majority of patients with a poor prognosis, and therefore, short survival times. These neurocognitive sequelae are usually subtle, may take months to years to manifest, and occur in varying degrees. The most feared neurologic complication is radiation-associated dementia. Thankfully, modern planning WBRT techniques, radiation dose limits to 3 Gy per day or less, and the omission of radiosensitizers during WBRT whenever possible have decreased the severity of neurocognitive sequelae. Current severe dementia rates from WBRT with modern techniques and conventional fractionation schemes, are <5% in long-term follow up of patients who have good overall disease control [76]. This is in contrast to a long-term study from the Memorial Sloan Kettering Cancer Center published in 1989 that treated patients with WBRT with curative intent and demonstrated an 11% risk of dementia in patient subjects at 1 year following treatment [25]. Since this information is often misquoted to patients, it is important to note that the adverse neurocognitive effects from this study were seen when doses “exceed 3 Gy per fraction”, and the 11% rate of severe dementia was solely contained within a patient subgroup which exceeded 3 Gy per day. Many patients within the same subgroup also received concurrent systemic radiosensitizing chemotherapy such as adriamycin. Therefore, it is not a surprise these patients sustained adverse reactions attributed to radiotherapy. As a consequence, some institutions have adopted the 2.5 Gy fraction size as the standard protocol for patients with a good prognosis. Additional investigations have introduced the concept of multifactorial cause for the dementia (comorbidities,

paraneoplastic syndromes, and chemotherapy) and some studies have found no objective evidence of decline in mental status after radiotherapy [77, 78]. Nevertheless, despite current data, the stigma of neurocognitive toxicity remains.

The decision as to optimal timing of WBRT in asymptomatic patients is currently an area of significant controversy. The overriding rationale rests on the assumption that a delay in WBRT translates to a delay in any untoward neurocognitive effects. Despite the fact that the neurocognitive effects are poorly understood and appear to impact a small minority of patients, multiple studies suggest that uncontrolled tumor produces far worse consequences for neurocognition, and ultimately, quality of life [22, 79–81]. Another possible negative consequence for delaying WBRT in patients who are at high risk of harboring micrometastatic disease, is that when WBRT is eventually given, it is less likely to be fully effective. Once lesions are big enough to image on MRI, it is unlikely that radiation alone at doses and fractionation that are amenable to normal brain tissue will be adequate to eradicate disease. In other words, the potential cost of withholding WBRT translates into higher intracranial relapse rates [82]. Current investigations into radiation mitigators, as well as techniques for sparing the hippocampus during WBRT are under current investigation as a means to further decrease the adverse neurocognitive effects that occur in some patients.

Rarely, does a patient have brain metastasis as their only site of active disease. Therefore, it makes sense to segregate those with brain-only disease and active extracranial disease in the analysis. Several studies have suggested that those with brain-only disease have the greatest benefit from an aggressive approach to include a combination of WBRT and SRS boost [83, 84]. Recursive partitioning analysis (RPA) from brain metastasis patients enrolled in RTOG trials from 1979 to 1993 were categorized according to pre-treatment and treatment-related variables. Class I patients were defined as having a Karnovsky performance status (KPS) score >70, age <65, and controlled extracranial primary tumor. Class I patients were noted to have a median survival of 7.1 months. Class II patients were defined as having a KPS <70, an age >65, **or** an uncontrolled primary tumor. Class II patients had a median survival time of 4.2 months. Class III patients were defined as having a KPS <70, age >65 **and** uncontrolled primary tumor. Class III patient demonstrated the poorest prognosis, with a median survival time of only 2.3 months. Traditionally, Class I RPA patients have been treated most aggressively with surgical resection or SRS with or without WBRT. In addition to patient prognosis, it is important to note that the volume of disease or numbers of metastases may also dictate appropriate therapy.

Regardless of RPA class, patients with multiple brain metastases have traditionally received WBRT alone [85, 86] with the goal of limiting tumor progression, and in the most poorly performing patients, to limit the use of corticosteroids which have multiple unwanted side effects. Patients with 2–3 lesions in Class I or II may also be considered for multiple modalities including surgery with or without WBRT. Several retrospective and randomized studies have shown that surgery added to WBRT confers both survival and local control advantage in select patients presenting with a limited brain metastasis [85, 87]. When comparing surgery alone to surgery combined with WBRT, the addition of WBRT did not demonstrate an

improvement in survival, however, patients in the radiotherapy arm experienced a decrease in local recurrence. Furthermore, the addition of WBRT markedly decreased the incidence of local recurrence (46% versus 10%), distant brain recurrence (37% versus 14%), and death from a neurologic cause (44% versus 14%). This has led some to recommend that surgery without WBRT is advised only for patients with a particular risk of radiation-induced dementia, or for patients with histologies deemed "radioresistant" [82, 88].

To answer the question of when the addition of SRS boost is most beneficial following WBRT was the goal of the prospective randomized study RTOG 95–08 [84]. This trial included 331 patients randomized to receive WBRT (37.5 Gy in 15 fractions) versus WBRT plus SRS boost. All histologies were eligible, with patients stratified according to number of metastases. SRS dose varied according to guidelines established by a previous Phase II study, RTOG 90–05, which found that the dose limiting toxicity for lesions up to 2 cm to be 24 Gy as a single dose, lesions 2–3 cm at a limit of 18 Gy as a single dose, and for lesions >3 cm up to 15 Gy as a single dose. Patients who received the addition of SRS boost had a significantly improved rate of stability or improvement in performance status at 6 months (27% vs. 43%), and a slightly improved median survival from 4.9 vs. 6.5 months. In patients with single brain metastasis, and meeting the criteria for RPA class I, median survivals were extended to 11.5 months with the addition of SRS boost. 1 year relapse rate of 18% was noted with SRS vs. 29% without. Therefore, WBRT + SRS may be considered alternative to craniotomy. Subgroup analysis suggested a potential for benefit in patients with up to three brain metastasis, especially those patients with minimal extracranial disease, younger age and lung cancer histology.

2.1.1 Prophylactic Cranial Irradiation

The use of WBRT based on a high likelihood of the presence of micrometastatic disease within the brain, but without radiographic evidence of metastasis, is termed prophylactic cranial irradiation (PCI). The use of PCI has been most extensively studied as a preventative measure in the treatment of small-cell and non-small cell lung cancers. In a trial comparing PCI versus observation in small-cell lung cancer to patients with extensive stage disease who had a favorable response to chemotherapy, PCI was found to reduce the incidence of symptomatic brain metastases and prolong disease-free and overall survival [89]. The cumulative risk of brain metastases within 1 year was 14.6% in the irradiation group versus 40.4% in the control group. The 1-year survival rate was 27.1% in the PCI group and 13.3% in the control group. Although PCI did produce some side effects, it was not found to produce a clinically significant effect on global health status. Similarly, in non-small cell lung cancer, a randomized trial of PCI versus observation in patients who had responded favorably to treatment of their primary disease yielded similar results. PCI in this study was delivered to 30 Gy in 15 fractions, with a primary end point of overall survival. Patients in the observation arm were 2.52 times more likely to develop

brain metastases than those in the PCI arm [90]. However, unlike its small-cell lung cancer counterpart, there was no difference in overall survival in this trial.

Therefore, if PCI reduces the incidence of brain metastases, possibly leading to improved overall survival, what dose of PCI is ideal to combat micrometastatic disease? Doses used in PCI are typically less than that used in the treatment of gross disease, at 2.0–2.5 Gy instead of 3.0 Gy per fraction. Based on first radiation principles, more durable control of disease can be obtained with a limited radiation dose if less disease is present at the time of treatment. Accordingly, a randomized clinical trial compared the effect of standard versus higher PCI doses on the incidence of brain metastases in patients with small cell lung cancer. 720 patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy were randomly assigned to a standard (25 Gy in 10 daily fractions of 2.5 Gy) or higher PCI total dose (36 Gy) delivered using either conventional (18 daily fractions of 2 Gy) or accelerated hyperfractionated (24 fractions in 16 days with two daily sessions of 1.5 Gy separated by a minimum interval of 6 h) radiotherapy. The primary endpoint was the incidence of brain metastases at 2 years. There was no significant difference in the 2-year incidence of brain metastases between the standard PCI dose group and the higher-dose group, at 29% and 23%, respectively. Two-year overall survival was 42% in the standard-dose group and 37% in the higher-dose group. The study concluded that in patients with good local control of systemic disease, a significant reduction in the total incidence of brain metastases was observed after higher-dose PCI, but with a trend toward an adverse impact on mortality. These data suggest that 25 Gy should be considered the optimal PCI dose in limited-stage small-cell lung cancer [91].

When WBRT is utilized in a scenario without proven metastases, the risk to benefit ratio is reevaluated and minimization of normal tissue toxicity becomes a higher priority. Therefore, much attention has been paid to the neurocognitive effects in this particular patient population who receive PCI. Some investigations have demonstrated that many patients undergoing PCI have neurocognitive deficiencies at baseline, and the addition of PCI does not result in additional deficits [92]. In an evaluation of neurocognitive functions and quality of life assessments in patients with non-small cell lung cancer who receive either PCI or observation, there were no statistically significant differences at 1 year between the two groups in any component of several global assessments of neurocognition and quality of life. However, a test with greater sensitivity for subtle differences in neurocognitive parameters did note statistically significant declines in immediate recall and delayed recall in the PCI arm at 1 year. Nevertheless, PCI significantly decreased the risk of brain metastasis in the group that did receive PCI [93].

When neurocognitive function and quality of life assessments were performed in patients with small cell lung cancer who received PCI at a standard dose of 25 Gy in 10 daily fractions versus a higher PCI dose at 36 Gy, the data revealed there was no significant differences between the two groups in 17 selected items assessing Quality of Life (QOL) and neurological and cognitive functions [94]. However, a mild deterioration across time in communication deficit, weakness of legs, intellectual deficit and memory were noted in both patient groups. Again, there were some

mild adverse effects of PCI, which were outweighed by the benefit of PCI on overall survival and delayed development of brain metastases in patients with small cell lung cancer.

It is possible that future advances in imaging and/or development of biomarkers may reveal the presence of micrometastases at earlier and earlier stages. This may open up the investigation of potential use of PCI in other patients at high risk of developing CNS metastases. Currently PCI is actively utilized in the setting of lung cancer, but may prove beneficial in preventing brain metastases in other primary disease sites as well.

2.2 Stereotactic Radiation

Stereotactic radiation is a procedure designed to deliver a highly conformal dose of radiation to a small volume. Multiple converging static fields or arcs centered on a single isocenter are used to generate the high dose region. These techniques utilize multiple beams spread in a large solid angle to minimize entrance dose and volume of normal tissue irradiated. The term "stereotactic" as it pertains to radiotherapy implies the use of highly precise localization techniques and treatment planning in three-dimensional space with a highly conformal radiation plan and rapid dose fall-off outside of the target margin, typically through the use of an external three-dimensional reference system capable of submillimeter precision. Stereotactic radiation is a technique which may be accomplished using multiple methods, including Gamma Knife, robotic-assisted stereotactic radiotherapy, helical tomotherapy, as well as linear accelerator-based radiosurgery. Linear accelerators commonly used to provide standard external beam radiation treatments may be modified to allow for stereotactic radiation treatment with specialized adaptors which may be mounted to the head of the machine. Although there are minor advantages and disadvantages to each type of stereotactic equipment, stereotactic radiation may be best described by the analogy of different types of automobiles with different appearances and engines. They all do essentially the same job.

