Central Nervous System Metastases

Diagnosis and Treatment

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To Priyanka, Surya, and Samira – you make every day better.

To my parents – thank you for your example.

To my patients – thank you for the daily inspiration.

Rohan Ramakrishna

My heartfelt gratitude goes to my family for their support and of course to our patients who continually demonstrate how to approach adversity with kindness, dignity, and determination.

Rajiv S. Magge

To my beautiful daughter, Hannah, who has filled our hearts with endless joy.

Ali A. Baaj

To my parents, Samuel Emerson and Kristine Sandberg Knisely, and to my wife, Mary Jean Hu. You always supported me as I engaged myself with problems that I found particularly challenging, and for that, I am grateful beyond where language can take me.

Jonathan P.S. Knisely

Foreword

The editors and authors are to be congratulated for organizing this comprehensive, multidisciplinary text reviewing the contemporary management of brain and spinal metastasis. They draw upon the breadth of experience from an international group of authors while still integrating epidemiology and basic biology with diagnosis, evaluation, and treatment. All aspects of metastatic disease including local control, leptomeningeal disease, paraneoplastic syndromes, and neurocognitive implications are reviewed. Beyond standard care, alternative and complimentary therapies are also reviewed in relation to their impact on quality-of-life issues, neurocognition, and pain control.

Advances in our biological understanding of radiation, new technologies, and combinational therapies have transformed our approach toward central nervous system metastasis. Recent data supporting the synergistic effects of radiation therapy and immunotherapy has modified the treatment paradigms used. This text provides a framework for understanding the biology of radiation therapy as it relates to the multiple technological choices available to the treating physician. The authors also provide a detailed perspective of the specific advantages and disadvantages of the multiple radiation therapies available. New technologies are reviewed from the perspective of maximizing efficacy and minimizing toxicity, independently and as combinatorial therapy. The newest advances in radiation therapy which maximize the tumoricidal effect while minimizing neurocognitive decline are clearly reviewed in concise prose.

Management of metastatic disease requires the integrated efforts of surgeons, oncologists, neuro-oncologists, neurologists, radiation oncologists, pathologists, precision medicine, imaging specialists, neuropsychologists, neuro-psycho-pharmacologists, and social workers. A complex disease management team applying the newest medical, surgical, and technological tools to alleviate this devastating oncologic process is required to work in conjunction with cognitive experts in order to maximize the quality of life and maintain family stability. This book does an excellent job of tying all of these facets together in order to give the reader a clear and concise treatment paradigm. The complexity in managing metastatic disease is not only biological but also psychosocial. The authors emphasize the importance of integrating all aspects of cancer care for our patients.

I strongly recommend *Central Nervous System Metastases: Diagnosis and Treatment* to all practitioners in this arena. Being the first text of its kind, it is really a "must have" for the serious student and caregiver. Students, nurses, physicians, psychologists, physicians, psychologists, social workers, and psychiatrists will all find value in digesting components of this book. Management of metastatic tumors requires both scientific and emotional tools emphasized by the authors.

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Preface

We live in an interesting time as we treat patients with central nervous system metastases. Though systemic therapies have become more successful and diverse, the number of patients with central nervous system metastases is growing. Furthermore, patients are living longer with CNS metastatic disease. As such, it is imperative in the modern era that patients with CNS metastases are treated in a holistic, multidisciplinary fashion. Our goals as treating physicians can no longer be singularly focused on the local control of a CNS lesion. Rather, we must consider not only oncologic control but also quality of life, the interaction of our treatments with systemic therapies, pain control, and much more.

With that in mind, we have endeavored to produce a multi-specialty book on the diagnosis, evaluation, and treatment of CNS metastases of the brain and spine. Our authors span the globe and are noted experts in their fields. We have chosen authors who bring unique perspectives to the field of CNS metastases and hope that you find their contributions both educational and useful.

As you will see, we have designed this book to cover what we consider essential contemporary topics in CNS metastases care. Truly, a book like this would have not have been particularly interesting even 10 years ago given the subsequent advancements in systemic and targeted therapy, radiation therapy, and surgical therapy. In general, we have begun each section with chapters covering the fundamental biology of disease so that subsequent chapters on imaging, diagnosis, and treatment can be properly contextualized.

This book represents a herculean effort made possible by many individuals. I would like to thank all of our authors who have selflessly contributed their time and knowledge. Their expertise and perspective have proven invaluable. A huge thanks is also due to Philip Stieg at Weill Cornell Medicine who encouraged me to pursue this project and the development of a brain metastases program with gusto. Other mentors have been similarly influential including Richard Ellenbogen (University of Washington), Raymond Sawaya (MD Anderson), and Frederick Lang (MD Anderson), and I owe them all a debt of gratitude as well. In addition, I would like to thank Weill Cornell Medicine and New York Presbyterian Hospital – these institutions make coming to work a pleasure each day. I would like to also thank Springer, Richard Hruska, and Connie Walsh who have provided invaluable editorial assistance and author support. Finally, I would like to thank my coeditors Rajiv S. Magge, MD; Ali A. Baaj, MD; and Jonathan P.S. Knisely, MD, who have been instrumental partners in the completion of this book.

Please contact me directly (ror9068@med.cornell.edu) should you have feedback or constructive criticism on how to improve this text. We hope this text helps you take care of your patients with CNS metastases.

New York, NY, USA Rohan Ramakrishna, MD

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Part VII Pain

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Part I

Fundamentals

1 Epidemiology and Socioeconomic Impact of CNS Metastases

Jessica A. Wilcox and Lisa M. DeAngelis

Introduction

Metastatic brain tumors are the most common intracranial neoplasm in adults and affect up to one-third of adults with cancer [1]. Most patients present with neurologic symptoms such as headache, focal weakness or numbness, cognitive impairment, or seizures. The diagnosis of central nervous system (CNS) metastases often requires focal therapy, including neurosurgical or radiotherapeutic options, as most conventional chemotherapies have limited ability to penetrate the blood-brain barrier. However, pharmacologic treatment of brain metastases has grown in the last two decades due to the advent of immunotherapies and targeted therapies based on molecular and genomic tumor profiling. Despite such advances, brain metastases remain a significant cause of morbidity and mortality with a poor prognosis for many. Furthermore, the presence of brain metastases has historically been an exclusion criterion for many clinical trials, leaving an unmet need for these patients.

The most common cancers to spread to the CNS include lung, breast, melanoma, renal, and colorectal malignancies. The incidence of metastatic brain tumors from most primaries is on the rise. This epidemiologic trend is thought to be secondary to many factors, including longer patient survival, improvements in screening programs, and increasingly sensitive imaging techniques allowing for earlier detection.

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Epidemiologic Studies

Epidemiologic studies are important for understanding the burden of disease, impact of advances in treatment, and appropriate allocation of resources. The three major means of analyzing incidence of brain metastases are via population, hospital, and autopsy series.

Autopsy Series

Autopsy studies often cite a greater incidence than population studies, with intracranial metastasis rates as high as one-third of all patients with cancer [2, 3]. In 1978, Posner et al. found an intracranial metastasis rate of 24% of 2375 patients who died of cancer [2]. Fifteen percent of patients had parenchymal metastases, 8% had leptomeningeal metastases, and 20% had dural disease. Takakura et al. quoted a similar incidence of 26% with intracranial metastases in 3359 autopsied patients in 1982 [3]. A much larger 1983 autopsy series including 10,916 patients found an intraparenchymal metastasis incidence of 8.7% [4].

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Autopsy studies, which are the most accurate assessment of brain metastasis frequency in terminal patients, do have some limitations. The incidence of CNS disease for end-stage cancer patients will always be higher than that of newly diagnosed patients. In addition, due to the dramatic reduction in autopsy rates in the last 30 years, the existing autopsy series are outdated and do not reflect the current landscape of oncologic care and outcomes. For this reason, most recent epidemiologic studies are either population based or hospital based.

Population and Hospital Series

National population-based registries have long been used to gauge epidemiologic trends. Primary brain tumors are often recorded in large-scale cancer data sets such as the Surveillance Epidemiology and End Results (SEER) database; however, it was only recently that data regarding brain metastases were included. Hospital-based studies, conversely, are reliant on autopsy results, imaging data, pathology, and medical records. These results may be biased in the selection for patients from large tertiary referral centers, which are not commonly reflective of the population at large. Regardless of the methodology, examining series over time demonstrate the rising incidence of CNS metastases in most studies. For example, in 1970 a study from Iceland estimated an annual incidence of 2.8 brain metastases per 100,000 persons compared to an incidence of 7.8 primary brain tumors per 100,000 [5]. A 10-year Finnish study reviewing hospital and death records from 1975 to 1985 found brain metastases and primary brain tumors to occur in 3.4 and 12.3 per 100,000, respectively [6]. Within the United States, records from the Mayo Clinic over a 33-year time period revealed slightly more comparable incidences of 11.1 and 12.5 per 100,000 for metastatic and primary brain tumors, respectively, in 1972 [7]. These older studies have several limitations precluding a true estimation of brain metastasis incidence. Asymptomatic brain metastases may have escaped clinical detection as screening of the CNS was impossible prior to widespread availability of neuroimaging; computed tomography (CT) scans became available in 1974 and magnetic resonance imaging (MRI) in the 1990s. Additionally, neurologic symptoms in older patients or those with end-stage metastatic disease might not have been investigated or recognized.

More recent studies give a more accurate picture of current epidemiologic trends of brain metastases (Table 1.1). Barnholtz-Sloan et al. calculated the incidence proportions (IPs) for the most common primary malignancies to spread to the brain by analyzing the Metropolitan Detroit Cancer Surveillance System (MDCSS) between the years 1973 and 2001 [8]. The total IP of brain metastases for the five most common primary sites combined—lung, breast, melanoma, renal, colorectal—was 9.6%. The IP for each specific malignancy was 19.9% for lung, 6.9% for melanoma, 5.1% for breast, 6.5% for renal, and 1.8% for colorectal cases. Risk was further stratified based on ethnicity, age, gender, and SEER stage. The malignancy with the highest IP of CNS dissemination was metastatic melanoma with an IP of 36.8% across all age groups. African Americans had higher rates of brain metastases from lung, melanoma, and breast cancers as compared to white patients, and significantly lower rates of brain metastases from renal cancer. With the exception of lung cancer, men had a higher IP of brain metastases than women. Age at initial diagnosis was also influential. For example, those diagnosed with lung cancer between ages 60 and 69 years exhibited the highest absolute frequency of brain metastases; however, the peak IP for brain metastases was among those diagnosed between 40 and 49 years of age. Melanoma, renal, and colorectal cases all shared a common IP peak for brain metastasis when the primary site was diagnosed between 50 and 59 years of age, whereas the IP peak for brain metastasis from breast cancer occurred when the primary tumor was diagnosed between ages 20 and 39. Although younger breast cancer patients had a higher risk for brain metastases with an IP of 10%, the absolute frequency of brain dissemination was relatively lower in this population compared to older age groups. The authors surmised

Table 1.1 Incidence proportions of brain metastases from different primary cancers in recent epidemiologic studies

	Lung			NSCLC			SCLC			Breast			Melanoma			Renal			Colorectal		
Reference	No. with BM	Total *N*	IP%	No. with BM	Total *N*	IP%	No. with BM	Total *N*	IP%	No. with BM	Total *N*	IP%	No. with BM	Total *N*	IP%	No. with BM	Total *N*	IP%	No. with BM	Total *N*	IP%
Schouten et al.[a] [9]; 1986–1995; Maastricht Cancer Registry, Netherlands; *n* = 2724	156	938	16.3	96	742	12.6	60	196	29.7	42	802	5.0	12	150	7.4	12	114	9.8	10	720	1.2
Barnholtz-Sloan et al. [8]; 1973–2001; Metropolitan Detroit Cancer Surveillance System, USA; *n* = 169,187	11,763	59,038	19.9							2635	51,898	5.1	566	8229	6.9	467	7205	6.5	779	42,817	1.8
Duell et al. [13]; 2003–2010; Asklepios Lung Hospital, Germany; *n* = 678				118	678	17.4[c]															
Goncalves et al. [11]; 1973–2011; Metropolitan Detroit SEER Registry, USA; *n* = 34,681[b]				2712	30,466	8.9	760	4235	17.9												

(continued)

Table 1.1 (continued)

Reference	Lung			NSCLC			SCLC			Breast			Melanoma			Renal			Colorectal		
	No. with BM	Total *N*	IP%	No. with BM	Total *N*	IP%	No. with BM	Total *N*	IP%	No. with BM	Total *N*	IP%	No. with BM	Total *N*	IP%	No. with BM	Total *N*	IP%	No. with BM	Total *N*	IP%
Cagney et al. [10]; 2010–2013; National SEER Dataset, USA; *n* = 1,302,166	21,804	185,199	11.8	18,241	162,689 75,043	11.2 24.3[c]	3563	22,510 15,186	15.8 23.5[c]	973	239,102 12,844	0.4 7.6[c]	508	77,876 1804	0.7 28.2[c]	809	54,495 7463	1.5 10.8[c]	365	134,813 26,923	0.3 1.4[c]
Zhang et al. [55]; 2010–2015; National SEER Dataset, USA; *n* = 121,255													1,547	116,119 4369	1.3 35.4[c]						

Abbreviations: *BM* brain metastasis, *IP%* incidence proportion, *NSCLC* non-small-cell lung cancer, *SCLC* small-cell lung cancer, *SEER* Surveillance Epidemiology and End Results

[a]IP% listed is 5-year cumulative incidences published by Schouten et al.