Stereotactic radiosurgery (SRS) implies the use of high-dose, single treatment regimens, where the goal is obliteration of all tissue within the target volume. There is no invasive surgery in the traditional sense where the skull is physically penetrated with surgical instruments. With SRS, the treatment is entirely with radiation. SRS is sometimes offered in place of traditional invasive surgery because many patients are poor medical candidates or have lesions in locations not amenable to resection. In addition, patients with multiple lesions have rarely been offered surgery because the morbidity is often felt to be excessive [95]. As with excisional surgery, SRS is a focused treatment that would not be expected to address the risk of distant brain progression. Based on Patchell's randomized data, WBRT would be expected to decrease the risk of distant brain progression [85]. This study demonstrated a surgery benefit in survival, local recurrence, time to recurrence, time to neurologic death, and QOL when given in conjunction with WBRT in a favorable

subset of patients with a single brain metastasis at a median follow up of 40 weeks. The use of SRS was then extrapolated from these data as a possible substitute for surgical resection. Metastases are ideal targets for SRS because most lesions are small, pseudospherical and well demarcated from the surrounding CNS tissue. Rates of local control in large series of SRS treatment for brain metastases have averaged 80-90% [96]. Although there are no randomized trials directly comparing SRS to surgery, the preponderance of retrospective data supports an equivalence of modalities for small, single lesions. For example, a retrospective, matched comparison analysis of 108 patients concluded that survival for patients with a single metastasis was similar whether they received SRS alone or surgery and WBRT [97]. However, these studies are limited by extremely short-term follow up in the range of 6 months–2 years. In a recent retrospective study of stereotactic radiosurgery treatment failures, a rare occurence at a rate of 1.2%, concluded that radionecrosis and radiation resistance were the primary risk factors [98].

The goal of radiosurgery is to provide an area of small volume destruction, resulting in the radiobiological inactivation of the ability of a tumor cell to divide and multiply. Preservation of the surrounding normal brain is achieved by the very sharp fall-off of the radiation dose gradient and can reduce the risk of complications to normal brain, especially in contrast to surgical extirpation. For malignant tumors, radiosurgery used in conjunction with fractionated radiation therapy may take advantage of the single fraction destructive effects of radiosurgery followed or preceded by conventional fractionated radiation therapy. Radiosurgery intentionally excludes normal tissue within its target volume, and by definition, is a poor technique choice compared to conventional planning methods in clinical situations when coverage of microscopic disease is necessary for improved outcome. In the United States, the vast majority of centers provide SRS based on the multidisciplinary input of neurosurgeons, radiation oncologists and medical physicists. The team provides both the necessary experience as well as the different perspectives that facilitate safe intervention and effective outcomes.

Radiobiological studies have suggested that it is necessary to have doses in excess of 15 Gy in a single fraction to achieve the collapse of vasculature that is the hallmark of SRS [10]. Although stereotactic radiosurgery is a competing modality to surgical resection for small brain lesions, there are size and dose limits. As mentioned in the previous section, RTOG 90–05 [99] established the mean tolerated doses of SRS after WBRT to a median dose of 30 Gy. Dose recommendations are a function of size, up to a maximum diameter of 3–4 cm.

The therapeutic effect of stereotactic radiosurgery is related primarily to geographic accuracy and rapid dose fall-off outside the tumor volume rather than exploiting the differential ability of normal and tumor tissue to repair DNA damage as seen with large field, conventionally fractionated radiotherapy. As a consequence, the immobilization systems used in many stereotactic radiosurgery techniques consist of a stereotactic frame that is bolted to the patient's head prior to the target-localization procedure. The placement is often uncomfortable for the patient, requiring local anesthesia, and is therefore only used for single-fraction treatments. Fiducial markers for three-dimensional target localization and image correlation are

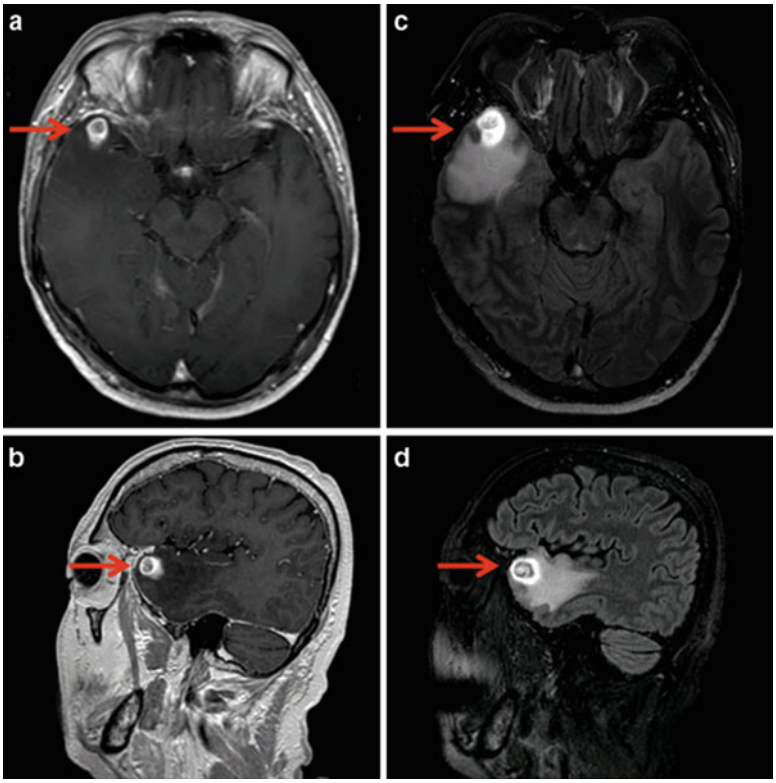

Fig. 9.5 MRI images of a 60 year-old male with a single brain metastasis in the right temporal lobe from a non-small cell lung cancer primary. (**a**) T1-post gadolinium contrast axial image. (**b**) FLAIR axial image. (**c**) T1-post gadolinium contrast sagittal image. (**d**) FLAIR sagittal image

present on a variety of attachments that are rigidly fixed to the frame. The stereotactic frame, which remains in place from the beginning of the localization procedure until the treatment is completed, is fixed to the treatment couch in a reproducible fashion during the treatment to facilitate accurate treatment delivery.

Corticosteroids are commonly given in conjunction with SRS treatment to decrease the probability of complications due to acute tumor swelling. The gross tumor volumes are defined by the contrast enhanced tumor on a pre-treatment planning MRI brain scan, with the patient in the treatment position (Fig. 9.5). The maximal cross-sectional diameter is typically < 3.0 cm. The dose should be prescribed to the highest isodose line encompassing the gross tumor volume, which can range from 50% to 80% of the maximum dose. Prescription doses for metastases are generally based on tumor size as per RTOG 90–05. Dose conformity, also considered as the ratio of the prescription isodose volume to the target volume, should be between 1.0 and 2.0. For lesions less than 5 mm in size, a ratio up to 3.0 is generally acceptable. The treatment parameters should be modified to optimize the fit of the prescription volume to the target volume while minimizing dose to critical structures.

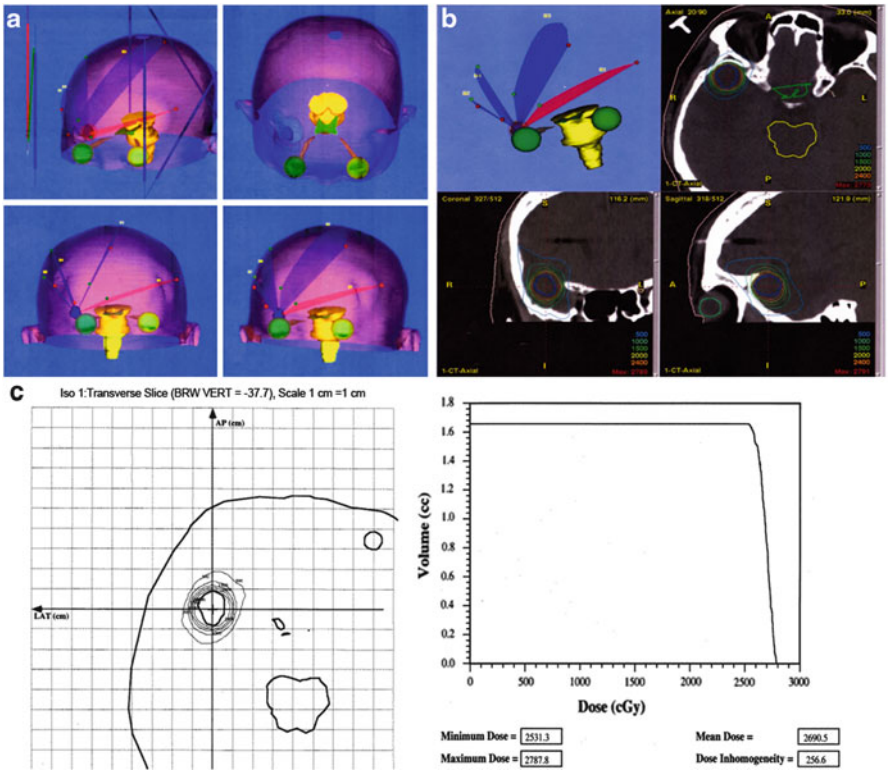

Fig. 9.6 Stereotactic radiosurgery boost following WBRT to 30 Gy to a dose of 24 Gy (2,400 cGy). (**a**) The treatment plan consists of four arcs with 6 MV photons, configured by XKnifeRT™ 4.0.1 software (Integra Radionics, Burlington, MA). (**b**) Dose is prescribed to the 87% isodose line as 24 Gy delivered in a single fraction. Please note that the prescription isodose is highly conformal to the lesion, however, there is still a significant volume of normal brain, which does receive a significant radiation dose. (**c**) Isodose lines and DVH (dose-volume histogram) of the treated metastasis showing sharp dose fall off around the target

Common institutional constrains suggest that the dose to the optic chiasm and optic nerves should be less than 8 Gy to any point in the structure. Dose to the brainstem should be kept less than 12 Gy to any point (Fig. 9.6). Some doses do fall outside of the treatment field, and when multiple lesions are treated, the integral dose to the entire brain can be substantial, and not unlike WBRT in its radiobiological equivalent. Some radiation dose may be deposited several centimeters outside of the radiation beam due to lateral electronic disequilibrium [100], and may occur in radiosurgery techniques due to the outscatter of electrons.

When is SRS alone without WBRT of benefit? Can WBRT be eliminated for some patients with brain metastasis? These are currently questions which raise a significant amount of controversy and are areas of active investigation. Results from retrospective analysis suggest an increased likelihood of relapse but not necessarily survival with the use of SRS alone [101]. The argument for withholding WBRT is

based on the perception of late neurotoxicity from retrospective data utilizing unconventional fractionation schemes without sensitive neurocognitive testing [25]. Given the consistent evidence derived from the surgical and SRS literature supporting a clear increase in the rate of intracranial recurrences when WBRT is withheld [82, 101], and the strong association of intracranial recurrences with a detriment in neurocognitive function [22, 79], the data suggest against the routine use of SRS alone. Sneed et al. reported a retrospective comparison of outcomes in 569 patients treated at 10 institutions either with WBRT + SRS or with SRS alone. They found no survival difference, but patients in the SRS alone group required salvage treatment more often (37% vs. 7%) [101]. Retrospective data have demonstrated that freedom from progression of brain metastases was significantly worse for patients who received SRS alone versus those who received SRS + WBRT, (28% vs. 69% at 1 year). However, an argument in favor of SRS alone comes from recent data that suggest that patients treated with SRS plus WBRT were at a greater risk of a significant decline in learning and memory function compared with the group that received SRS alone as measured by the Hopkins Verbal Learning Test-Revised at 4 months post-treatment [102]. Unfortunately, later timepoints were not evaluated, so there is no indication, as other studies have suggested [78], that function recovers after 4 months. Again, most of these studies have short-term follow up, and it is unknown whether this control is applicable for someone who survives for many years with brain metastasis.

Nevertheless, the American College of Surgical Oncologists opened a phase III trial of radiosurgery randomized to observation or WBRT in patients with one to three cerebral metastases. The goal of the trial is to compare 6 month overall survival in patients with SRS alone vs. SRS and WBRT. At the time of this writing, results are still forthcoming. At the current time, it is unclear whether the addition of conventional WBRT to SRS results in either survival advantage or decreased risk of neurological death. It is possible that even if there is no survival advantage to WBRT, quality of life may be improved and treatment may be cost effective, due to avoiding the psychological distress of brain recurrence and the future need for subsequent salvage therapy. On the other hand, the potential side effects of WBRT may outweigh the potential benefits.

However, SRS isn't without its own set of side effects [103]. When SRS is used in definitive therapy for meningiomas, the patient is expected to live to many years. In long-term follow up of these patients, 13% experienced treatment-related complications at a median follow up of only 5 years. Complications included cranial nerve deficits, symptomatic parenchymal changes, carotid artery stenosis, and symptomatic cyst formation.

While stereotactic radiosurgery is a single "fraction" treatment, stereotactic radiotherapy (SRT or fSRT) connotes a fractionated approach where a stereotactic planning technique is utilized using rigid immobilization, but the dose is divided into multiple treatment sessions. Since the bolted system is impractical for fractionated treatments, relocatable fixation systems have been developed (Fig. 9.1b). Thus, use of SRT combines the benefits of the two approaches. Stereotactic radiotherapy techniques yield the precision of stereotaxy within 1–2 mm, as well as allowing for normal structures to repair sublethal damage. For example, if a patient has a large

metastasis, greater than 3–4 cm that is not amenable to surgical resection, a regimen of fractionated stereotactic radiotherapy may be effective. Cyberknife, or robotic-assisted stereotactic radiation, is essentially an SRT planning technique, using hypofractionated radiotherapy typically delivered over five sessions.

A note of caution about the potential indiscriminate use of radiosurgery is that the central nervous system is the most unforgiving organ in terms of late radiation effects. In general radiobiologic principles, hypofractionation typically leads to poorer tumor control, and more frequent and severe normal tissue complications compared to conventional fractionation schemes. It makes sense to encourage the investigation of radiosurgery as a boost following conventional fractionated radiotherapy, or further explore benefits of treatment with stereotactic radiotherapies in carefully selected patient populations.

2.3 Treatment of Spinal Metastases

Like brain metastases, the goal of most spinal metastasis treatments is to prevent neurological complications from tumor progression, with a lesser consideration of overall survival. Spinal metastases may present as leptomeningeal seeding of the thecal sac, or localized tumor extension causing compression of the nerves or cord. Spine tumors are frequently symptomatic with associated pain or neurologic dysfunction. Conformal radiotherapy is an option offering palliation to the majority of patients [104]. However, the ability to deliver doses that can effectively control gross tumor with this approach is limited by spinal cord tolerance. As a result, those patients who go on to develop symptomatic progression within their previous radiation field are offered surgery to avoid the potential complications associated with re-irradiation. For patients with localized disease, stereotactic body radiotherapy (SBRT) can sometimes be considered as a non-invasive alternative to surgery. For patients with disseminated disease, treatment of the entire thecal sac, termed “craniospinal radiation” may be required to prevent re-seeding of a treated area and to provide adequate disease control (Fig. 9.7).

Spinal cord compression secondary to malignancy is seen in 5–10% of all cancer patients [105]. Symptoms of cord compression occur in a predictable pattern. Back pain is seen in almost all patients and is usually the first symptom, progressing to radicular pain, weakness, sensory deficits, eventual loss of bladder or bowel control, and then paralysis. A full neurologic assessment is required during the physical examination of patients in who cord compression or nerve entrapment is suspected. Imaging the extent of disease and identifying the involved vertebral levels may be achieved with a screening spine MRI. If no pathologic diagnosis of metastasis exists, consideration of biopsy is done prior to corticosteroid administration, since corticosteroids may obscure the accurate diagnosis of certain histologies such as lymphomas. Treatment options are then contemplated including decompressive surgery and radiotherapy. Radiotherapy is indicated for most patients, whether alone or after surgery to improve local control [106]. Treatment fields traditionally include

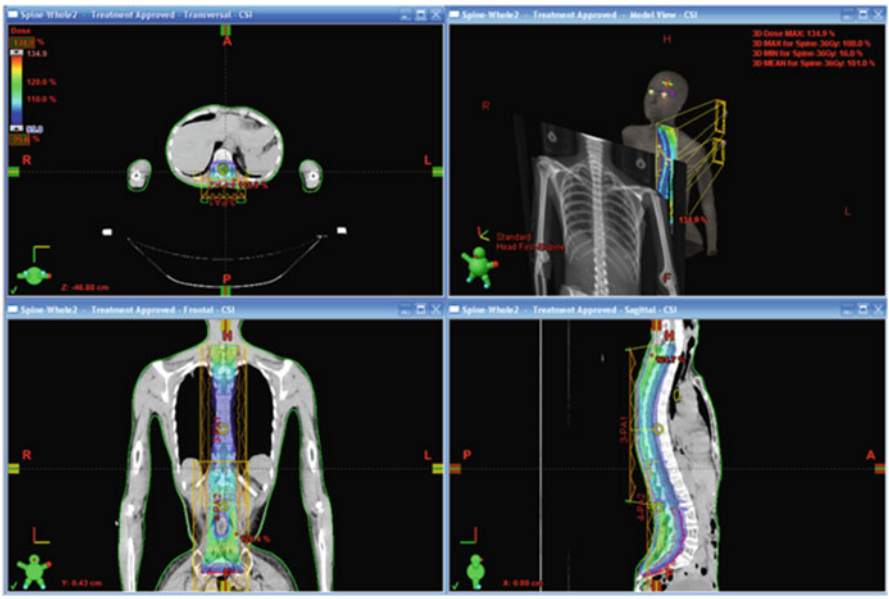

Fig. 9.7 Craniospinal irradiation plan for a 51-year old female with drop metastases and leptomeningeal seeding from a metastatic carcinoma, producing pain, gait ataxia and weakness of bilateral lower extremities. A cranial field (not shown) was planned similar to that displayed in Fig. 9.2. The entirety of the thecal sac is covered in the spinal field, dosed to 36 Gy with 6 MV photons

the spinal lesion with the addition of two vertebral bodies above and below the lesion for margin. Consideration may be given to decreasing the margin when larger fields would result in significant toxicity. Fraction size for standard therapy depends on field size, anatomic location and patient prognosis and comorbidities. There are a wide variety of acceptable fraction sizes, ranging from 8 Gy delivered in one dose to up to 40 Gy delivered in 20 fractions. However, 30 Gy in 10 fractions or 37.5 Gy delivered in 15 fractions is used most commonly [107]. Significant reduction of back pain after radiation occurs in 80–90% of patients. The return of neurologic function depends on pretreatment function, duration of motor deficits, and tumor cell type. In general, full neurologic function is obtained for >90% of patients who are ambulatory at the time of spinal cord compression presentation and treatment. In contrast, only 28% of patients presenting with paresis, and 21% of patients with paraplegia regain ambulatory capacity after treatment [108].

SBRT doses delivered to the tumor (10–16 Gy in one fraction; 20–30 Gy in 5 fractions) allow for keeping dose to the cord within conventional fraction sizes. This approach appears to offer durable palliation in the majority of patients (84–90%) without an apparent neurologic toxicity [109, 110]. SBRT appears to be a safe and effective palliative treatment for spinal and paraspinal metastasis, although further study is necessary to establish the long-term safety and efficacy of this approach,

as well as to better define the dose constraints of the cord. For patients presenting with mild-moderate cord compression, SBRT may be used for pain relief and improved neurologic status [111]. Patients with frank cord compression are poor candidates for SBRT because the inflammation produced by the hypofractionated radiotherapy may produce more significant compressive symptoms, possibly resulting in permanent paralysis.

2.4 Economic Considerations

Treatment of CNS metastases carries a significant financial cost, which must be weighed against potential benefits in potential survival and functional independence. One study in 1997 suggested that the average cost per week of survival at that time was $310 for whole brain radiotherapy alone, $524 for resection plus radiation, and $270 for radiosurgery plus radiation [112]. Therefore for selected patients, aggressive strategies such as resection or radiosurgery are warranted, as they result in improved median survival and functional independence. However, radiosurgery appeared to be the more cost-effective procedure as compared to surgical resection.

A recent study analyzed the cost-effectiveness of SRS followed by observation versus SRS in addition to WBRT in patients with 1–3 cerebral metastases, in terms of actual life years saved, quality-adjusted life years, and by an incremental cost-effectiveness ratio. Compared with SRS and whole brain radiation therapy, SRS and observation had a higher average cost at $74,000 versus $119,000, respectively [113]. Therefore, patient selection is key to improving the economic cost to benefit ratio. As treatments for CNS metastases improve, and patients have extended overall survival times, aggressive therapies will render themselves a better economic value.

3 Future Directions

It is no exaggeration to say there is much to be done to improve the lot of patients with CNS metastases. Currently enrolling trials include novel methods to spare hippocampus in the radiation therapy plan and delivery, as well as evaluation of temozolomide and erlotinib during WBRT and SRS treatments (www.clinicaltrials.gov). However, improving radiotherapy will have challenge the notion that all tumor types respond to radiation therapy the same. Future directions should aim to distinguish and devise therapies that are intended to be palliative versus those where eradication of disease is the goal. At present, whether a patient has a brain metastasis from breast cancer versus lung cancer, they receive nearly the same treatment options, dosing and fractionation. Further studies need to be done to optimize therapy for certain histologies and patient groups with CNS metastases. Improvements in

radiographic visualization of the physical boundaries of tumor extension and function as well as critical normal structures will greatly enhance current radiotherapy techniques and effectiveness.

Molecular investigations into serum biomarkers, genetic signatures to stratify patients at risk of radiation toxicity, as well as the development of next-generation normal tissue radioprotectors and tumor-specific radiosensitizers are currently being investigated. Techniques borrowed from other disciplines might include the future use of neuronal stem cell rescue, as well as manipulation of pathways to overcome molecular mechanisms of radiation resistance.