[b]*n* limited to nonmetastatic (local and regional) disease at diagnosis

[c]IP% of BM at diagnosis of de novo metastatic disease

that this peak IP in younger breast cancer patients may reflect the increasing trend for longer overall survival, giving patients more time to develop brain metastases after initial diagnosis; it may also reflect the biology of breast cancer in the young adult.

A smaller, population-based Netherlands study also reported on IP of brain metastases between the years 1986 and 1995 using the Maastricht Cancer Registry [9]. A total of 2724 patients were included in this registry, of which 232 (8.5%) were ultimately diagnosed with brain metastases. At 5 years, the cumulative incidences for brain metastases were 16.3% for lung, 5.0% for breast, 7.4% for melanoma, 9.8% for renal, and 1.2% for colorectal carcinomas. Among the lung cancers, the 5-year cumulative incidence was greater for small-cell carcinoma (29.7%) than non-small-cell carcinoma (12.6%). Unlike other studies suggesting an increasing trend in brain metastases for breast and lung carcinomas, this study found a non-statistically significant decrease between the early and later years, albeit subject numbers were lower than other larger-scale population studies.

The SEER program, sponsored by the National Cancer Institute, publishes cancer incidence and survival data from various population-based registries in the United States. In 2010, the SEER database began to include data on the presence or absence of brain metastases at primary cancer diagnosis. With this new information, Cagney et al. reviewed the SEER database from 2010 to 2013, capturing 1,302,166 patients diagnosed with extracranial solid tumor malignancies and known status of CNS disease [10]. Of this cohort, a total of 26,430 patients had brain metastases at diagnosis, accounting for 2.0% of all patients and 12.1% of patients with systemic metastatic disease. The authors estimate that this translates to a brain metastasis incidence of 23,598 per annum for patients with newly diagnosed cancer in the United States. The most common primary malignancies to present with brain metastases at initial diagnosis were small-cell lung cancer (SCLC; 15.8%) and lung adenocarcinoma (14.4%). Brain metastasis IPs at the time of initial primary diagnosis for breast cancer, renal cancer, and melanoma were only 0.4%, 1.5%, and 0.7%, respectively. However, the presence of systemic metastases at initial presentation significantly increased the rates of brain metastases for all cancer types: 28.2% for metastatic melanoma, 26.8% for lung adenocarcinoma, 23.5% for small-cell lung cancer, 15.9% for squamous cell lung cancer, 10.8% for renal cell carcinoma (RCC), and 7.6% for breast cancer.

Epidemiologic Trends Per Primary Malignancy

Lung Cancer

Despite the general trend toward increasing incidence of brain metastases for solid tumor malignancies in general, this pattern has not been observed for primary lung cancers. Data from the Maastricht Cancer Registry between the years 1986 and 1995 included 938 patients with small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC) [9]. Both groups showed a drop in cumulative incidence of brain metastases in the latter diagnosis years. NSCLC patients had a 5-year cumulative incidence of brain metastases of 8.4% for stages I and II disease, 4.3% for stage III disease, and 10.8% for stage IV disease. The SCLC group had a much higher 5-year cumulative incidence at 29.7%. A second study using the Metropolitan Detroit SEER registry was conducted to ascertain the incidence of brain metastases for patients who presented initially with nonmetastatic SCLC and NSCLC [11]. Between the years 1973 and 2011, the IPs for CNS dissemination for NSCLC and SCLC were 9% and 18%, respectively (Table 1.2). The incidence of brain metastases was also significantly decreased in the latter years for both lung cancer types.

Non-Small-Cell Lung Cancer

NSCLC is the most common primary malignancy to metastasize to the brain, at an incidence of 17–44% [12, 13]. This risk is higher for those with advanced disease, with rates for CNS recurrence of 30–50% after initial treatment of locally advanced stage III NSCLC [14, 15]. For early-stage disease,

Table 1.2 Incidence and characteristics of brain metastases from SCLC and NSCLC

	No. with BM	Total *N*	IP%
SCLC[a] [11]	760	4235	17.9
Sex			
Male	385	2251	17.1
Female	375	1984	18.9
Age			
<60	303	1325	22.9
≥60	457	2910	15.7
NSCLC[a] [11]	2712	30,446	8.9
Sex			
Male	1553	18,719	8.3
Female	1159	11,727	9.9
Age			
<60	1225	8414	14.6
≥60	1487	22,032	6.7
Histology			
Adenocarcinoma	1181	10,543	11.2
Squamous cell	722	12,432	5.8
Large cell	243	1984	12.2
NSCLC, not specified	566	5487	10.3
Tumor genotype[b] [21]			
EGFR-mutated	19	78	24.4
ALK-rearranged	5	21	23.8

Data from Goncalves et al. [11] and Rangachari et al. [21]
Abbreviations: *IP%* incidence proportion, *BM* brain metastasis, *SCLC* small-cell lung cancer, *NSCLC* non-small-cell lung cancer
[a]IP% calculated using the Metropolitan Detroit Surveillance Epidemiology and End Results registry for patients with non-metastatic first primary lung cancer diagnosed between 1973–2011.
[b]IP% calculated at initial evaluation for a cohort of patients treated at Beth Israel Deaconess Medical Center between 2012–2014.

predictors for the development of brain metastases include younger age, larger tumor size, lymphovascular invasion, and hilar lymph node involvement [14]. Increasing primary tumor size has been demonstrated in other studies to be a strong predictor of metastases to the brain, for both early and advanced stages [16, 17]. The median time from primary diagnosis to the development of brain metastases has ranged from 7.5 to 12.5 months [14]. Women were found to have a higher incidence of NSCLC brain metastases in multiple studies, for reasons that are unclear [8, 11]. This may be partially explained by the observation that women are more likely to harbor activating epidermal growth factor receptor (EGFR) mutations, which confers a survival advantage and candidacy for certain targeted therapies [18]. Women are also more likely to be nonsmokers and have adenocarcinoma subtypes.

Given the high incidence of brain metastases among lung cancer patients, debate has arisen as to whether neurologic screening at NSCLC disease diagnosis is indicated. The presence of asymptomatic brain metastases is common, and a retrospective review of 809 patients who had routine screening brain MRI or CT at initial NSCLC diagnosis found that 22% of patients actually harbored brain metastases and 34% were asymptomatic [19]. Adenocarcinoma and large-cell carcinoma had higher odds of producing brain metastases as opposed to squamous cell carcinoma, particularly in the absence of nodal involvement in the latter. In fact, 33% of patients with de novo brain metastases were N0 by imaging criteria, and 31% had no evidence of extra-thoracic metastases at NSCLC diagnosis, indicating that complete resection for what is believed to be local disease does not preclude the possibility of asymptomatic brain metastases. As a result, routine screening for brain metastases is recommended as per standard guidelines for stages III and IV NSCLC [20].

The development of targeted therapies with blood-brain barrier penetration may reduce the incidence of brain metastases in certain subsets of NSCLC patients. Patients harboring EGFR mutations and anaplastic lymphoma kinase (ALK) rearrangements carry a high incidence of brain metastases, with nearly 50% of those patients developing CNS dissemination within 3 years of initial diagnosis [21]. Gefitinib and erlotinib are small molecule tyrosine kinase inhibitors (TKIs) of EGFR that are efficacious in patients with relapsed NSCLC or as initial therapy in those with advanced NSCLC with specific EGFR mutations. Brain metastasis response rates to these two agents have varied from 10% to 70%, with higher response rates reported for treatment-naïve never-smokers [15]. However, CNS progression can occur in patients who otherwise respond systemically to EGFR TKIs [22]. CNS treatment failure may be attributed to relatively lower drug concentration in the CNS, longer patient survival, and acquisition of TKI-resistance mutations within the CNS. Heon et al. evaluated the incidence of brain metastases in patients with stage IIIB/V or relapsed NSCLC with EGFR mutations treated with gefitinib or erlotinib as initial therapy for advanced disease [15, 23], and found an incidence of CNS progression of 28% at a median follow-up of 42 months. This is much

lower than the 40–55% crude incidence reported in the pre-gefitinib era [24, 25]. Nearly 20% of these patients had preexisting brain metastases, the vast majority of whom received CNS-directed treatment with surgery or radiotherapy prior to administration of the TKI [15]. The risk for CNS progression was slightly higher in the cohort with preexisting brain metastases compared to those without known brain metastases, with an overall median time to CNS progression of 19 months. Two patients underwent surgical resection of brain metastases that developed while on TKI treatment; both had EGFR-TKI resistance mutations within the CNS lesion. As reported in other studies, young age was associated with a higher likelihood of CNS progression. More recently, osimertinib has also emerged as an attractive third generation TKI with CNS penetration and activity against EGFR mutant lung cancer with T790M resistance mutations.

Brain metastases are present in approximately 20% of patients with ALK-positive NSCLC at initial diagnosis [21]. Crizotinib, a first generation ALK inhibitor, has shown significant activity in the treatment of ALK-positive NSCLC, but it has low durable intracranial response rates due to its poor blood-brain barrier penetration. To circumvent this issue, second- and third-generation ALK inhibitors such as ceritinib, alectinib, brigatinib brigatinib, and lorlatinib were designed to confer improved CNS permeability. A recent review of existing data regarding efficacy of ALK inhibitors for the treatment of brain metastases found pooled intracranial objective response rates of 59% for alectinib, 57% for ceritinib, and 26% for crizotinib as first-line therapies [26]. Use of these agents as part of initial treatment for systemic disease may ultimately reduce subsequent intracranial disease progression, but this awaits future study.

Small-Cell Lung Cancer

Multiple reports suggest decreasing overall incidence of SCLC brain metastases, perhaps owing to the steady decline in SCLC incidence [27] and prophylactic cranial irradiation (PCI). The Netherlands population-based study of the Maastricht Cancer Registry indicated a cumulative incidence of brain metastases from SCLC of 32.5% in 1986–1990 and 26.0% in 1991–1995 [9]. A similar trend was noted in the Metropolitan Detroit SEER database for more recent years [11]. Incidence of brain metastases are much higher in the younger (<60 years) than older (>80 years) populations [11]. As opposed to NSCLC, there does not appear to be a consistent gender bias for brain metastases from SCLC [11]. One small study found that men had a statistically significant higher rate of brain metastasis relapse and shorter brain metastasis-free survival after chemoradiotherapy for limited disease SCLC [28], but this has yet to be replicated. At least two studies suggest that SCLC brain metastases incidence may be slightly higher in African Americans compared to Caucasians; however, this has not always reached statistical significance [8, 11].