However, with improved therapies must also come the recognition of needed improvements in QOF parameters. Lessons extrapolated from cognitive rehabilitation in traumatic brain injury patients, improved recognition of depression and its treatment, as well as aggressive involvement of palliative care specialists could do as much to improve survival as the radiation and chemotherapies themselves.

4 Conclusions

There is a love affair with new medical technologies both on the part of physicians and patients. New technologies are easily sellable to patients on the incorrect assumption that new technology automatically equals improved outcomes and fewer side effects. It is no wonder that a sense of pessimism prejudices the field, that research has not kept pace, and that the process of CNS metastasis is an underfunded disease entity. The discussion presented here has put forth that we have much more work to do in understanding the basic mechanisms of how radiation damages and ablates CNS metastases, which pharmacologic agents might prove beneficial, how normal tissue may be protected from both a technical, radiobiological and pharmaceutical perspective, and what treatments are most effective for individual disease-related metastatic processes. A “one size fits all” approach needs to be discarded, and as we shift our focus from the use of radiotherapy as a palliative measure to that of a definitive one, we have to tailor the therapy to the tumor itself, the biological background of the individual, and more effectively integrate the use of radiation as a localized measure into the overall systemic treatment plan of the individual patient. Patients need not assume what is good for their neighbor will be in their own best interests or produce the same results.

Advancements may be achievable with quality trial design and specific trials dedicated to particular tumor types. The other side of the coin requires patient trial participation to move the field forward. Because radiation therapy is, by definition, a local treatment, it is no surprise that using a local therapy to control a systemic process has not produced astounding increases in overall survival. However, more than 50 years of experience has shown radiation to be a fantastically effective tool for local control, and it will continue to be an essential ingredient in the future recipe of how we cure individuals with advanced metastatic cancer and brain metastases.

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Chapter 10
Leptomeningeal Metastasis

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Abstract Neoplastic meningitis is a common complication in cancer with a median survival on the order of weeks to months. Although there is no current standard of care, management of neoplastic meningitis typically requires a multidisciplinary approach that may include surgery, radiation and chemotherapy. Results from retrospective analyses have suggested that intrathecal chemotherapy improves patient outcomes in neoplastic meningitis. Chemotherapeutic agents commonly administered into the cerebrospinal fluid include methotrexate, thiotepa, cytosine arabinoside and liposomal cytarabine. Systemically administered agents are an alternative to intrathecal chemotherapy, and targeted agents are showing promise. Larger randomized controlled studies are needed to determine the optimal treatment regimen for this devastating manifestation of cancer.

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1 Introduction

Neoplastic meningitis (NM, also referred to as leptomeningeal metastases and carcinomatous meningitis) is not an infrequent complication of cancer, occurring in up to 8% of patients with solid tumors and up to 15% in patients with leukemia and lymphoma [1, 2]. The incidence is rising likely because of longer survival times and improved diagnostic techniques. Median survival is typically on the order of weeks to several months, despite therapy [1]. Management of NM requires a multidisciplinary approach that may include radiation, chemotherapy or surgery; the objective is palliation of symptoms and prolongation of survival. In this chapter, we review the epidemiology, pathogenesis, clinical presentation, and treatment approaches of NM.

2 Epidemiology

Approximately 1–8% of patients with cancer develop NM; the most frequent solid tumors to metastasize to the leptomeninges are lung, breast and melanoma [3, 4]. Although melanoma has the highest rate of metastasis to the leptomeninges (20% rate), breast cancer accounts for the majority of cases because of its higher incidence [3–5]. Approximately 5–15% of patients with lymphoma and leukemia develop leptomeningeal metastases. However, given the difficulties in diagnosing NM, the reported incidence of NM may be an underestimate of the actual incidence [6].

3 Pathogenesis

The pathogenesis and molecular mechanisms that drive certain tumors to metastasize to the leptomeninges are poorly understood. Infiltration of the cerebrospinal fluid (CSF) by cancer cells can occur by a variety of mechanisms: (a) direct extension of tumor from vertebral, subdural, epidural, parenchymal metastases into the meninges; (b) hematogenous spread from the arachnoid vessels; (c) migration of tumor along cranial or peripheral nerves, or perivascular spaces; and (d) de novo tumors arising within the meninges (melanoma, lymphoma, sarcoma, etc.). Once within the CSF, cancer cells can disseminate and deposit anywhere within the neuraxis, causing symptoms. Localized deposits can obstruct CSF flow, leading to hydrocephalus [7]. Common sites of infiltration include the base of the brain, the Sylvian fissures and the cauda equina [8].

4 Clinical Presentation

In up to 75% of cases, NM occurs in the setting of progressive metastatic disease, but can occur as the initial presenting manifestation of cancer in 5–10% of patients, or during periods of remission [3, 5]. Common presenting symptoms include headaches,

change in mental status, confusion, seizures, weakness, neck or back pain and cranial nerve dysfunction [3, 4]. The specific signs and symptoms depend on the site of leptomeningeal involvement. Symptoms of increased intracranial pressure occur in the setting of CSF obstruction. Meningeal signs occur secondary to tumor invasion and inflammation of the leptomeninges. Cranial nerve involvement results in more focal symptoms. The most common symptom of cranial nerve dysfunction is diplopia, but optic neuropathy, trigeminal sensory or motor loss are also common [3, 4, 8]. Invasion of the spinal roots – the most common being the roots of the cauda equina – can result in radicular pain, paresis, and loss of bowel or bladder function. Multifocal disease within the neuraxis in a patient with a history of malignancy should always raise suspicion for NM.

5 Diagnosis

The diagnosis of NM can often be challenging and should always begin with a thorough clinical history and comprehensive neurologic examination, followed by neuro-imaging of the entire neuroaxis and CSF examination. Other conditions that can mimic NM should be ruled out, and these include infection, ischemia, post-radiation effects, metabolic disturbances, medication-related neurotoxicities, and hemorrhage.

5.1 Examination of the Cerebrospinal Fluid

If safe, examination of the CSF should be carried out in patients with suspected NM, both to confirm the diagnosis and to monitor response to treatment. CSF examination may reveal an elevated opening pressure, decreased glucose, elevated protein, and increased leukocytes. Positive cytology in the CSF is diagnostic of leptomeningeal carcinomatosis. However, the sensitivity of CSF cytology, particularly after one lumbar puncture, is low, and up to 41% of patients may be cytologically negative with one lumbar puncture [9]. A second lumbar puncture can increase sensitivity to 80%. To minimize false negative results, large CSF volumes (>10 mL), repeat lumbar punctures, sampling from an area of known leptomeningeal disease, and immediate processing of the CSF specimen is recommended [10].

Levels of glucose, protein and leukocytes vary depending on the location of the neuroaxis from which the CSF was drawn, even in the absence of CSF flow obstructions [11]. Cell count and chemistries are frequently normal, even in the setting of positive cytology. In a series of 63 patients with cytologically confirmed leptomeningeal metastases, 29% of lumbar punctures with positive cytology yielded normal cell counts [3]. In the presence of negative cytology and normal cell counts, elevated tumor markers within the CSF such as carcinoembryonic antigen (CEA), prostate specific antigen (PSA), CA-125 and CA15-3 can support the diagnosis of NM;

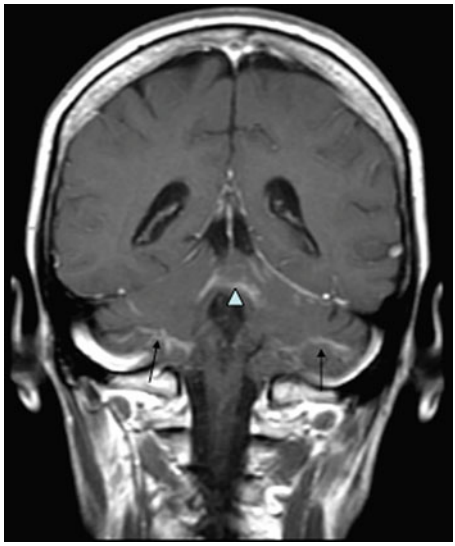

Fig. 10.1 T1-weighted post-contrast coronal MRI showing prominent leptomeningeal enhancement within the bilateral cerebellum (*arrows*) and vermis (*arrowhead*)

however, given the low sensitivity of this test, low levels of biochemical markers in the CSF does not rule out the diagnosis [12–16]. Other novel biochemical markers that have shown promise as diagnostic tests are angiogenesis-related markers including vascular endothelial growth factor (VEGF) and urokinase-type plasminogen activator (uPA) [17], but more evidence is needed to validate these results before they can be integrated into clinical practice.

A promising technique currently being investigated is flow cytometry immunophenotyping (FCI) of CSF samples. In a recent study of 78 patients with solid tumors and clinical symptoms suggestive of NM, cells expressing the epithelial cell antigen EpCAM and their DNA content were identified from CSF samples. The sensitivity and negative predictive value were higher for FCI when compared to cytology, and the negative predictive value and specificities were similar [18].

5.2 Imaging

Magnetic resonance imaging (MRI) with gadolinium is the imaging modality of choice in patients with symptoms suspicious for NM, as CT scans have a low sensitivity in this setting [19]. The entire neuroaxis should be examined (brain and spinal cord) given the potential for diffuse involvement of the CNS. T1-weighted images with and without gadolinium, and T2-weighted images should be obtained [20]. Leptomeningeal enhancement is visualized as a fine signal intense layer following the gyri and sulci on MRI [20]. This is often most obvious in the posterior fossa as enhancement within the folia of the cerebellar hemispheres and vermis on coronal T1-post contrast views (Fig. 10.1). Other etiologies for leptomeningeal enhancement

include inflammation, infection, metabolic disturbances, subarachnoid hemorrhage, increased CSF pressure, trauma, and local ischemia [20]. Thus, the imaging results must be considered in combination with the clinical presentation and other laboratory abnormalities, particularly CSF results. Other MRI findings also include cranial nerve enhancement, communicating hydrocephalus, or enhancing intradural extramedullary nodules frequently in the cauda equina. Optimally, an MRI should be obtained prior to a lumbar puncture, as the lumbar puncture itself can cause dural-arachnoidal enhancement [21]. Radio-isotope CSF-flow studies can be useful to evaluate the patency of CSF pathways. CSF flow abnormalities have been documented in up to 70% of patients with NM and are associated with worse prognosis and increased treatment-related neurotoxicities [7, 22, 23]. Restoration of flow using involved-field radiation can prolong survival and decrease the rate of treatment-related morbidities [22]. Uncorrected hydrocephalus is a contraindication to instillation of intrathecal chemotherapy.

6 Prognosis

Untreated, median survival is 4–6 weeks, with neurologic deterioration as the cause of death in most patients [4]. In some patients, survival can be extended to 4–6 months with treatment [24]. Poor prognostic factors include bulky leptomeningeal metastases, extensive systemic disease, obstruction of CSF, poor Karnofsky performance status, multiple fixed neurologic deficits, significant cranial nerve palsies and presence of encephalopathy [1, 5, 7, 22, 25]. In a multivariate analysis of 70 patients with leptomeningeal carcinomatosis, an elevated glucose (≥2.7 mmol/L), good performance status (Radiation Therapy Oncology Group score ≤2), infratentorial symptoms at onset, and intrathecal treatment were associated with improved overall survival and better response to treatment [24]. Positive CSF cytology did not influence survival in a retrospective series of 84 patients divided into 2 cohorts with or without positive CSF cytology matched for known prognostic variables [5].

7 Treatment

The goals of treatment in NM are to improve or stabilize neurologic symptoms and prolong survival. Treatment typically requires a multidisciplinary approach of surgery, radiation, and chemotherapy. Given the heterogeneity in this patient population and the paucity of randomized controlled trials, there is no standard treatment approach for NM. Unfortunately, current treatments have high rates of treatment-related toxicities and efficacy is limited. More than half of patients progress several weeks after initiation of treatment [24]; resistance to treatment is high, likely because this patient population is heavily pretreated, there are barriers to effective CNS drug delivery, and because of progressive systemic disease. Most systemically administered

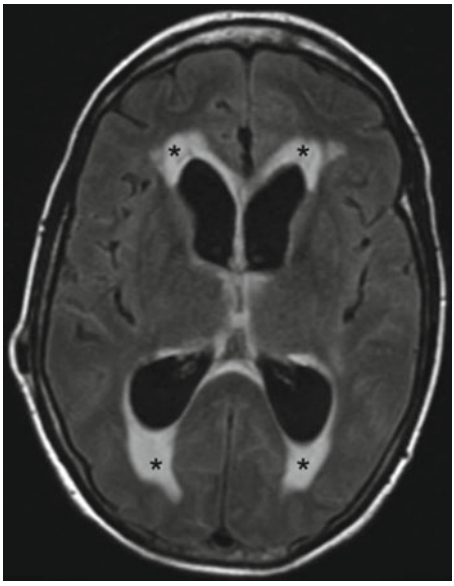

Fig. 10.2 FLAIR MRI sequence demonstrating dilated ventricles with abnormal hyperintense signal in the periventricular white matter (*asterix*), consistent with acute hydrocephalus with transependymal flow of CSF

chemotherapeutic agents have limited penetration into the CSF, with the exception of high-dose intravenous methotrexate, cytarabine and thiotepa. Nevertheless, certain patients do gain benefit, particularly in terms of quality of life, from an aggressive treatment approach. Early detection and treatment of NM can result in good palliation and local disease control [25, 26].

7.1 Surgery

Surgery plays a role in the treatment of NM in two ways: (1) placement of a ventricular reservoir for direct administration of therapy into the CSF and (2) relief of hydrocephalus using ventriculoperitoneal shunting. When compared to repeated lumbar punctures, drug delivery via a ventricular reservoir is more uniform and more comfortable for a patient [27]. Hydrocephalus is common in leptomeningeal carcinomatosis and is often present at diagnosis (Fig. 10.2). Hydrocephalus is important to recognize in patients with NM, not only because it increases risks of neurotoxicity from intrathecal chemotherapy, but also because patients can benefit palliatively from shunting for relief of headaches and other symptoms due to elevated intracranial pressure (ICP)[28]. Although there is theoretical concern about seeding the peritoneal cavity with cancer, in practice the risk appears to be very low [28, 29]. Most commonly, hydrocephalus and NM itself are managed by separate procedures. However, a shunt construct is available that allows for both CSF diversion and injection of intrathecal drug, and a recent study suggests that this approach may be safe and effective in patients with NM. Lin et al.. employed a CSF reservoir-on/off valve-ventriculoperitoneal shunt (RO-VPS) construct for the diversion of

CSF and injection of intrathecal agents in 24 patients with hydrocephalus and NM. Twenty patients experienced symptomatic relief and eighteen patients received intrathecal chemotherapy. Compared with demographically matched patients who only underwent CSF reservoir placement only, there was a survival benefit in the patients who underwent RO-VPS placement [29]. The safety profile was excellent, with only one shunt failure, no infections and no severe intrathecal chemotherapy-related side effects reported. This was a promising preliminary study and cerebrospinal diversion should be considered in patients with NM and hydrocephalus.

7.2 Radiation Therapy

Radiation therapy is generally administered to patients with bulky metastatic deposits, as intrathecal chemotherapy has limited penetration into tumor [30]. Furthermore, radiation may help correct CSF flow abnormalities that would otherwise hinder homogenous distribution of intrathecal chemotherapy [7]. Glantz et al. reported a survival benefit in patients with carcinomatous meningitis with CSF flow blockage corrected by focal radiotherapy compared to those that did not have their blockage corrected [22]. Intrathecal administration of chemotherapy in the setting of significant flow abnormalities, if uncorrected, can result in significant neurotoxicity, systemic toxicities, and treatment failures [22]. Universal addition of radiation therapy to all patients with leptomeningeal metastasis has not been demonstrated to procure a survival benefit. Craniospinal radiation is generally felt to be too toxic for palliative benefit in the solid tumor NM patient population.

7.3 Intrathecal Chemotherapy

Results from retrospective analyses have suggested that intra-CSF chemotherapy may improve patient outcomes in NM. Chemotherapeutic agents commonly administered into the CSF include methotrexate, thiotepa, cytosine arabinoside and liposomal cytarabine (Table 10.1). Methotrexate is a folate anti-metabolite with a half-life in the CSF of 4.5–8 h. Pharmacokinetic studies have demonstrated that intraventricular administration of methotrexate through an Ommaya results in a more reliable CSF distribution when compared to lumbar administration [27]. However, no studies to date have demonstrated a survival benefit of the intraventricular route compared to the lumbar approach.

Cytarabine (Ara-C) is a pyrimidine nucleoside analog with a half-life of 3.4 h [26] that has been used for the treatment of NM since the 1970s [35]. Liposomal cytarabine is a slow-release formation of ara-C that maintains cytotoxic concentrations in the CSF for more than 2 weeks. A study of intrathecal DepoCyt vs ara-C in 25 patients with lymphomatous neoplastic meningitis demonstrated superiority of DepoCyt over ara-C with a hazard ratio of 0.12 (0.02, 0.07) for progression-free

Table 10.1 Selected randomized trials for the treatment of leptomeningeal carcinomatosis

Reference	Treatment	Patients	Clinical response	Median survival
Boogerd et al. [31]	IT treatment vs no IT treatment (appropriate systemic therapy in all patients)	N = 35 with neoplastic meningitis (breast cancer)	IT treatment vs no treatment: neurologic improvement vs stabilization: 59% vs 67%	18 vs 30 weeks (P = 0.32)
Grossman et al. [25]	IT MTX vs IT thiotepa	N = 52 with neoplastic meningitis	MTX vs thiotepa: No significant neurologic improvement	15.9 wks vs 14.1 wks in all tumor types
Glantz et al. [26]	IT DepoCyt vs IT ara-C	N = 28 with lymphomatous meningitis	DepoCyte vs ara-C: 71% vs 15% (P = 0.006)	99.5 days vs 63 days (P > 0.05)
Glantz et al.[32]	IT DepoCyt vs IT MTX	N = 61 with neoplastic meningitis	DepoCyt vs MTX 26% vs 20% (P = 0.76)	105 vs 78 days (P = 0.15)
Hitchins et al. [33]	IT MTX + IT ara-C vs IT MTX	N = 44 with meningeal carcinomatosis	MTX vs MTX/Ara-C: 61% vs 45% (P > 0.10)	12 wks vs 7 wks (P = 0.084) in all tumor types
Shapiro et al.[34]	IT DepoCyt vs IT ara-C	N = 25 with lymphomatous meningitis	DepoCyt vs ara-C: 33% vs 17% CR (P = 0.3640)	HR 0.12; Median PFS 35 vs 50 days

Abbreviations: *ara-C* cytarabine, *CR* complete response, *HR* hazard ratio, *IT* intrathecal, *MTX* methotrexate, *PFS* progression-free survival, *wks* weeks

survival. The serious adverse event rate was high in both groups (86% in DepoCyt arm vs 77% in ara-C arm) [34]. In a randomized controlled trial of DepoCyt versus methotrexate in 61 patients with NM, response rates (26% vs 20%; $p=0.76$) and median overall survival (105 days vs 78 days; $p=0.15$) were similar between the two groups. However, the time to neurological progression was significantly increased in the DepoCyt group (58 versus 30 days; $p=0.007$). The severity and frequency of treatment-related toxicities were similar between the two groups [32]. Given the less frequent administration of DepoCyt, DepoCyt may be considered as the intrathecal agent of choice in the treatment of NM.

Thiotepa is a potent alkylating ethyleneimine with a half-life of 3–5 min in the CSF [36]. In a randomized cooperative group study, 59 patients with NM from non-leukemic malignancies received either intrathecal methotrexate or thiotepa. Radiation was administered for symptomatic or mass lesions. Systemic chemotherapy was administered concomitantly. No patients had significant neurologic improvement with therapy. Median survival was similar in the two groups (15.9 for the methotrexate arm vs 14.1 weeks in the thiotepa arm). Though the rates of severe toxicities were similar in the two groups, neurologic complications and mucositis were more common in the methotrexate arm [25].

The first randomized study of combination intrathecal chemotherapy, where 44 patients were randomized to intrathecal methotrexate versus intrathecal methotrexate plus Ara-C, did not reveal a significant increase in response rate with the addition of Ara-C [33]. Median survival was poor in both groups (12 weeks in methotrexate arm vs 7 weeks in combination arm, $p=0.084$) [33]. When the combination of intrathecal ara-C, methotrexate and thiotepa was administered to 22 patients, the toxicity profile was unacceptable. Myelosuppression occurred in 77% of patients. No patients had a complete response, and median survival was 10 weeks [37].

Other agents are currently being investigated for intrathecal administration. A pilot study demonstrated that intraventricular etoposide, a topoisomerase-II inhibitor administered daily for 5 days every 2–5 weeks was well-tolerated in patients with metastatic brain tumors that included leptomeningeal and parenchymal disease [38]. Topotecan can also be delivered intrathecally, and a phase II multicenter study of 62 patients showed that response rates and tolerability with twice weekly injections were similar to those of other intrathecal agents [39]. Intrathecal bevacizumab was investigated in a rabbit model of NM and was well-tolerated [40]. Human trials are being designed to study this further. Intrathecal administration of radiolabelled antibodies has also been studied. Though the reported toxicities have been minimal thus far, data demonstrating clinical responsiveness and efficacy is sparse thus far [41].

There have been several case reports that have demonstrated that intrathecal trastuzumab is safe and may have activity in patients with leptomeningeal carcinomatosis from HER2+ breast cancer. Intrathecal trastuzumab is currently being investigated as monotherapy or in combination with methotrexate or cytarabine [42].