Given its propensity to spread to the brain, isolated relapse in the CNS is common. Incomplete thoracic surgical resection and higher pathologic stage are independent predictors of CNS relapse [29]. Therefore, current guidelines recommend radiographic CNS screening in all patients who present with SCLC and PCI for those with limited- or extensive-stage SCLC who achieve a complete or partial response to initial therapy. This practice guideline is endorsed both by the American College of Chest Physicians and the American Society of Clinical Oncology due to multiple clinical trials demonstrating increase in overall survival and decreasing incidence of brain metastases for those who receive PCI [30–33]. A meta-analysis of four phase II/III trials found 1- and 3-year survival rates of 56% and 18% for those who received PCI, respectively, as compared to 32% and 5% for those who did not [30]. These findings were irrespective of age, gender, and stage. Total radiation doses greater than 30 Gy are more toxic than a 25 Gy regimen, with resultant shortened survival and increased chronic neurotoxicity, particular for those older than 60 years of age [30, 34]. For this reason, 25 Gy is the standard regimen for those undergoing PCI. However, despite clear benefit of PCI on overall survival and the development of brain metastases, PCI is not universally utilized due to concern for long-term cognitive damage. In one institution-based study of 283 patients with limited-stage SCLC, only 55% of eligible patients

ultimately received PCI. The most common reasons for PCI omission were patient refusal due to concerns for neurotoxicity, followed by physician assessment of the patient being medically unfit and advanced age [35]. A hospital-based review of SCLC patients treated in France between the years 1997 and 2017 found slightly increased PCI utilization in more recent years, which might provide an explanation for the recent decline in SCLC brain metastasis incidence on a global scale [36]. However, the same review also found no improvement in overall survival or response to chemotherapy over the years assessed, indicating a significant need for new treatment strategies for SCLC.

Breast Cancer

Breast cancer is estimated to be the second most frequent cause of brain metastases, and recent studies suggest that the incidence of brain metastases in this population might be increasing. Population studies indicate that brain metastases are diagnosed in approximately 5% of patients, but the incidence was found to be much higher in prior autopsy series at 18–30% of patients [8, 9, 37]. Although radiographic screening for brain metastases in breast cancer patients is not standard, Miller et al. reviewed screening imaging of 155 breast cancer patients and found that 14.8% had occult asymptomatic brain metastases [38]. Taking this discrepancy into account, one can theorize that approximately 20–30% of all women with breast cancer will develop symptomatic or asymptomatic brain metastases during the course of their illness, with certain subpopulations being at greater risk [37]. Median time from breast cancer diagnosis and detection of brain metastases, regardless of tumor subtype, is approximately 35 months [39]. Admission rates for brain metastases have been rising steadily since the late 1990s, according to the National Cancer Register in Sweden [40]. Compared with patients diagnosed with breast cancer in 1998–2000, those diagnosed between 2001–2003 and 2004–2006 had a 17% and 44% increased risk, respectively, of being hospitalized for complications related to brain metastases.

Table 1.3 Incidence and median OS of patients with brain metastases from newly diagnosed metastatic breast cancer stratified

	No. with BM	Total *N*	IP%[a]	Median OS[b]
HR+/HER2+	136	1704	8.0	21.0 months
HR+/HER2−	361	6607	5.5	14.0 months
HR−/HER2+	106	926	11.5	10.0 months
HR−/HER2−	173	1522	11.4	6.0 months

Data from Martin et al. [41]
Abbreviations: *BM* brain metastasis, *IP%* incidence proportion, *OS* overall survival, *HR* hormone receptor, *HER2* human epidermal growth factor receptor 2
[a]IP% calculated using the Surveillance Epidemiology and End Results registry for patients with newly diagnosed metastatic breast cancer between 2010 and 2013
[b]Median OS for patients with brain metastases at the time of initial breast cancer diagnosis

Several factors have been associated with a greater incidence of brain metastases. These include: younger age at diagnosis, advanced stage, aggressive histologic features, BRCA1 mutations, triple-negative subtypes, and human epidermal growth factor receptor 2 (HER2) amplification (Table 1.3) [12, 41]. Within the HER2-amplified group, the administration of trastuzumab, a non-blood-brain barrier penetrating drug, is further associated with later CNS dissemination of disease [37, 42].

One small study discovered that among 15 patients with germline BRCA1 mutations, 67% developed parenchymal brain metastases compared to none of the germline BRCA2 and 10.3% of the BRCA noncarrier patients [43]. Median time from first breast cancer metastasis to the diagnosis of brain metastases in BRCA1 carriers was 7.8 months. These findings are also in line with the observation that BRCA1 mutations are often associated with triple-negative breast cancer, another factor associated with increased incidence of brain metastases [12].

The HER2/neu proto-oncogene is amplified in 25–30% of primary breast cancers [44]. The incidence of brain metastases in this group of patients

has ranged from 30% to 40% [45], significantly higher than that of the entire breast cancer population. Amplification of this receptor is associated with cellular proliferation, migration, and neoangiogenesis [44]. The introduction of trastuzumab, a humanized monoclonal antibody directed at HER2, has significantly improved extracranial disease control and survival in HER2-amplified breast cancer patients [46]. However, despite its success with systemic disease, trastuzumab has been associated with an increased incidence of brain metastases affecting 25–48% of such patients [42, 46]. The median time from start of treatment with trastuzumab to the development of brain metastases ranges from 4 to 24 months [47]. This is presumed to be secondary to "gained deaths," meaning that the survival benefit from trastuzumab results in patients living long enough to develop brain metastases at a later, more advanced stage. Additionally, possible loss of HER2 overexpression in brain metastases and the failure of trastuzumab to cross the blood-brain barrier might also account for this rise in brain metastases. Due to its high molecular weight of 145 kDa, trastuzumab penetration into the CNS is highly impaired, leaving the brain relatively unprotected during treatment as compared to extracranial sites.

To better delineate this observation, four major randomized clinical trials were conducted (NSABP B-31, NCCTG N9831, HERA, PACS 04) that explore the safety and efficacy of adjuvant trastuzumab. All trials indicate a trend toward increase in brain metastases in the trastuzumab-treated groups, which in meta-analyses reached statistical significance [46, 48, 49]. The overall relative risk for the development of CNS metastases as a site of first recurrence ranged from 1.35 to 1.57 for patients that received adjuvant trastuzumab as compared with patients who did not receive trastuzumab [46, 49], and the ratio of CNS to non-CNS metastases was doubled in the trastuzumab-treated arm [49]. However, despite this reproducible trend, the overall incidence of brain metastases as a site of first recurrence remained low in the time intervals studied: 2.56% versus 1.94% in the trastuzumab and control groups, respectively [49]. Bria et al. concluded that more than 160 patients would need to be treated with trastuzumab in order to observe one event [46]. Furthermore, although the brain has a higher rate of first recurrence in the trastuzumab-treated groups, this is partially explained by early failure in other organs in the control arms. Lapatinib, an oral HER2 and EGFR inhibitor, has emerged as an efficacious treatment for patients who have developed brain metastases after pretreatment with trastuzumab, due to the ability of lapatinib to cross the blood-brain barrier. A meta-analysis including 799 patients with brain metastases found that lapatinib in combination with capecitabine achieved response rates in 30% of patients that had been pretreated with trastuzumab [50].

Melanoma

Melanoma is the third most common cause of brain metastases, with an incidence of 7–75% according to population and autopsy data [8, 9, 51–54]. More recent population-based studies suggest that melanoma brain metastases are present at primary diagnosis in 1.3% of all-comers; however, that number rises to 28.2–35.4% when patients present with de novo metastatic disease [10, 55]. Although melanoma only represents 1% of all malignancies, the incidence of cutaneous melanoma has been steadily increasing [53]. Melanoma also has the highest propensity of all primary cancers to disseminate to the brain [2]. Brain metastases from melanoma are notoriously hemorrhagic, and are more likely to seed the cortex rather than the gray-white junction as seen in other malignancies. Data suggest that melanoma brain metastases are most likely to occur before or during the first line of systemic therapy, leading some practitioners including the National Comprehensive Cancer Network to recommend brain imaging for initial staging of patients with advanced melanoma [56, 57].

Among primary melanoma tumor characteristics, primary ulceration and origin on the head and neck are the strongest independent predictors

of development of brain metastases [58]. Other significant associations include thick lesions, nodular melanoma, and tumors with higher mitotic index. Certain molecular phenotypes are also associated with the development of brain metastases, notably *BRAF*, *NRAS*, and *PTEN* mutations [56].

Overall survival after the development of brain metastases from melanoma has historically ranged from only 3 to 6 months [56, 58]. Patients with solitary or oligometastatic disease that can be treated with surgical resection or stereotactic radiosurgery (SRS) have a survival advantage of an additional 3–7 months [59]. Fortunately, data suggest that survival in recent years has improved from the time of brain metastasis diagnosis [56]. One retrospective study found that median overall survival was nearly three times as long in patients diagnosed with brain metastases in 2011 as compared to the years 2000–2008 (22.7 months versus 7.5 months, respectively), likely owing to improvement in radiation techniques, targeted agents, and immunotherapies [56]. Combination therapy with ipilimumab and nivolumab in patients with asymptomatic, untreated brain metastases demonstrated an intracranial response rate of 57% in a phase II study, although more than half experienced grade 3 or 4 treatment-related adverse events [60]. A recent review of the National Cancer Database revealed that among melanoma patients who present with brain metastases, treatment with immune checkpoint inhibitors led to significant improvements in both median (12.4 versus 5.2 months) and 4-year overall survival (28.1% versus 11.1%) [61].

The use of SRS with either BRAF inhibitors or immune checkpoint inhibitors has also yielded improvement in intracranial control with a trend toward increased survival [53, 56, 62, 63]. SRS, when delivered within 4 weeks of initiation of immunotherapy, has been shown to improve response rates with a trend toward longer overall survival, theoretically because radiation increases immunogenicity and susceptibility of tumors to immune checkpoint inhibitors [64, 65]. Concurrent treatment with programmed cell death protein-1 (PD-1) inhibitors conferred a greater reduction in brain metastasis size compared to ipilimumab, an antibody against cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) [64].

Combination of the BRAF and mitogen-activated protein kinase (MEK) inhibitors dabrafenib and trametinib, respectively, in patients with BRAF V600-mutant melanoma also halted brain metastasis growth, albeit for a shorter duration when compared to the combination's extracranial disease control [66]. Despite the demonstration of CNS activity of the newer agents, the rate of de novo brain metastases was not significantly lower for those receiving BRAF or checkpoint inhibitors when compared to standard chemotherapies [56].

Renal Cell Carcinoma

Brain metastases are observed in patients with renal cell carcinoma (RCC) at an estimated incidence of 2–17% [8, 9, 67]. However, brain metastases are only present in approximately 1.5% of patients at diagnosis [10]. Factors associated with higher odds of brain metastases at diagnosis include larger primary tumors (>10 cm), higher stage and tumor grade, nodal metastases, clear cell histology, white race, and lower socioeconomic status [68]. Between 2010 and 2013, the incidence of brain metastases at diagnosis was shown to be lower than the 6.5% reported in 2001, perhaps owing to escalation of body imaging in the last decade leading to earlier local diagnosis of small renal masses.