Intrathecal therapy is not without its risks. The most common complication is a chemical aseptic meningitis which occurs in 20–40% of patients, characterized by symptoms of headaches, lethargy, fevers, nausea, vomiting, at times indistinguishable from acute bacterial meningitis. These symptoms usually resolve within 12–72 h, and respond to steroids, antipyretics and antiemetics [43]. Surgical complications

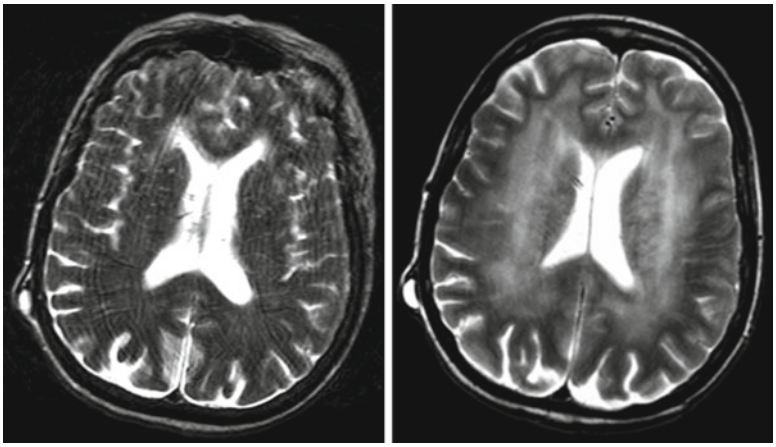

Fig. 10.3 T2-weighted images of a patient before (*left*) and after (*right*) administration of several months of intrathecal methotrexate. In the image on the right, there is interval development of abnormal T2 hyperintense signal involving the bilateral subcortical and periventricular white matter, in a pattern consistent with treatment-related leukoencephalopathy

following ventricular reservoir placement include infection, equipment malfunction and hemorrhage [44]. For patients that survive more than 4 months, there is a risk of a delayed leukoencephalopathy in patients (Fig. 10.3), particularly in those have received combined chemotherapy and radiation [45].

7.4 Systemic Chemotherapy

Given the risks of intrathecal chemotherapy and the lack of definitive evidence for its benefits, some clinicians prefer systemic therapy. Systemically-administered chemotherapies that achieve cytotoxic levels in the CSF include high-dose methotrexate, thiotepa and cytarabine. However, the timing and dosing of these chemotherapeutic agents may often be challenging, and may have significant toxicities when patients are on other chemotherapeutic regimens for their systemic disease or have received prior brain irradiation.

Prospective randomized studies directly comparing intrathecal therapy with systemic chemotherapies are lacking. In a small study of breast cancer patients with leptomeningeal metastases, 35 patients were randomized to intrathecal chemotherapy vs non-intrathecal treatment, with appropriate radiation and systemic therapy administered in both groups. Median time to progression was similar in the two groups (23 weeks vs 24 weeks). There was no evidence of improved survival in the intrathecal group (18.3 weeks in intrathecal group vs 30.3 weeks in non- intrathecal group; P=0.32). Neurologic toxicities were significantly higher in the intrathecal group (47% vs 6%; p=0.0072). However, the results of this study must be carefully considered as there was an unequal distribution of prognostic variables between the two groups [31].

The most common alternative to intrathecal chemotherapy is high-dose systemic methotrexate with leucovorin rescue; however, studies have yielded mixed results. A pharmacokinetic and toxicity study of 16 patients with NM from breast cancer, osteosarcoma or lung cancer, who received high-dose intravenous methotrexate demonstrated no objective antitumor response [46]. In contrast, in a study by Glantz et al.., 16 patients with solid tumor NM were treated with intravenous high-dose methotrexate and leucovorin rescue, and compared to a retrospective cohort of 15 patients treated with intrathecal methotrexate. Cytotoxic levels of methotrexate were maintained for longer with intravenous dosing, and toxicities were minimal. Median survival was also significantly longer in the group that received systemic methotrexate (13.8 vs 2.3 months, P = 0.003) [47]. Though these data need to be verified prospectively, it is not unreasonable to treat NM from cancers that are methotrexate-sensitive with systemic methotrexate [47].

Several case reports have suggested that capecitabine, an oral prodrug of 5-fluorouracil, may have activity in leptomeningeal carcinomatosis from breast cancer and esophageal carcinoma [48–50]. A case report of cisplatin and temozolomide administered in leptomeningeal carcinomatosis from an ethmoid-sinus intestinal type adenocarcinoma demonstrated a prolonged response and disease control [51].

Tyrosine kinase inhibitors (TKI) may have efficacy in leptomeningeal carcinomatosis arising from EGFR-positive non-small cell ling cancer. In a retrospective study of patients with an EGFR mutation or clinical factors predicting sensitivity to an EGFR inhibitor (never smoker, prior response to a TKI), 11 patients were treated with erlotinib or gefitinib followed by erlotinib. Nine patients demonstrated an improvement in ECOG performance status, with 6 patients surviving more than 6 months. Overall survival was not reached at the time of the publication [52]. Pulsatile administration of high-dose erlotinib (1,500 mg once weekly) was also demonstrated to be well-tolerated in a series of 9 patients with EGFR-mutant lung cancer diagnosed with leptomeningeal and/or parenchymal brain metastases while on conventional doses of erlotinib or other EGFR TKIs. A partial radiographic response was observed in 67% of patients, and stable disease in 11% of patients, with a median overall survival of 12 months [53]. Though these results need to be validated in larger prospective studies, TKIs in select patient populations should be considered.

Unfortunately, much of the evidence supporting the use of systemic therapies in NM is based on retrospective series and small phase II trials. Larger randomized controlled studies are needed to determine the optimal drugs, and route of administration in this setting.

7.5 Palliative Care

Aggressive supportive care should be incorporated into every treatment regimen. Patients with poor performance status (<60%) often are best treated with supportive care alone, as patients may not be able to tolerate other approaches. Symptom management with analgesics, antiemetics, anxiolytics, or antidepressants may be necessary. Corticosteroids play a role in the treatment of symptomatic vasogenic edema, and

can also alleviate radicular pain and headaches. Approximately 15% of patients with NM have seizures, thus adequate anticonvulsant therapy may be critical for maintaining a good quality of life in this patient population. Prophylactic anticonvulsants are usually not indicated. Radiation therapy may provide the best palliation when there are focal symptomatic metastatic deposits.

8 Conclusions

Neoplastic meningitis is a common complication in cancer, with a rising incidence, and poor prognosis. Given the relative paucity of randomized controlled studies in this area, there is no current standard of care. Management of NM typically requires a multidisciplinary approach that may include radiation, intrathecal chemotherapy or surgery; the goal is to alleviate or stabilize neurologic symptoms and prolong survival.

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Chapter 11
Quality of Life with CNS Metastasis

Lauren A. Chandler and Kathleen L. Fuchs

Abstract Quality of life (QOL) is a concept that involves an individual's general sense of well-being and satisfaction, and may include concerns regarding physical ability and comfort, mental health and sense of autonomy, and social situation (including relationship and economic factors). Given the generally poor prognosis and survival for persons with central nervous system (CNS) metastases, addressing concerns about and enhancing QOL for patients is vital, particularly as many patients report poor quality of life prior to engaging in treatment for the metastases. This chapter addresses important topics related to QOL for such patients, including common difficulties encountered in assessment of QOL, instruments used to evaluate QOL, predictors of better perceived quality of life (e.g., disease parameters, treatment, and psychological factors), and interventions to support QOL in individuals with CNS metastasis.

1 Introduction

Quality of life (QOL) is a construct that encompasses an individual's sense of well-being and satisfaction. As such, it is more than the sum of one's symptoms, prognosis, mood, and outlook. Despite the potential for wide variability in definition and assessment of QOL in illness and in health, there is general agreement on some

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of the factors that contribute to it including physical ability and comfort, mental health and sense of autonomy, and social situation (including relationship and economic factors). In essence, QOL is based on self-assessment of function and satisfaction/acceptance of it. At this time, the prognosis for individuals with central nervous system (CNS) metastases is poor and survival is often measured in months. Although the underlying cancer cannot be effectively eradicated, local therapies for brain metastases have advanced such that the majority of patients don't succumb to their brain metastases but rather to their primary cancer. As such, symptom management and enhancement of QOL are paramount. To that end, assessment to understand the issues important to patients and development of treatments to positively impact them are central to advanced cancer care. This chapter will review the assessment instruments used clinically and in research studies to evaluate QOL and the interventions that may contribute to maintaining or improving QOL.

2 Assessment Instruments for QOL

> Clearly, quality-of-life measurements are important in patients likely to be cured, but they may be more important in those likely to die. In fact, in the latter group, quality-of-life data may be the only information on which to base selection or comparison of alternate treatments. [1, p. 415].

Both subjective and objective measures have been used in studies assessing quality of life in patients with brain metastases (Table 11.1). Objective measures typically focus on general well-being and performance status of the patient, such as level of functioning and ability for self-care, and are typically scored by an observer rather than by the patient. One of the most commonly used measures in research and in clinical trials of patients with cancer is the Karnofsky Performance Status (KPS) [2]. The KPS is rated on a scale of 0 to 100 (in increments of 10), with 100 meaning "normal" and 0 meaning "death."[3] Other instruments that measure performance status and are typically used to assess patients with cancer include the Eastern Cooperative Oncology Group (ECOG) performance score [4], the Katz Activities of Daily Living Index, [5] and the Barthel Index of Activity of Daily Living [6]. The Functional Independence Measure (FIM) is frequently used in studies addressing rehabilitation after injury (stroke, brain injury, etc.) or subsequent to treatment of cancer [7].

In addition to assessing aspects of quality of life, performance status instruments are also often used for determining eligibility in research studies and clinical trials. The KPS in particular is used as one aspect of determining recursive partitioning analysis (RPA) class for brain metastases, which stratifies patients into 3 different prognostic categories [8]. Patients with a KPS score of less than 70 are typically classified as RPA Class III, which has the shortest median survival time (2.3 months). Patients with KPS scores of 70 or above are classified as RPA Class I or II (median survival of 7.1 and 4.2 months, respectively) depending on other disease factors (e.g., controlled vs. uncontrolled disease status, age, extracranial metastases, etc.).