A retrospective review of the phase III Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET) evaluated the development of brain metastases for patients with metastatic RCC receiving sorafenib, an oral TKI that targets vascular endothelial growth factor receptor (VEGFR) and platelet derived growth factor receptor (PDGFR) [69]. In this trial, all patients had negative head imaging at treatment initiation, and those who received sorafenib achieved a two-fold increase in progression-free survival compared to placebo. Treatment with sorafenib was associated with a significant reduction in the

occurrence of brain metastases, with incidence of 3% and 12% in the sorafenib- and placebo-treated groups, respectively, at a median follow-up of 19 months. This retrospective study is limited by small patient numbers; however, it does suggest efficacy of sorafenib in treating or delaying the development of brain metastases. This finding is supported by a case report demonstrating reduction of gadolinium-contrast enhancement from renal cell leptomeningeal carcinomatosis in a patient treated with sorafenib [70]. A similar anti-angiogenic TKI, sunitinib, has also shown efficacy for the treatment of RCC brain metastases in case reports [71, 72]. Few studies suggest intracranial response when using immune checkpoint inhibitors for the treatment of brain metastases from RCC [73]. However, this response tends to be less robust than what is observed in other malignancies.

Colorectal Cancer

Colorectal cancer (CRC) is the fourth most common adult malignancy, but only infrequently metastasizes to the brain. Recent review of existing literature on brain metastases from CRC suggests an incidence of only 0.6–3.2% [74]. Part of this stable trend may be due to the relative paucity of effective agents for metastatic CRC. As treatment options for advanced CRC have expanded in recent years to include irinotecan, oxaliplatin, and bevacizumab to name a few, patient survival has been prolonged [75, 76]. It has been suggested that with this survival advantage, metastatic patterns of CRC might be evolving to include uncommon sites of disease dissemination, including the CNS. However, recent hospital- and population-based studies on this question have demonstrated mixed results.

A large review of existing literature in 2016 found a weighted mean of 1.55% incidence of brain metastases from CRC, with no significant difference in reported incidence with the year of data collection [74]. The weighted incidence of brain metastases from rectal cancer was 48.5% compared to colon cancer, which is striking given the relatively lower incidence of rectal cancer in general. Median age at brain metastasis development was the seventh decade for most studies. Diagnosis of CNS dissemination averaged between 20 and 40 months from the primary diagnosis, with more advanced systemic disease at initial diagnosis leading to earlier CNS metastases. The presence of lung metastases seems to be uniformly associated with an increased risk of brain metastasis development, with an incidence of brain metastases of 6.2–22.6% in those with lung metastases. Interestingly, the presence of liver metastases seems to have an inverse relationship with CNS dissemination [77]. One plausible explanation for this discrepancy is that CRC has more routes of hematogenous spread to the lung and brain than it does to the liver. This includes direct extension from the vertebral plexus to the brain and indirect extension from the vena cava to the lungs and then the brain. Molecular markers have also been studied in their relationship to CNS dissemination; however, the only mutation routinely associated with brain and lung metastases involve *RAS* [78]. Other markers including *PIK3CA* and *BRAF* mutations, EGFR expression, and CEA and CA19.9 levels have all been investigated, but none with any clear certainty of relationship to brain metastases [74].

Cancers with Rare CNS Metastases

Prostate cancer incidence and mortality have both declined in the United States in the last decade, although this trend has not been reported in all countries [79, 80]. A retrospective series of 16,280 patients treated at M.D. Anderson Cancer Center between 1944 and 1998 found a 0.63% incidence of parenchymal brain metastases [81]. Nearly 90% of the patients presented with a solitary metastasis, with squamous cell carcinoma and cribriform subtypes metastasizing to the CNS more commonly than adenocarcinomas. Following the incorporation of docetaxel as a first-line treatment for castration-resistant prostate cancer (CRPC) in 2004, the longer overall survival and lack of docetaxel penetration through the blood-brain barrier may lead to an increased

incidence of brain metastases. Patients with CRPC treated with docetaxel between 2002 and 2010 had a 3.3% incidence of brain metastases [82]. While this figure is much higher than what has been reported historically, direct comparison is challenging because discrimination by castration-resistance status in the pre-docetaxel era had not always been reported in prior epidemiologic studies.

Similarly for urothelial cancer, the incidence of brain metastases is thought to have risen from a historical 1–3% to 16% after the advent of MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) due to improvements in overall survival but lack of blood-brain barrier penetration [83]. More recent studies elucidating the incidence of brain metastases in urothelial cell carcinoma are lacking.

Gynecologic malignancies generally have a low propensity to spread to the brain. Although the incidence of brain metastases for ovarian cancer varies widely per study, with historical reports as high as 11.6%, most current studies hypothesize a relatively stable incidence of 1–2.5% [84, 85]. There is a slight tendency toward multiple as opposed to solitary brain metastases [85]. Rates of new cervical cancer diagnoses have been steadily decreasing according to SEER statistics, likely owing to improved screening practices and the human papillomavirus vaccination [80]. Cervical cancer brain metastasis incidence is also very low, with reports ranging 0.4–2.3%; however, it may be increasing due to longer overall survival in this patient population [86]. Endometrial cancer has the lowest propensity to spread to the brain, with a pooled rate of only 0.6% of patients developing brain metastases as per a recent review [87].

Brain metastases from thyroid cancer remain exceedingly rare, and are generally thought to occur in only 0.15–1.3% of patients [88]. One retrospective review of 3117 patients with thyroid carcinoma at a single institution found an incidence of brain metastases of 1.5% between clinical and autopsy data [89]. The most common thyroid cancer to cause brain metastases was the differentiated subtype in 68%, followed by anaplastic cancer in 23% and medullary cancer in 9%. Affected patients tended to be older and have distant metastases at initial cancer diagnosis.

Socioeconomic Impact of Brain Metastases

With the increasing incidence of brain metastases across the general population, one would expect a rise in socioeconomic burden. While studies comparing the overall economic cost of treating brain metastases now versus prior decades are lacking, the literature does reveal a marked increase in health care expenditure after the diagnosis of brain metastases. A claims analysis of patients with breast cancer between the years 2002 and 2004 found that the average total cost at 6 months was $60,045 for those with brain metastases versus $28,193 for those without [90]. Similarly, a second claims analysis for individuals with lung cancer found a rise in total 6-month cost per patient from $70,157 to $86,027 when comparing the pre- and post-brain metastasis diagnosis intervals [91]. Among a cohort of patients with ALK-rearranged NSCLC treated with crizotinib, monthly health care expenditure increased from $5983 to $22,645 per patient following the diagnosis of brain metastases, with the main economic contributors being pharmacy (42.0%), inpatient (29.6%), and outpatient (26.0%) costs [92]. A similar rise in monthly health care expenditure from $7277 to $14,489 has been observed for patients with melanoma following the diagnosis of brain metastases [93].

Among all studies included, one of the largest drivers for increased health care expenditure arises from inpatient hospitalizations, in terms of the number of admissions, length of stay, and total cost. In 6 months, breast cancer patients with brain metastases averaged 1.1 hospitalizations of 8.0 days duration compared to 0.5 admissions of 2.5 days duration in controls [90]. This correlated with an increase in 6-month hospitalization costs from $5362 to $17,462 [90]. Lung cancer patients had higher rates of admission fol-

lowing brain metastasis diagnosis with 10.7-day longer lengths of stay on average [91]. Mean prescription costs, radiology services, physician visits, and other outpatient visits are also uniformly increased for those diagnosed with brain metastases [90–93].

In addition to the dramatic rise in direct health care expenses, the cost of productivity loss on the patients, payers, and employers is also significantly affected [91]. Salary losses averaging over $8000 per 6 months, largely secondary to unpaid sick days, were calculated for lung cancer patients after brain metastasis diagnosis. The absentee rate from work approached 50% in this population. This is felt to be a gross underestimation of global employment days lost as this number does not include the additional consequences on families and caregivers. Furthermore, quality of life scores vary among studies, but generally are stable to worse following treatment with whole brain radiotherapy, reflecting a high unmet need for improved treatment options [94].

Conclusion

Brain metastases are the most frequently encountered tumors of the CNS, and epidemiologic data suggest that the incidence of brain metastases is increasing. Lung, breast, renal, melanoma, and colorectal cancers are the most common malignancies to spread to the brain. The general rise in brain metastasis frequency can be attributed to longer patient overall survival with better therapies and earlier diagnosis of brain metastases. In the era of targeted therapeutics based on genetic and molecular cancer subtypes, improved systemic disease control has led to the brain as a common site of late recurrence. In addition to the detrimental impact on quality of life, this overall trend also has significant socioeconomic implications given the dramatic rise in health care expenditure following the diagnosis of brain metastases. Further population-based epidemiologic studies are needed to determine if newer CNS-penetrating treatments will be effective in preventing CNS relapse.

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Basic Biology of Brain Metastasis

2

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Introduction and Epidemiology

Brain and other nervous system cancers are extremely lethal and represent 1.4% of all new cancer cases in the United States (SEER 2018, 2008–2014). In 2018, there were an estimated 23,380 new cases of brain and other nervous system cancers and 16,380 estimated cancer deaths. Brain cancer (BC) is divided into two different types depending on origin site: (1) primary cancer, confined to the brain; (2) secondary cancer, metastasized to the brain from a different primary site. Secondary brain tumors are extremely aggressive and about 30–40% of cancer patients with primary tumor (melanoma, breast, lung, etc.) have been diagnosed with brain metastasis (BM) at some stage after initial cancer diagnosis (Table 2.1). Lung and breast cancer are the most frequent cancers that metastasize to the brain in men and women respectively [1]. Certain molecular subtypes such as HER2 amplification in breast cancer and anaplastic lymphoma kinase (ALK) positivity in non-small-cell lung cancer (NSCLC) carry a higher rate of brain metastasis [2, 3]. Other factors associated with incidence of brain metastasis include age, ethnicity, and geographic location [1].

Table 2.1 SEER-based incidence of brain metastases determined by primary tumor site

Primary cancer site	Estimated new cases, 2018	Estimated deaths, 2018
Breast cancer (female)	266,120	40,920
Lung and bronchus cancer	234,030	154,050
Prostate cancer	164,690	29,430
Colorectal cancer	140,250	50,630
Melanoma of the skin	91,270	9320
Bladder cancer	81,190	17,240
Non-Hodgkin lymphoma	74,680	19,910
Kidney and renal pelvis cancer	65,340	14,970
Uterine cancer	63,230	11,350
Leukemia	60,300	24,370

Among all primary cancer types, the overall 2-year and 5-year survival rates for brain metastatic patients are 8.1% and 2.4%, respectively [1, 4]. The therapeutic management of brain metastasis depends on the number and location of metastatic tumors, and can include whole brain radiation therapy (WBRT), surgical resection, stereotactic radiosurgery, systematic chemotherapy, targeted therapy, and immunotherapy. Poor blood-brain barrier (BBB) permeability can

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limit the effectiveness of systemic chemotherapy to effectively treat brain metastasis [5]. Combined targeted and immunotherapeutic approaches can produce shrinkage of brain metastasis, can slow tumor growth, and can prevent or/delay neurologic symptoms [1]. In brain metastatic clinical trials, multimodal combination therapies provide more survival benefit to patients than individual treatments; however, posttreatment toxicity may adversely affect patients' quality of life (QOL) [1, 6]. Therefore, it is imperative to understand the complexity of the brain metastatic cascade and translate these findings in clinical settings to develop effective therapies with the ultimate goal of increasing patients' QOL and survival. In this review, we will discuss the molecular and genetic properties of the tumor progenitor cells responsible for brain metastatic seeding and colonization, as well as their modulation through tumor-host niche interactions, the neuro-inflammatory cascade, and neovascularization.

Seed and Soil

The realization that the profile of metastatic sites did not reflect a stochastic distribution of the seed based on passive blood flow and target organ mass suggested that specific cellular and molecular mechanisms were actively involved in regulating metastasis. Stephen Pagett first proposed that this phenomenon is governed by the unique match of the metastatic cancer seed with a conducive soil—the "seed and soil" hypothesis [7]. To achieve successful metastasis, cancer cells must shed from their primary site, survive and self-renew in the circulation (blood/lymph), intravasate, and colonize distant organs where they must survive and grow (Fig. 2.1) [8–10].

The heterogeneous populations of tumor cells that comprise the primary tumor possess distinct molecular and cellular phenotypes evidenced by their differential proliferative, invasive, angiogenic, and metastatic abilities [11, 12]. The metastatic cascade exerts further selection pressure

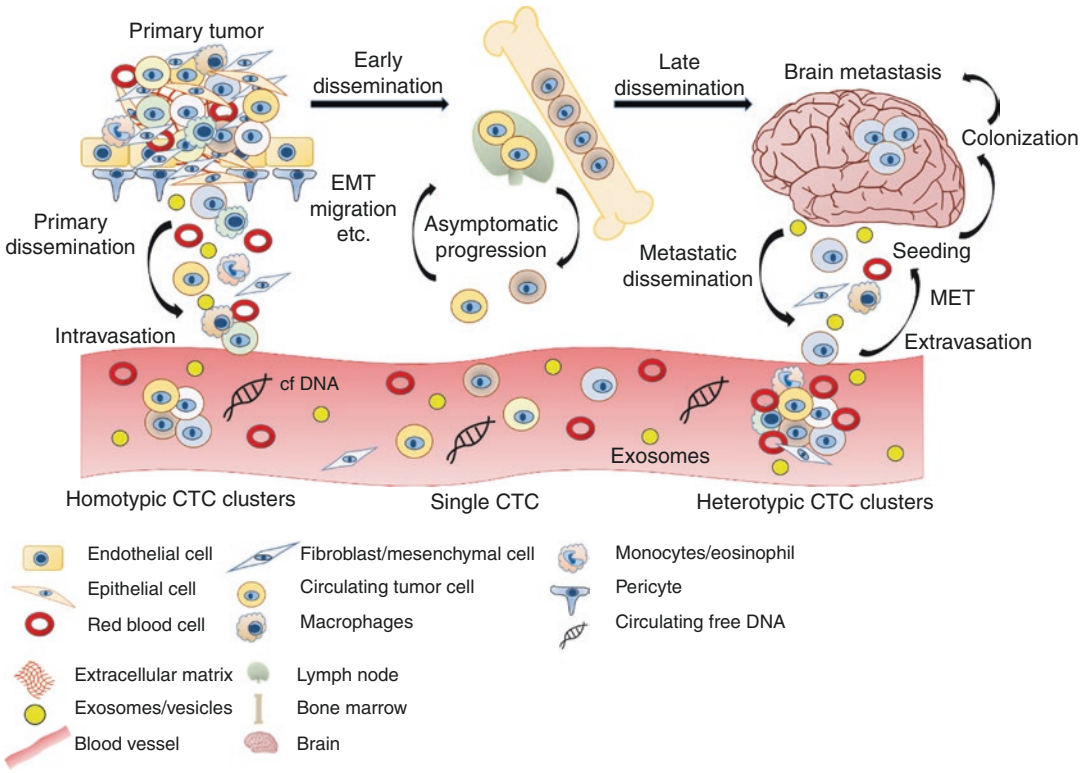


Fig. 2.1 Steps of brain metastatic cascade

that influences cell proliferation, quiescence, adhesion, invasiveness, plasticity, cell-surface (growth and hormone) receptors, and immunogenicity that ultimately defines the metastatic potential [8, 9]. The metastatic "seeds" mobilize and invade the lymphatic or vasculature system where they disseminate as single cells or cell clusters (tumor emboli) [9, 13, 14]. These cells then are often home to, and interact with, conducive microenvironments at distant organs (soil) where stromal and host factors govern their colonization, survival, and growth. Therefore, organ-specific colonization and macro-metastases formation are highly complex processes that depend upon specific "homeostatic mechanisms" and interactions with extracellular matrix (ECM) proteins and cells (immune, stromal, fibroblasts cells, etc.) that comprise the target organ microenvironmental niche [8, 9, 15, 16]. The unique properties of the brain environment (BBB and neural niches) and how they impact BM formation and growth are discussed more in detail below.

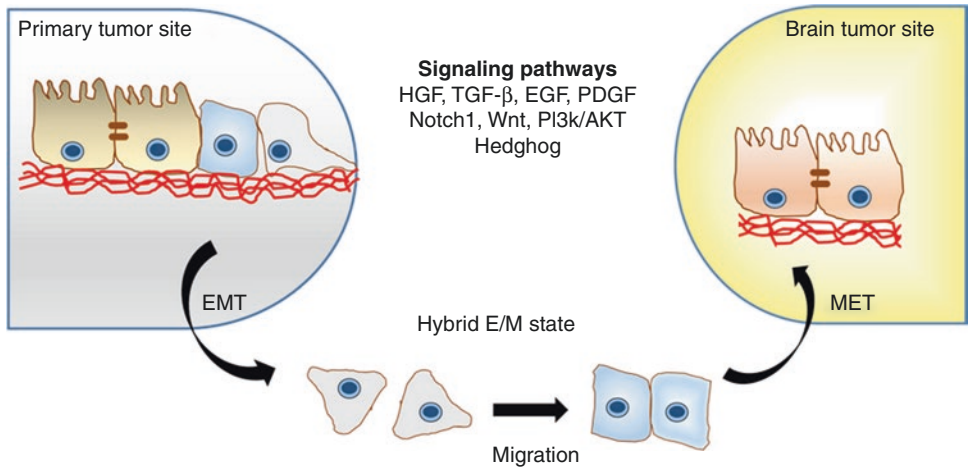
The Early Dissemination Phase of Brain Metastasis

Epithelial-Mesenchymal and Mesenchymal-Epithelial Transitions: EMT/MET

Implied in the "seed and soil" hypothesis and critical to the manifestation of a metastasis is the capacity of a primary cancer cell or aggregate to navigate an imposing biological gauntlet, roughly divided into discrete stages: (i) separation from the primary tumor mass and invasion into and survival in the blood stream (intravasation), (ii) exit from the blood stream to achieve colonization within a distant organ (extravasation), and (iii) survival and growth in a distant organ (Fig. 2.1). A major advance in the conceptualization of metastasis came with the realization that the cellular phenotypes required of the first stage (intravasation) of the metastatic cascade recapitulated the features of a developmentally and morphogenetically recognized phenomenon termed epithelial mesenchymal transition (EMT) first described by Elizabeth Hay in the context of embryogenesis [17].

At the molecular level, EMT is driven by transcription factors such as ZEB1/2, SNAIL, SLUG, and TWIST1 and signaling through HGF, TGF-β, EGF, PDGF, Notch1, Wnt, PI3k/AKT, and Hedgehog pathways that together promote motility, migration, and invasion of tumor cells (Fig. 2.2) [18–25]. For example, TWIST1 is critical for mammary epithelial carcinoma cell extravasation and is implicated in metastatic capacity for numerous cancers [26]. Downregulation of E-cadherin (an epithelial cellular adhesion protein) and upregulation of N-cadherin (the so-called "cadherin switch") accompany EMT allowing a cell typically held in tight apposition to become mobile and correlate with the metastatic potential of cancers metastasizing to the brain [27, 28]. This is followed by degradation of the epithelial basement membrane and invasion through the endothelial basement membrane, and then transit into the blood vessel [29–31]. In addition to promoting invasiveness, EMT promotes malignant phenotypes through effects on immunosuppression, treatment resistance, and cancer stem cells (CSCs) [25]. Therefore, EMT contributes broadly to BM formation through production of metastatic "seeds," activation of malignant cellular properties, and reprogramming of the tumor microenvironment.

To successfully generate metastases, disseminated tumor cells must survive in the blood stream (see below), extravasate from the circulation, colonize, and grow in distant organs. Despite the presumed importance of EMT in the initial dissemination of metastatic cancer cells, metastatic tumors frequently retain epithelial features of the primary tumor [25]. These conflicting observations are reconciled by recognizing that the final phase of the metastatic cascade (extravasation, colonization, and macro-metastatic growth) requires reversal of the mesenchymal to epithelial phenotype; a process termed the mesenchymal-epithelial transition (MET) [32–34]. Activators of EMT signaling are lacking at sites of metastatic colonization, including the brain, which promotes MET and macro-metastatic growth [8, 25, 35]. This cross-talk between



Epithelial markers	Transcription factors	miRNA	Stem-cell markers	Mesenchymal markers
E-cadherin	Twist1/2	mir-21	Nanog	N-cadherin
Claudin	Snail	mir-200	Sox-2	Fibronectin
Occludin	Zeb1/2	mir-205	Oct4	FSP-1
Desmoplakin	Slug	mir-34a	LGR5	Vimentin
Mucin-1	bHLH	mir-145	CD133	Vitronectin
Cytokeratin	β-catenin	Let-7		SMA
				FGFR2
				MMPs

Fig. 2.2 Molecular mechanisms of epithelial (E)-mesenchymal (M) transition during brain metastasis

extravasated cancer cells and the microenvironment of distant organs underscores the importance of the metastatic niche or "soil" for successful generation of metastases. Here, we will discuss the mechanism of cross-talk between metastatic cancer cells and the brain that specifically contributes to BM formation. While the precise mechanisms of EMT and MET that regulate BM formation have yet to be elucidated, it is significant that both processes promote the phenotypes of CSCs, the putative "seeds" for BM formation [7, 25].

Cancer Stem Cells

Many cancers possess a subpopulation of cancer stem cells (CSCs) that play critical roles in tumorigenesis, treatment resistance, and progression and are commonly considered the "seed" for metastasis [11]. Although they comprise a minority population of tumor cells, CSCs are of great clinical importance by virtue of their increased resistance to treatment and putative role in formation and/or growth of BMs (Fig. 2.3) [36]. Cancer stem cells (CSCs) are operationally defined by properties of proliferation, self-renewal, multi-lineage differentiation, and, importantly, the capacity to recapitulate the cancer phenotype in vivo [37]. The correlation of specific molecular markers with CSC phenotypes has facilitated the investigation of the role of CSCs in BMs. For instance, in breast cancer the CD44 hi/CD24 low CSC phenotype is responsible for maintaining self-renewal and proliferation through Notch signaling and drives metastatic progression in the brain [22, 38, 39]. On the other hand, the chemokine CXCR4/12 signaling axis provides microenvironment cues to CSCs for proper homing and brain colonization [40]. Of note, targeting CSC phenotypes CD44 hi/CD24, CD133, and BMI1 or inhibiting CXCR4/12 and the Notch signaling axis effectively eradicates brain metastatic spread and improves therapeutic efficacy [39, 41, 42]. In concert with MET and local angiogenesis, they drive growth of macroscopic brain tumors [43, 44]. Another critical observation is that cancer cells can switch