Table 11.1 Common assessment instruments used to assess quality of life in patients with brain metastatses

Name of instrument	Assessment type	Subscales	Number of items	Scoring	Focus of the scale	Areas of QOL assessed	Brain tumor specific items
Karnofsky Performance Status (KPS) [2]	Observer rated	None	N/A	Graded on a scale of 0–100 (0 = death, 100 = normal)	ADL/IADL performance	Functional independence	No
Eastern Cooperative Oncology Group Performance Score (ECOG) [4]	Observer rated	None	N/A	Graded on a scale of 0–5 (0 = fully active, 5 = death)	ADL/IADL performance	Functional independence	No
Katz Activities of Daily Living Index [5]	Observer rated	None	6	Each item scored 0 or 1 Scores totaled with higher score indicating more independence	ADL performance	Functional independence	No
Barthel Index of Activity of Daily Living [6]	Observer rated	None	10	Each item scored 0, 1, or 2 (unable, needs help, independent) Scores totaled on a scale of 0–100 Higher total scores indicate more functional independence	Self care and basic ADL performance	Functional independence for increasingly difficult tasks (continence, climbing stairs, bathing, etc.)	No

(continued)

Table 11.1 (continued)

Name of instrument	Assessment type	Subscales	Number of items	Scoring	Focus of the scale	Areas of QOL assessed	Brain tumor specific items
Functional Independence Measure (FIM) [7]	Observer rated	None	18	Each item scored from 1 to 7 (with 7 being full independence)	Specific motor and cognitive skills (often used in rehabilitation research)	13 motor categories (self care, transfer ability, locomotion, etc.) 5 cognitive categories (communication, social cognition, etc.)	No
Spitzer Quality of Life Index (SQLI) [9]	Interview or self-report	None	5	Each item rated from 0 to 2 Verbal description of scores also provided Items sum for index score (0–10; higher score indicates better quality of life)	Common concerns for patients with cancer or chronic illness	Activity level ADLs Health Social support Outlook/emotional state	No
Edmonton Symptom Assessment Scale (ESAS) [11]	Self-report	None	9	Each item rated from 0 to 10 Higher scores denote worse functioning	Common symptoms in cancer patients	Physical symptoms Emotional/wellbeing symptoms	No

European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire (EORTC-QLQ) [12]	Self-report	C30 (general cancer) BN20 (brain cancer) Other cancer subscales available (lung, breast, prostate, liver, etc.)	30 items on the general scale 20 items on the brain cancer scale	Scores transformed to a linear scale (0–100)	Health related quality of life Symptoms reported over the last week	3 general symptom scales (fatigue, pain, etc.) 5 functional scales (physical, cognitive, emotional, social, role) Financial impact of disease Cancer specific symptoms	Yes
Functional Assessment of Cancer Therapy (FACT) [13]	Self-report	FACT-G (general) FACT-Br (brain cancer) Other cancer subscales available	27 items for core measure 23 items on brain tumors (−Br only)	Sum of item scores Higher scores indicate better quality of life	Health and psychosocial quality of life	Physical well-being Social/family functioning Emotional well-being Functional well-being Neurologic and cognitive deficits (−Br only)	Yes
M.D. Anderson Symptom Inventory (MDASI) [18]	Self-report	MDASI-BT (brain tumor module)	13 core symptom items 6 items on functional interference BT has 9 additional items	Each item rated on a 0–10 scale Higher scores indicate worse quality of life	Health related symptoms, interference with life Symptoms within the last 24 h	Affective symptoms Cognitive dysfunction Focal neurologic deficits Constitutional and gastrointestinal symptoms Interference with daily life	Yes

ADL activities of daily living, *IADL* instrumental activities of daily living

While quite useful for the purpose of describing a group of patients, performance status measures do not address other aspects of quality of life, such as mood, perception, and overall satisfaction. Unfortunately, at this time, there is no standard questionnaire that is used across research studies or clinical trials to assess quality of life in patients with brain metastases. There are, however, several scales developed for use in cancer patients, a few of which have specific sections to address issues that commonly affect persons with brain cancer. One such measure is the Spitzer Quality of Life Index (SQLI) [9]. It is frequently used to assess some of the more subjective aspects of quality of life for patients with cancer. It includes 5 domains rated on a scale from 0 to 2: general activity, daily living, health, support, and outlook. Each score is accompanied by a verbal description as well (e.g., "great" for 2, "up to par" for 1, and "lousy" for 0 when describing energy). A study by Scott et al. found that the SQLI was a better predictor of survival in patients with brain metastases than the KPS [10].

Similar quality of life instruments include the Edmonton Symptom Assessment Scale [11], European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire [12], the Functional Assessment of Cancer Therapy-General Scale (FACT-G) [13], as well as scales developed for specific research studies [14–17]. Other measures such as the M.D. Anderson Symptom Inventory (MDASI) [18] look specifically at health-related quality of life factors such as common physical, cognitive, and emotional difficulties, as well as degree of interference the symptoms cause in the patient's life. The EORTC, FACT, and MDASI have modules designed for use with patients who have brain cancer. These subscales assess specific issues that may apply to patients with brain cancer, including symptoms, effects of treatment, outlook, self-care, cognitive concerns, activities of daily living, and interference in daily life [12, 13, 18].

While these broader measures may better encapsulate a patient's overall experience and perception of their quality of life, there are some challenges associated with using such measures. One particular concern regarding the use of subjective self-report scales is length of the measure and associated demand on subjects, particularly due to the typically short length of survival for patients. Several studies have had difficulty measuring quality of life, particularly for poor prognosis brain cancer patients, due to difficulty with data collection [19–22]. Functional impairment may also impact a patient's ability to complete assessment measures. For example, in developing the FACT-BR the authors noted that only higher-functioning patients (KPS > 60) were able to complete the questionnaire [12].

Similarly, neurocognitive dysfunction may make it difficult for the patient to accurately complete such measures. A few studies have attempted to address this latter concern by using proxy raters, with mixed results. A study by Sneeuw and colleagues [23] did find a high correlation between patient and caregiver ratings, but noted a trend in which rating agreement decreased as the patient's level of physical and cognitive impairment increased. Other studies have found proxy ratings (by surgeons or caregivers) on quality of life scales to be poorly correlated with patient reports on those same scales [20, 24], suggesting that proxy ratings for quality of life measures should generally be avoided. As such, a major concern in assessing

quality of life is to ensure that the measure is both effective enough to capture the important factors that may impact overall quality of life, while also being as simplistic and brief as possible to ensure compliance [25].

3 Predictors of QOL

In studies of patients with primary brain tumors, disease severity and associated symptoms appeared to have a significant negative association with patient's reported health-related quality of life [15, 26–29]. Neurological symptoms, such as seizure frequency and motor deficits, appear to have a particularly notable impact on perceived health-related quality of life [30, 31]. However, other studies have found disease histology and severity are not significant predictors of quality of life [32, 33], perhaps due to the generally poor reported quality of life in patients with brain tumors (compared to the general population).

Other research suggests that tumor status (stable vs progressive), as opposed to the grade of the tumor, may be more important to perceived quality of life in patients with primary brain tumors [34]. For patients with brain metastases, severity of prognosis appears to correspond with perceived quality of life, with persons in RPA class II for brain metastases (better prognosis) having better QOL scores and less severe symptom ratings than those in RPA class III [35]. Similarly, better prognosis has also been found to be associated with improved quality of life subsequent to whole brain radiation therapy in patients with brain metastases [10, 36, 37].

Investigations of demographic predictors of quality of life in patients with brain tumors have found older age [32] and female sex [15, 32, 38, 39] to be predictive of lower overall quality of life scores. In assessing the quality of life for caregivers of patients with advanced cancer, it has been found that caregiver mental health and the physical well being of the patient are associated with better quality of life [40]. Similarly, for caregivers of patients with brain tumors, disease severity of the patient was predictive of poorer quality of life ratings for the caregiver [32].

4 QOL and Treatment of Metastases

> Quality of life can be seen as a balance between minimizing treatment risks and maximizing benefits, including physical and psychological effects. [17, p. 26]

Studies of patients with brain metastases have found that at baseline (prior to treatment for metastases) many patients report low activity and health-related quality of life scores despite reported independence for activities of daily living [35]. DiBiase et al. point out that in patients with brain metastases, median survival time is often less than 4 months and as such, less invasive treatments that maximize quality of life are essential [41]. To that end, they evaluated QOL in

patients undergoing stereotactic radiosurgery for brain metastases and found that in patients without tumor progression (intra- or extracranial) QOL scores (using the SQLI) remained unchanged or improved at follow up. Those with tumor progression had lower QOL scores.

Although patients report more side effects with whole brain radiation than with radiosurgery [14], individuals with brain metastases treated with a palliative course of whole brain radiation did not show a significant difference from baseline in quality of life 1 and 2 months after treatment. However, there was a trend toward worsening general and brain-specific QOL scores on the FACT-BR [20].

Similar to the report of reduced QOL in patients prior to treatment for brain metastases, the majority have impairments in cognitive functioning [42, 43]. Although the literature is inconsistent due to methodological factors, there appears to be a relationship between systemic chemotherapy and reduced performance on neuropsychological tests even when factors such as age, baseline IQ, time since treatment, and mood disturbance have been controlled for [44]. Imaging studies 1 year after treatment have found reduced white and gray matter volumes in individuals treated with chemotherapy as compared to controls, and these changes correlated with worse performance on cognitive tests [45]. Given that many individuals with brain metastases will have already received some form of chemotherapy for their primary cancer, it is likely that most, but perhaps not all, will enter into the metastatic phase with some degree of "chemo-brain" which could compromise quality of life. As reviewed by Kayl et al., other agents may also negatively affect cognitive functioning including steroids and antiepileptic medications [46]. Kayl et al. also highlight the potential impact of anemia, fatigue, depression, and anxiety. A decline in neurocognitive functioning has been shown to be associated with significant a decline in self-reported quality of life in patients with primary brain tumors [30] and brain metastases [43, 47], with some authors suggesting that efforts to prevent worsening neurocognitive functioning could help patients to maintain better quality of life.

In a pilot study to assess neurocognitive functioning in patients with 1–3 metastatic lesions treated with stereotactic radiosurgery, 67% showed some degree of impairment at baseline, typically in the domains of executive functioning, motor dexterity, and new learning/recall. While some degree of cognitive decline was noted in all patients 1 month after treatment, among those (few) surviving 200 days after enrollment, most displayed stable or improved cognitive functioning [48]. A trial comparing the cognitive effects of stereotactic radiosurgery vs. stereotactic radiosurgery plus whole brain radiation treatment in patients with newly diagnosed brain metastases was stopped early as patients receiving the combined treatment were significantly more likely to show a decline in learning and memory functioning. However, a higher percentage of patients in the combination treatment arm were recurrence-free at 1 year [49]. In a retrospective study, Sneed et al. found that the risk of dementia from whole brain radiation in long-term survivors is such that it can be deferred as a salvage treatment in favor of using stereotactic radiosurgery for initial treatment of brain metastases [50].

Meyers et al. have suggested that when assessing the clinical benefit of a new treatment for CNS metastases, a survival endpoint may be of limited value as

patients frequently die as a result of systemic disease progression [51]. As such, they used measures of neurologic and cognitive function to assess whether a putative radiation sensitizer (motexafin gadolinium) improved outcome in a randomized phase II study. Baseline cognitive test performance was highly correlated with the volume of the target lesions but not with the number of brain metastases, suggesting that cognitive function is more affected by tumor burden than number of lesions. Additionally, baseline cognitive functioning was predictive of overall survival – especially measures of memory, motor speed and dexterity, executive functioning, and an index of global neurocognitive impairment. In a related lead-in study, Mehta et al. found scores on measures of executive functioning and fine motor coordination were associated with survival [42].

5 Outlook and QOL

As might be predicted, individual expectations regarding prognosis and impact of the illness on one's life appear to also play a role in determining quality of life. A study by Wan et al. of patients with advanced cancer who were functional with regard to activities of daily living (referred to as ADLs) found that the most significant predictor of health-related quality of life was performance status, followed closely by overall expectation rating [52]. That is, those patients who had better ratings of current activity level and a better than expected experience were more likely to report better physical well-being. Additionally, the size of the gap between the patient's expectations and actual experience was found to be a significant predictor for all aspects of quality of life measured. The study authors suggest that those patients with the greatest discrepancies between actual experience and expectations experience poorer quality of life and as such may be most in need of interventions to improve it.