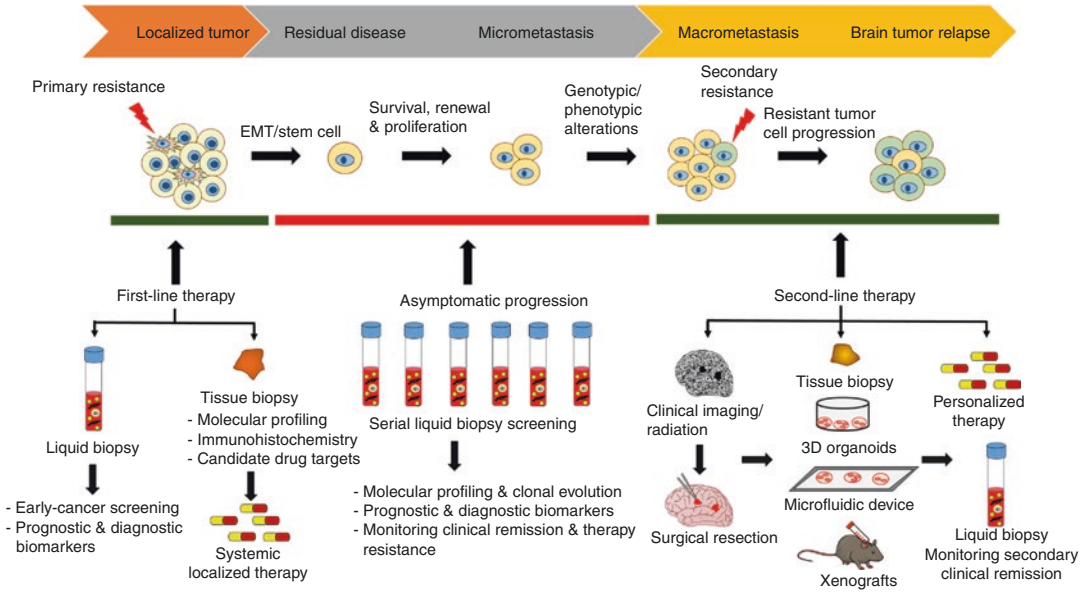


Fig. 2.3 Molecular landscape of brain metastasis and its therapeutic implications

between non-CSC and CSC phenotypes in response to microenvironmental cues such as hypoxia [44–46]. This plasticity has profound implications for context-dependent identification and assessment of CSC burden and development of CSC-targeted therapies. Regardless of how metastatic cells acquire stem-like properties, they must all navigate and survive a journey through the blood stream. The recent refinement of methods to identify and characterize circulating tumor cells (CTC) has shed further light on the phenotypes and mechanisms employed by CSCs to colonize the brain (Fig. 2.3).

The "Liquid" Phase of Brain Metastasis

Circulating Tumor Cells (CTCs) and Dormant Cancer Cells (DCCs)

As putative metastatic "seeds," circulating tumor cells (CTCs) drive metastasis and disease recurrence [47, 48]. CTCs may colonize distant sites and rapidly progress to form macro-metastases or remain as dormant cancer cells (DCCs) in permissive pre-metastatic niches that after months or years are triggered to form macro-metastases. CTCs may also derive not only from the primary tumor site but also from distant macro-metastases—a mechanism termed "self-seeding" (see Fig. 2.1).

CTCs are a minority heterogeneous cancer cell population that can be isolated from patient blood by various techniques such as flow cytometry, magnetic beads, and microfluidic devices and identified based on immune phenotyping, cell size, and deformability [48–51]. CellSearch™, which captures EpCAM-positive epithelial-derived CTCs, is currently the only Food and Drug Administration (FDA)-approved platform for CTC analysis, although it excludes potential EpCAM-negative CTCs that may be a significant contributor to BM formation [39]. Disseminated CTCs intravasate and migrate into the blood circulation and survive as single cell or cluster/emboli. CTC clusters have survival advantages as they more effectively resist anoikis, bloodstream shear forces, environmental or oxidative stresses, and immune surveillance [52–54]. Higher CTC counts in peripheral blood correlate with disease burden and worse patient survival in various malignancies such as melanoma and breast, lung, prostate, and pancreatic cancers [54–56].

Although CTCs are not routinely identified in the majority of BM patients, BM formation presumably requires the existence of CTCs at some point prior to their clinical manifestation. More than two CTCs were detected in only 5.9% of patients with oligo-metastatic NSCLC to the brain; the frequency of more than three CTCs in BM patients with systemic metastases and other tumor types ranges widely from 0% to 25% [55]. These data underscore several important considerations: (i) CTC dissemination and thus detection may be intermittent with periods of dormant residence in other sites, and (ii) in addition to unidirectional production of CTCs from the primary cancer, CTCs may also arise from metastatic deposits including BMs, the so-called "self-seeding" mechanism. The identification of CTCs in cerebrospinal fluid (CSF) from BM patients with concurrent leptomeningeal disease (LMD) may represent a form of "self-seeding" [57].

CTCs are heterogeneous and specific subpopulations may have unique tropism for colonizing the brain [9, 48, 58, 59]. Using an expanded CTC isolation protocol, Boral et al. demonstrated that inclusion of EpCAM-negative CTCs with CSC markers markedly increased CTC yields in breast carcinoma patients [60]. Stratifying these metastatic patients based on the presence of BMs, they identified a 121-gene signature associated with BMs [60]. Other studies have shown that a specific subpopulation of EpCAM-negative CTCs from breast cancer patients has a unique propensity for forming BMs in experimental models [61]. These studies indicate that identifiable subpopulations of CTCs may have specific capacity to generate BMs that could theoretically be targeted systemically to prevent BMs. Clinical and biological relevance of CTCs is an area of ongoing investigation, but one that appears to have great promise to inform prognosis, treatment responses, metastatic risk, and even new therapeutic approaches. The utility of liquid biopsies for BMs extends beyond the detection of CTCs, allowing profiling of exosomes and circulating-tumor DNA (ctDNA) (see Fig. 2.3).

Exosomes

Exosomes are small membrane bound extracellular vesicles secreted by cancer cells that contain DNA, RNA, proteins, and lipids [62]. Exosomes function locally within primary and metastatic tumors as well as remotely through vascular dissemination and cellular uptake at metastatic sites [63]. They are increasingly analyzed in liquid biopsies since they inform tumor growth, evolution, and pathogenesis and in BMs are responsible for inducing a plethora of biological processes, such as EMT, angiogenesis, metastasis, therapy resistance, and epigenetic/stem-cell regulation (Figs. 2.1 and 2.3) [64]. In breast cancer, expressions of mir-122 and mir-210 were associated with brain metastasis [65, 66]. In melanoma, CD46 receptors are responsible for uptake of tumor-associated exosomes in BBB endothelial cells [67].

An important function of exosomes in BM biology is their capacity to generate organotropic pre-metastatic niches conducive to DCC growth or CTC homing, colonization, and proliferation. In experimental studies, the brain preferentially takes up exosomes from neurotropic metastatic cancer cell lines through specific direct interactions with CD31+ BBB endothelial cells [68]. Exosomal organotropism also appears to be related to specific integrin profiles with ITGB3 highly upregulated in brain tropic exosomes [69]. Remarkably, "educating" mouse hosts with exosomes redirects the organotropism of cancer cell lines to reflect patterns of exosomal uptake. These data suggest that targeting brain-specific exosomes may be a useful future strategy to mitigate BM formation.

In addition to roles in organotropism, exosomes are implicated in promoting immunosuppressive "havens" for DCCs, angiogenesis that triggers progression and growth of micrometastases, and disruption of the BBB [62, 63, 70]. Of note, experimental evidence implicates exosomal microRNAs (miRNAs) generated from astrocytes and BM cells during tumor growth through reversible epigenetic downregulation of PTEN and conversion of resident microglia from the

M1 to M2 immunosuppressive phenotype [71, 72]. These observations demonstrate the important roles of both primary tumor-derived and local neural cell-derived exosomes in orchestrating the complex processes of BM tropism and growth. Exosome-based targeted therapies therefore may be a useful strategy to mitigate BM formation and progression [63].

ctDNA

Circulating-tumor DNA (ctDNA) is released into biological fluids by apoptotic or necrotic cancer cells. ctDNA is detected in most systemic cancers with increased levels corresponding with metastasis [73]. In breast and melanoma carcinomas, two cancers with high propensity for BMs, ctDNA is detectable in over 80% of cases [73]. Levels of ctDNA are associated with tumor burden and patient survival [64, 74, 75]. To our knowledge no data exist demonstrating an association between ctDNA and BM incidence or a pathogenic role in BM genesis. However, analysis of ctDNA from cerebrospinal fluid (CSF) is emerging as a useful marker for patients with parenchymal BMs and leptomeningeal disease that may be more sensitive and specific than plasma-derived ctDNA [76, 77]. For instance, in patients with central nervous system (CNS)-restricted metastatic disease, CSF ctDNA was detected in 58% versus 0% from plasma and importantly, changes in CSF ctDNA detection corresponded with clinical treatment responses [77]. In another study, genomic mutations were identified after sequencing of CSF DNA in 63% (20 of 32) of patients with parenchymal CNS metastases, while detection of ctDNA in CSF has been reported for 75–100% of patients with LMD [76, 78]. These studies indicate the potential for ctDNA to serve as a biomarker for tracking tumor progression and treatment response [75, 79, 80]. Multicenter large cohort studies are required to evaluate the evolutionary changes of ctDNA over the course of metastatic cancer treatment and their correlation with disease status and patient survival.

The Final Metastatic Phase: Brain Colonization, Growth, and the Role of the Brain Microenvironment

In the final stage of BM formation, CTCs and/or DCCs, which have colonized permissive pre-metastatic niches, engage the brain microenvironment (BME) and through reciprocal interactions undergo macro-metastatic growth. The complex interactions between BM cells and resident neural cells (astrocytes, neurons, and microglia), infiltrative immune cells, brain microvasculature, extracellular matrix proteins, metabolic changes, cytokine signaling, and even synaptic inputs result in reprogramming of BM cells and BME to facilitate BM survival and growth. An additional important element of the BME is the blood-brain barrier (BBB) and subsequent formation of a blood-tumor barrier (BTB), critical to the process of CTC extravasation, immune cell infiltration, and systemic delivery of therapeutic agents. With selected examples we will address clinically relevant highlights of these interactions.

The Blood-Brain Barrier (BBB) and Blood-Tumor Barrier (BTB)

The blood-brain barrier (BBB) is a highly specialized semipermeable structure consisting of endothelial cells, pericytes, and astrocytes, which form tight junctions that restrict access to the brain from the circulation [1]. The neurovascular unit of the BBB maintains homeostatic environmental conditions for normal neuronal function and provides a barrier to CTC extravasation that must be overcome for BM formation (reviewed in Ref. [81]). Three molecules, cyclooxygenase COX2 (also known as PTGS2), the epidermal growth factor receptor (EGFR) ligand HBEGF, and the α2,6-sialyltransferase ST6GALNAC5 have been identified as mediators of cancer cell extravasation across the BBB [82]. ST6GALNAC5 promotes adhesion of tumor cells to brain endothelial cells, whereas COX2 and HBEGF promote cell migration across the BBB [82]. In addition, matrix metalloproteinases

(MMPs) and vascular endothelial growth factor (VEGF) facilitate extravasation, seeding, and micrometastasis formation through ECM destruction and creation of a vascular niche [1, 83–87].

In the BM peri-tumoral region, the BBB is modified to generate a so-called blood-tumor barrier (BTB) characterized by increased local permeability. Changes in BBB characteristic of the BTB are mediated by alterations in endothelial cell tight junctions and pericyte function, and are associated with neuroinflammation and changes in ECM components [1]. The molecular mechanisms underlying permeability changes in the BTB include upregulation of VEGF and downregulation of zona occludens (ZO) and vascular endothelial cell adhesion molecule (VE-CAM) in endothelial cells, altered expression of desmin and CD13 in pericytes, and elaboration of other molecules including membrane transporters, tumor necrosis factor (TNF) receptors, claudin-5, and angiopoietin-2 [1, 88–92]. Of clinical relevance, these changes in permeability result in heterogeneous uptake that may enhance uptake of drugs and antibodies normally restricted by the intact BBB [1, 54, 93–96].

Immune BM Microenvironment

BMs generate an inflammatory and immunosuppressive microenvironment that promotes tumor growth and treatment resistance [97]. The immune BM microenvironment involves complex interactions between tumor and resident neural cells and infiltrating cells of lymphoid (cytotoxic-CD4+, helper-CD4+, T-regulatory [T-reg] cells, and natural killer) and myeloid (dendritic/antigen presenting cells, macrophages, and myeloid-derived suppressor cells [MDSCs]) lineage [98–101]. Intense interest in tumor-infiltrating lymphocytes (TILs) has been fostered by the success of immune checkpoint inhibitors (ICIs) in treatment of systemic melanoma, and, more recently, other cancers with a propensity for BMs including NSCLC and breast cancer [102–105]. In fact, recent trials have demonstrated variable activity of ICIs against BMs [98, 106]. CTLA4 and PD-L1/PD-1 inhibitors block tumor-mediated immunosuppressive mechanisms that typically decrease cytotoxic T-lymphocyte (CTL) function [105].

Harter et al. profiled the quantity and topography of all TILs (CD3+) and specific subpopulations of T-reg cells (FoxP3+) and CTLs (CD8+) and PD-1/PD-L1 expression in BMs in both mixed tumor and breast carcinoma-restricted cohorts [105]. TILs and their subpopulations were detected in all BM types but with different frequencies (highest in renal cell carcinoma) and patterns of distribution (diffuse in melanoma, stromal in carcinomas). In contrast to other studies, where expansion of cytotoxic T-lymphocytes and infiltration of T-cells correlate with patient survival, none of the TIL or PD-L1/PD-1 metrics were associated with patient survival [107–109]. By contrast, the presence of a peri-tumoral and to a lesser extent stromal mononuclear infiltrate and lower PD-1/PD-L1 expression in lung adenocarcinoma BM patients predicted better survival after resection [110]. In another study of NSCLC patients, disparate responses of the primary and BM lesions to PD-1 blockade mirrored a decrease in BM-specific PD-1 expression in paired primary and BM samples [102]. In paired breast cancer primary and BM samples, TILs are decreased in BMs as was the proportion of "adaptive" immune phenotypes (TIL+/PD-L1+) expected to be responsive to ICIs [103, 104, 111]. In melanoma BMs, increased immune cell infiltration corresponded with increased PD-L1+, survival, and enrichment of oxidative phosphorylation compared with non-CNS metastases [100]. Overall the melanoma BMs had reduced immune cell infiltrates, and gene expression analysis revealed an immunosuppressive phenotype compared with non-CNS metastases. Of note, the metabolic signature positively correlated with patient survival, and preclinical models demonstrated that inhibition of oxidative phosphorylation was a promising therapeutic target of MAPK-resistant melanoma BMs [100].

In addition to TILs, other immune cells including myeloid cells are implicated in BM growth [72]. The association between reduction of peripheral myeloid-derived suppressor cells (MDSCs) and BM incidence in lung cancer

patients treated with combination systemic bevacizumab and TKIs suggests that MDSCs may play a role in the immunosuppressive BM microenvironment. Experimental studies of mouse mammary carcinoma BMs also demonstrated that MDSCs generate a "pre-metastatic niche" for BM formation [90]. T-regulatory (T-reg) cells suppress immune reactions by secretion of factors such as TGF-β and IL-10 and higher T-reg cell burden in tumors and peripheral blood is associated with poor clinical outcomes [112, 113]. In lung adenocarcinoma, FOXP3+ T-reg cells are detected in BMs albeit at lower numbers than in primary tumors [102]. Finally, resident microglia and systemically derived macrophages are implicated in early stages of BM formation and contribute to the immunosuppressive microenvironment [114]. In summary, the complex and immune BM microenvironment generates an immunosuppressive state and plays critical roles in BM formation from the pre-metastatic niches to macro-metastatic growth. Further elucidation of the diversity of immunosuppressive mechanisms in BMs is needed to develop more effective immunotherapy and strategies to reprogram the immune microenvironment of BMs to facilitate responses to immunotherapy.

As noted above, BMs are "cold tumors" and thereby less responsive to immunotherapy [1]. Therefore, techniques to activate the immune microenvironment in BMs have great clinical significance. For example, the abscopal effect is a presumed immune-mediated mechanism whereby local radiation to a single lesion resulting in release of tumor antigens and T-cell expansion can activate a dramatic generalized antitumor response distant from the site of radiation [115–117]. An experimental melanoma BM model demonstrated an abscopal effect with combined irradiation and PD-L1 blockade similar to the reported clinical potentiation of the abscopal effect with concurrent ICI therapy [118–121]. As several reports suggest, it may be possible to harness the abscopal effect to treat BMs through targeting a systemic lesion or conversely activate a systemic response through local irradiation of BMs [122, 123]. While the occurrence of an abscopal response is relatively rare, further investigations into its precise mechanisms are expected to provide insight into more effective strategies to activate the immune system to improve response for systemic and CNS-based cancers.

BM Cross-Talk with the Brain Metastasis Microenvironment

In addition to interactions with the vascular BBB/BTB niche and infiltrating immune cells described above, cross-talk with resident neural cells also plays an important role in BM biology (reviewed in Refs. [97, 99, 124]). The brain is generally a hostile microenvironment for extravasated cancer cells, the majority of which die; however, those that survive as dormant or actively propagating cells appear uniquely able to co-opt or adapt to the conditions in the brain microenvironment [81]. For instance, cancer cells that grow in the brain activate unique brain-enriched gene expression profiles, and undergo metabolic reprogramming so that they can effectively utilize non-glucose energy sources, like the brain (reviewed in Refs. [125, 126]). Expression of Serpins on BM cells counteracts with the cell-death and anti-migratory effects of brain-derived plasmin necessary for BM cell survival and engagement with brain microvascular cells for local invasion [127]. While neural cells can impede BM growth, specific interactions with neural cells have also been shown to promote BM survival and growth. For instance, astrocyte interactions promote BMs through gap junction-mediated transfer of cGAMP and astrocyte-derived exosomal miRNA-mediated suppression of PTEN function [72, 128]. Similarly, the activated state of microglia can either inhibit or promote BM growth [81]. BM cell secreted exosomal miRNAs can reprogram microglia to promote BM growth through immunosuppressive mechanisms [71]. Finally, based on the increasingly recognized impact of peripheral innervation in cancer metastasis and CNS neural activity to promote glioma proliferation, future studies should be directed to understanding how electrical activity may influence BM physiology [129–131].

Molecular Heterogeneity and Selection for Brain Metastasis

Given the complexity of mechanisms and environmental selection pressures summarized above, it is not surprising that primary cancers and their brain metastases exhibit extensive molecular heterogeneity. Since the seminal publication by Gerlinger et al. in metastatic renal cell carcinoma, intra-tumor molecular heterogeneity and branched evolution have been recognized to contribute to the genesis, progression, and treatment resistance of many cancers [5, 132–134]. Genomic instability and selective evolution are principle mechanisms driving heterogeneity at the genetic, epigenetic, and transcriptional levels [132, 133, 135]. Multiregional tumor biopsy sampling, research autopsies, spatial and temporal liquid biopsies, and single-cell sequencing are emerging approaches that will help decode the complex architecture of tumor, specifically as it relates to brain metastasis [132, 133, 135–137].

For BMs, studies of paired primary and metastatic lesions reveal several clinically relevant insights including (i) a high proportion of BMs possess mutations distinct from those of the primary site, (ii) BMs from individual patients share mutations distinct from those detected in the primary cancer, and (iii) BMs exhibit activation of oncogenic signaling pathways (e.g., PI3K/Akt/mTOR) distinct from those present in the primary cancer [5, 138–140]. These observations suggest that BMs may arise from unique cell subpopulations within the original cancer and/or that selection pressure for specific mutations and phenotypes drive successful BM formation and growth.

Genomic studies indicate that BMs retain ancestral mutations of their primary cancer but acquire additional unique mutations through branched evolution [136, 138, 139, 141]. In the largest study to date of paired primary and metastatic cancer samples, Brastianos et al. determined that BMs share mutations with the primary cancer but develop unique or "private mutations" in all cases, of which 53% represent potential actionable targets unique to their CNS disease [138]. As further shown by EGFR mutations shared by paired primary and BM specimens, these observations suggest that clonal selection during BM formation may be required for effective metastatic outgrowth and therapeutic resistance [133, 138, 142].

Activation of specific oncogenic signaling pathways occurs in BMs in concert with the evolution of genomic changes. In primary melanoma, lung and breast cancer patients, more than 50% of brain metastatic tissue contain clinically relevant oncogenic alterations in PTEN, PIK3CA, EGFR, and HER2 genes and cancer hot spot regions that activate PI3K–AKT–MTOR and EGFR/HER2 pathways involved in tumor cell growth and proliferation [5, 132]. Primary tumors treated with systemic therapy such as PI3K/AKT/mTOR, CDK, and HER2/EGFR inhibitors are more inclined to develop brain metastasis [138]. In squamous cell lung cancers (SQCLC), PI3K-aberrant tumors were associated with high metastatic tumor burden and increased incidence of brain metastasis [143]. However, colorectal cancer (CRC) shows less genetic heterogeneity (APC, KRAS, FBXW7, PIK3CA, BRAF, SMAD4, and ACVR2A mutations) with greater genetic concordance between matched primary and brain metastatic tumors [144].

Overall, brain metastases exhibit a branched evolution pattern reflecting primary tumor mutation profiles and acquisition of additional unique molecular profiles with respect to other non-CNS metastases. Additionally, molecular profiles of intracranial sites within individual patients suggest a high degree of homogeneity. This genomic concordance may provide guidance for systematic personalized therapy and facilitate our understanding of mechanisms involved in brain metastasis.

Spinal Metastasis

Metastatic spinal cord compression is considered an oncological emergency that may require immediate treatment either through surgical decompression, emergency radiotherapy, or a combination of the two. This occurs in 3–5% of cancer patients, with breast, lung, and prostate

being the most frequent source [145]. The majority of metastases affects the bone first and cause compression through direct mass effect or pathological fracture. Even more rare are intradural extramedullary and intramedullary metastases accounting for less than 6% and 1–2% of spinal metastasis, respectively [146–148]. The incidence of intramedullary spinal metastasis may be increasing perhaps with extended overall survival. Additionally, metastasis to the spine is generally a poor prognostic sign of overall patient survival with median survival of only 8 months in patients treated for intramedullary renal cell metastasis [149].

By virtue of their different recipient tissue microenvironments, it is not surprising that the cellular and molecular mechanisms that promote bone metastasis, and thereby osseous-based spinal cord compression, differ from those driving BMs (reviewed in Refs. [150–153]). Given the rarity of both extra- and intra-axial spine metastasis, studies of their specific mechanisms are scarce. Presumably, extramedullary spinal metastases result from local leptomeningeal growth of CSF-disseminated cells. Like BMs, molecular analysis of leptomeningeal cancer cells reveals mutations shared with and unique to the primary cancer site that can be monitored through analysis of ctDNA [154, 155]. By contrast, intramedullary spinal metastases are more likely to originate through mechanisms similar to those that regulate BMs. Intramedullary spinal cord metastasis (ISCM) is exceedingly rare with incidence of ~2% in systemic cancers [147, 156, 157]. It is most commonly seen with lung and breast cancers but has also been reported for colon cancer, Merkel cell carcinoma, renal cell carcinoma, gastric cancer, ovarian cancer, and thyroid cancer [148, 149, 158–162]. As with BMs, the increasing success of systemic therapies may be contributing to the increased incidence of ISCM [148]. Lung cancers frequently metastasize to the CNS, but intramedullary spine metastasis is detected in only 1.65% of 1215 autopsy cases and 1.8% of NSCLC patients; and these were highly associated with concomitant BMs suggesting common mechanisms for their colonization and growth [147, 157]. Anaplastic lymphoma kinase (ALK) gene mutations are associated with aggressive features in NSCLC including early CNS metastasis and higher rates of intramedullary spinal cord metastasis [146, 157, 163]. While rare, the consequences of spinal extra- and intramedullary metastases are devastating and warrant further study of their basic biology to develop more effective therapies. See the "Spinal Metastases" section of this book for in-depth coverage of this topic.