It is a popular and strongly held belief that mental attitude or having a "fighting spirit" can impact cancer survival [53, 54]. It follows then that intervention aimed at facilitating that attitude could potentially prolong life. While some studies appear to support this notion [55, 56], a closer examination of these and subsequent studies has pointed out methodological limitations that temper claims regarding the ability of psychotherapy to confer a survival benefit [57, 58]. In fact, Coyne et al. discuss the mechanisms by which psychotherapy could affect survival and find no evidence to support these [57]. In particular they point out that psychosocial interventions could promote adherence to treatment or other health-related behavior. As such, the effect of psychotherapy is confounded by the effect of medical treatment. Another proposed mechanism for psychotherapy is the indirect effect on neuroendocrine and immune function. However, Coyne et al. point out that studies have not found a relationship between psychotherapy, changes in immune functioning, and survival in persons with cancer [57]. In their review, Paton and Perez found that there is no conclusive evidence that group psychosocial interventions prolong survival in patients with metastatic cancer [58]. They allow that there are some limitations in

the literature as most research has been done on women with metastatic breast cancer and that the effects of individual psychotherapy have not been thoroughly evaluated through a randomized clinical trial. Their review suggests that a patient's baseline scores on global health-related quality of life measures or their physical functioning scores are better predictors of survival than attitude or participation in psychotherapy. In essence, they suggest a patient's health and quality of life at the start of the metastatic phase are better predictors of survival than any changes in psychological coping style. However, it is important to note that the authors do not argue that psychotherapy is without value. In fact, Paton and Perez conclude their paper by pointing out that psychosocial programs aimed at improving quality of life should remain an important component of care [58]. Thus it seems the debate over psychotherapy's ability to confer a survival benefit may be irrelevant if the goal of such treatment is to promote quality of life.

6 Depression and QOL

Compared to patients with chronic illnesses (diabetes, renal disease, etc.), cancer patients tend to report similar mental health concerns [59]. However, depression with brain metastasis may be shaped by the illness and its sequelae. For example, in a study comparing patients with motor neuron disease and metastatic cancer (both groups presumed incurable), scores on a depression inventory were similar, but the end stage cancer patients' scores reflected a greater degree of anhedonia versus higher scores for hopelessness and suicidal ideation in those with motor neuron disease. This latter group also tended to be younger with more physical disability [60]. Psychological distress has been found to be negatively correlated with health-related quality of life in various types of cancer [59, 61, 62]. Similarly, depression and anxiety have been found to be strongly correlated with poorer quality of life in patients with brain tumors [32, 38, 63, 64]. Studies of non-metastatic cancers have also found particular personality variables (hostility, sense of coherence) to be predictors of worse health-related quality of life [62, 65].

Depression has been linked to a diminished quality of life in cancer patients [66] and symptoms of depression may be magnified in individuals with metastatic disease as they move closer to death [67]. While cognitive therapy [68] aimed at identifying and modifying beliefs and self-statements coupled with the teaching and practice of stress-reducing behaviors has been shown to be effective in improving depressive symptoms in cancer patients when delivered in a group format [69, 70], few studies have specifically examined use of that therapeutic modality in patients with brain metastases. The difficulties conducting this type of study in individuals with a short life expectancy are clear, but short-term, individual cognitive-behavioral therapy has been shown to be effective in women with metastatic breast cancer in improving depressed mood, anhedonia, fatigue, and quality of life [71]. In that study, patients participated in 8 individual weekly session followed by 3 "booster" sessions with a goal of developing "an optimistic but realistic" attitude. The sessions

involved identifying negative thoughts such as fears of dying alone and in pain or of being a burden to family members and modifying these to more positive yet realistic thoughts such as confidence that physicians will be able to control pain and that there is still quality time to be had with family. An important point from that study is that it was possible, within a relatively brief period of time, to alleviate depression and thus improve quality of life. While antidepressant medications are frequently used to address mood disturbance, there is also some evidence that stimulant medication may confer a benefit to mood and cognition in individuals with cancer [72].

7 Interventions to Support QOL

Just as there are far fewer studies regarding the effects of treatment on QOL in patients with CNS metastases than in primary cancers, there are also very few studies assessing the impact of symptomatic interventions on QOL in this population. While it is tempting to generalize the findings from primary cancers, it is important to keep in mind the different prognosis and perhaps even goal of treatment for CNS patients.

Studies of patients with primary brain tumors have found that fatigue, pain, headache, and sleep disturbance are some of the most common health-related symptoms reported [33, 73, 74], with fatigue possibly being a more significant problem for patients with higher-grade tumors [33, 75, 76]. Similarly, fatigue, headaches, weakness, balance problems and reduced appetite are commonly reported in patients with brain metastases[17, 35, 77, 78].

Exercise has been found to be a particularly helpful intervention in addressing quality of life issues in patients with various types of cancer. For example, exercise was shown to slow decline in physical well being, as well as reduce fatigue scores on QOL measures in women with advanced breast cancer [79]. Similarly, other studies have shown that patients with various forms of advanced or metastatic cancer who participated in exercise therapy evidenced increased physical functioning, improved quality of life scores, and decreased fatigue [80–82]. One study even found an improvement in immune functioning after exercise training in breast cancer survivors [83].

Other studies have looked at the benefit of inpatient rehabilitation for patients with primary and metastatic brain cancer. Tang et al. found that patients with both primary and metastatic tumors made significant functional gains with inpatient rehabilitation treatment, and that those who made the most functional recovery tended to survive longer [84]. In fact, patients with brain metastases were found to have greater functional improvement than many of the patients with primary tumors. Other studies have found similar gains in functioning (including ability to return home post discharge) in patients with both primary and metastatic brain tumors [85, 86], which tended to be comparable to gains made by patients undergoing rehabilitation for stroke and traumatic brain injury [87–89]. Those patients with recurrent tumors tended to make smaller gains, regardless of tumor type [85].

Although not specific to CNS metastases, Stephenson et al. found that caregivers can be trained to deliver foot reflexology to their partners with metastatic cancer and

that this resulted in a reduction in pain and anxiety in contrast to minimal changes in a control group in which the caregiver read to the patient [90]. Along these lines, it seems feasible that other relaxation techniques such as yoga, directed stretching, and meditation could be of benefit in reducing stress and improving QOL. Given that many patients may have difficulties with attention and concentration, it seems that this type of intervention might be best delivered using a live instructor or audio/video directions.

Studies of patients with metastatic breast cancer have shown that interventions, including group psychotherapy, help to improve psychosocial outcomes by reducing anxiety and improving mood scores [19, 91–95]. However, no significant effects were found for supportive group therapy regarding global quality of life scores in two studies of metastatic breast cancer patients, in part due to significant decline in quality of life scores across time in most patients and small sample sizes [19, 96].

8 QOL and Survival Prediction

Clear information regarding prognosis/survival is rated as very important by individuals with advanced cancer and their caregivers especially as they struggle with decisions regarding treatment [97, 98]. Physicians often use the patient's Karnofsky Performance Status (KPS) as a basis for this type of estimate. While prediction of imminent death is fairly reliable when the score is low (i.e., <50), survival prediction is more variable at higher scores [99] and is often overestimated [100]. In their analyses, Hwang et al. showed that KPS is the most significant predictor of survival overall, but in patients with KPS ≥ 50, QOL indices of physical well-being and physical symptom distress were also significant predictors of survival as those with impaired quality of life or symptoms of distress had markedly decreased survival [101]. The authors posit that failure to take this type of information into account may explain why physicians who rely only on the KPS may overestimate survival.

Further, there may be a role for assessment of cognitive variables in predicting survival in metastatic cancer. As noted by Meyers et al., "The relation between cognitive functioning and survival, observed in these different studies, suggests that cognitive tests are a relatively sensitive measure of the functioning of the brain and that a combination of tumor prognostic variables and brain function assessments seem to predict survival better than tumor variables alone in patients with brain metastases" [51]. In a pilot study, Herman et al. demonstrated that a brief battery of standardized neurocognitive tests was tolerable to patients with brain metastases and could measure a sufficient breadth of abilities [102]. Also, even in the presence of a high KPS or Barthel index score, patients in that study exhibited deficiencies in memory, motor speed, and dexterity. Thus it appears that the results of cognitive assessment can contribute unique information that could factor into an understanding of a patient's overall quality of life and help guide physicians, patients, and their caregivers in making treatment and care decisions.

9 Summary and Observations

While the manner in which QOL is assessed may vary across studies and clinical practices, there is agreement in the literature of the value of supporting QOL in patients with CNS metastases and factoring in impact on QOL when making treatment decisions. It is important for work in this area to continue as new treatments emerge. Just as biochemical agents are developed to disrupt tumor growth based on the genetic characteristics of the tumor cells, certain treatments may be more or less indicated for certain individuals based on their personal characteristics, preferences, and ability to tolerate side effects.

One aspect of QOL not addressed in this chapter but that has been evident in our clinical work is the sense of failure some individuals experience when they are told that they have metastatic cancer. For many who readily adopted the "battle" mindset of fighting cancer, this news can be ego-shattering as they may have felt that up to this point, they had "won." Some respond with anger at themselves ("I was not strong enough"), their physicians ("My initial treatment was not aggressive enough"), or even loved ones ("My spouse was never really there for me"). Some who never fully got past the "Why me?" question with their initial diagnosis may revisit this and experience feelings of guilt regarding past lifestyle choices or behaviors that they may believe to be the roots of their cancer. Clearly these thoughts and feelings can impact mood and potentially lead an individual to "give up" and perhaps not consider treatments that could extend the quantity and quality of life. This can create distress within families who have also adopted an "attitude is everything" mindset. Thus it is important for health care professionals and family members to understand this grief phenomenon and sense of loss of control in order to support the patient in working through it. This is especially difficult for family members who are facing their own grief and who may be somewhat burnt out from their previous caregiving responsibilities. The importance of a cancer care multidisciplinary team to address these issues cannot be overstated.

We started this chapter suggesting that QOL is an individually-defined construct that clinicians and researchers seek to better understand through instruments to assess aspects of patient experience and to document change with intervention or disease progression. Given the variety of instruments used to assess QOL, it is clear that there is no one all-encompassing measure that can fully capture an individual's experience. As such it may be easier to understand QOL in smaller components that can be addressed by different members of a multi-disciplinary treatment team. Some aspects of QOL such as physical mobility can be readily observed and measured, but others such as anxiety, hopefulness, or contentment may be mercurial and dependent partly on long-standing traits or individual social circumstances. In addressing QOL it is clear there is a role not only for the treating physician in providing clear information regarding treatment options and prognosis, but also for the oncology nurse to assist in patient (and family) education and support. As noted in this chapter, there is evidence that rehabilitation interventions can enhance QOL as can supportive

psychotherapy and psychosocial interventions offered by psychologists, clinical social workers, and pastoral counselors.

Just as their is no one single facet of QOL that is equally important to all patients, there is no one clear technique or treatment that will guarantee enhanced QOL as a patient deals with CNS metastasis. Patients are different, their cancers are different, and their life circumstances are varied. Despite this, it seems that the ability to maintain a sense of self, connection with others, and a sense of purpose is vital. To date there is no pharmacological agent that can confer those qualities, but many patients will find them through friends and family, fellow patients, and compassionate medical care providers. While we attempt to understand quality of life in CNS metastasis through our questionnaires and studies, we should remain humbled by the struggles of our patients and remember that they have something to teach us about the human experience.

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