Conclusion

Brain metastasis is a devastating disease with increasing incidence. The increased rate is due to a lack of prognostic and diagnostic biomarkers at early disease stages. Systemic, longitudinal blood-based liquid biopsy (CTCs, cell-free DNA, exosomes, secretory proteins, etc.), alongside molecular imaging approaches, may provide novel biomarkers for designing early diagnostic tools (see Fig. 2.3). In brain metastatic patients, surgical resection is a key part of clinical management and provides an immediate opportunity for tumor molecular characterization for determining effective therapies. These studies can also assist in identifying therapeutic targets to eliminate residual disease or recurrence in brain metastatic patients with other primary cancers. Poor prognosis of brain metastatic patients is also related to drug resistance and tumor heterogeneity between primary and brain metastasis tumors. In the era of precision medicine and individualized therapy, deciphering the tumor heterogeneity based on spatiotemporal selection is clinically imperative. Multidisciplinary approaches are necessary to fill in the gaps in knowledge regarding the molecular landscape of brain metastasis. Preclinical models such as microfluidic device, organotypic 3D culture, and patient-derived xenografts may clarify both the interplay between metastatic cell and brain tumor microenvironment and the brain metastatic cascade (Fig. 2.3). These emerging tools overcome traditional cell-based technologies as they have

the potential to monitor real-time cancer progression and personalize therapy for patients. Further, the advancement in future multimodal studies will open new paradigms to understand the realm of brain metastasis and improve patient outcomes.

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Preclinical Models of Brain Metastasis

3

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Models for Brain Metastasis Research: An Overview

The complexity of the multistep process of metastases cannot be fully recapitulated in vitro. Consequently, the use of mice as the experimental model of choice is broadly accepted. The study of brain metastasis in preclinical models includes several steps that, in principle, are common to metastases in other organs (e.g., the ability of cancer cells to migrate toward and intravasate into capillaries at the primary tumor as well as the survival of tumor cells while in circulation). Given the interest of this book, we will consider aspects of metastatic dissemination of particular interest in the brain. Preclinical models have been used to study these specific steps within the metastatic cascade that involve extravasation through the blood-brain barrier (BBB), survival of extravasated metastasis initiating cells, reactivation of proliferation to re-grow the tumor in the brain as well as the interaction with the surrounding microenvironment.

In order to study brain metastasis in the laboratory, researchers obtained cancer cells from patients, usually from pleural fluids or lymph node metastases (Fig. 3.1a). These cancer cells were engineered with different reporters, including those compatible with non-invasive imaging (e.g., luciferase, Luc, for bioluminescence) and/or histology (e.g., green fluorescence protein, GFP). Labeled cancer cells were then inoculated in mice using different routes such as intracardiac (IC) injections through the left ventricle, intracarotid, or intracranial approaches [1–3]. Intravascular injection is the preferred method since it incorporates the strong selective step of the extravasation through the BBB. The advantage of intracarotid injection is the reduction of the incidence of extracranial metastases. However, at the same time, this procedure requires surgery and thus increases the time to develop the experimental procedure. Consequently, intracardiac injection of human cancer cells has been the method of choice to induce experimental brain metastasis. Frequently, inoculation of metastatic cancer cells recovered from pleural fluids or lymph nodes, the so-called parental cell line (P), into mouse circulation does not yield a significant number of mice with brain metastases [1, 3]. This parental (P) cell line is highly heterogeneous and may or may not contain cellular clones that could have the ability to target the brain. In order to enrich those cancer cell clones with the ability to grow in the brain, parental cells are inoculated in mice IC and when metastases are detected in specific organs, the metastatic lesion is dissected out and grown in vitro. This process of positive selection has to be repeated between 3 and 5 times to enrich those variants

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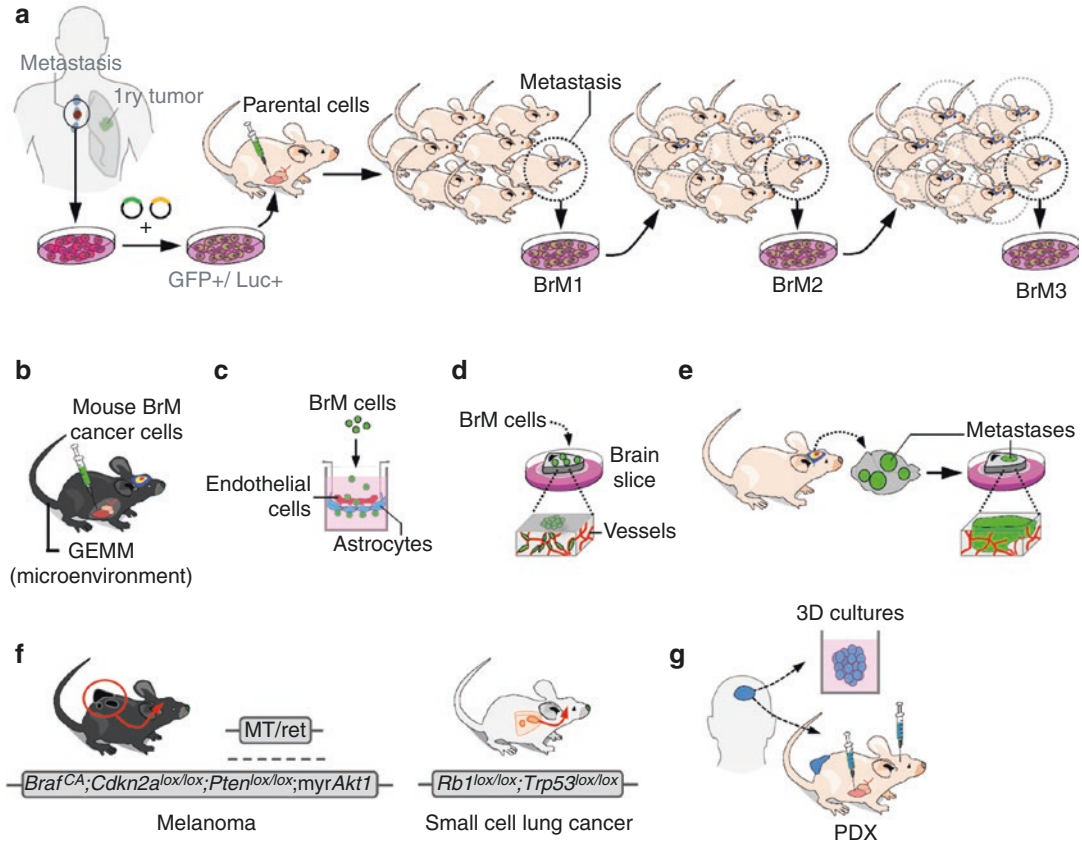

Fig. 3.1 Models for brain metastasis research. (**a**) Schema representing the generation of brain metastatic cell lines (BrM). (**b**) Syngeneic BrM cell lines could be used to evaluate brain metastasis in an immunocompetent host. This experimental model also allows interrogation of genetic modifications induced in specific components of the microenvironment by using genetically engineered mouse models (GEMMs). (**c**) Artificial blood–brain barrier (BBB) assay could be used to evaluate mediators of permeability as well as penetration of drugs. (**d**, **e**) Organotypic brain cultures allow modelling of initial (**d**) or advanced (**e**) stages of brain colonization. This preparation is a useful resource to analyze interactions with the microenvironment and it is compatible with genetic and pharmacologic manipulations. (**f**) Available GEMMs that have been described to generate spontaneous brain metastasis. (**g**) Human brain metastasis can be cultured in vitro or inoculated in immunosuppressed mice to establish brain metastasis patient-derived xenografts (PDX)

present in the P cell line with an increased ability to target the brain. These organotropic cell lines are termed brain metastatic (BrM) [1, 3–5] (Fig. 3.1a). This approach has been broadly applied to generate not only human BrM cell lines but also mouse BrM cell lines from the main sources of brain metastases, including breast, lung, renal cancer, melanoma and colorectal cancer among others, and representative of the most frequent oncogenomic profiles from each tumor type [3, 4, 6–10]. In addition, mouse BrM cell lines could be also used to study the contribution of the microenvironment by inoculating them into genetically engineered mouse models (GEMMs) (Fig. 3.1b). The use of these experimental models to study the last step of metastasis, brain colonization, has generated a significant amount of knowledge about the underlying biology by reporting multiple mediators of brain metastasis that have been validated in human samples [1, 3–5, 10–15]. Few of them have been translated into experimental therapeutic interventions with positive results, which later have been translated into clinical trials [3, 10].

In spite of the success of organotropic models, alternative and complementary approaches must be incorporated to preclinical research. For instance, models that generate spontaneous brain metastasis from orthotopic injections or from spontaneously developed primary tumors are highly needed. The significant inefficiency, the time required for detecting brain metastasis, and the limitation imposed by the faster growth of the primary tumor are all caveats that have prevented their use [16–18]. In addition, in order to incorporate the higher degree of genomic complexity in human cancer, it is mandatory to incorporate human brain metastasis through patient-derived xenografts (PDX) models [19–23]. However, their main caveats are that they require immunosuppressed hosts and they are not easy models to incorporate genetic manipulations.

In general, the field has been studying naive brain metastases when patients are usually heavily treated with neurosurgery, radiation, chemotherapy, targeted therapies, and immunotherapies. The next generation of brain metastasis preclinical models should include relevant therapies to validate the knowledge generated with naive models and to address critical questions including treatment resistance.

In addition, surrogates of the BBB have been studied not only to functionally validate molecular mediators required to cross the vascular barrier [1] but also to test drug permeability [3] (Fig. 3.1c). Brain organotypic cultures in which BrM cells are plated on the surface (Fig. 3.1d) or are already present after processing brains with established metastases (Fig. 3.1e) offer a good alternative to evaluate scientific hypothesis before testing them in vivo [3, 4, 10, 24, 25]. The main advantages of organotypic cultures are that they contain the brain microenvironment, which allows more in-depth studies, and that they are compatible with both human and mice tissues, in which both genetic and pharmacologic approaches could be tested.

Local Therapies in Experimental Models of Brain Metastasis

In spite of the broad use of neurosurgery to treat patients with brain metastasis, this approach has not been incorporated into experimental models. Given recent experimental protocols applied to other brain tumors [26], it is highly desirable that this clinically relevant model gets incorporated into brain metastasis research.

Recent clinical trials using whole brain radiation therapy (WBRT) have questioned the interest of this approach, given the limited benefit for patients and the negative impact on neurocognition [27–30].

Although limited scientific reports have addressed the efficacy of WBRT to challenge brain metastasis viability, their conclusions include the limited therapeutic benefit on established metastases.

As demonstrated clinically with the use of preventive WBRT on small-cell lung cancer (SCLC) patients [31–33], experimental models have confirmed that treating micrometastasis is more effective than treating established metastases [34, 35]. In a triple-negative breast cancer (TNBC) model, 88% reduction of micrometastases was observed upon delivery of a fractionated dose consisting of ten sessions of 3 Gy each. In contrast, only 55% tumor reduction was observed in macrometastases [34]. Similarly, when a single dose of radiation was applied 5 days after cancer cell injection, a 70% reduction of brain metastases was reported [35]. However, if radiation was delayed 3 weeks and applied once brain metastases from the breast cancer cell line MDA-IBC3 were detected, responses were minimal [35]. Modelling responses to WBRT using in vitro approaches suggest that clonogenic growth (oncospheres) faithfully predict the low responses found in vivo [35]. In fact, c-Met is among the enriched genes in oncospheres [36]. When its expression is targeted, clonogenic growth, which is not sensitive to radiation, becomes affected. In vivo, targeting c-Met sensitizes MDA-435 to radiation not only in the brain but also in extracranial tumors, which are intrinsically more sensitive to the application of this therapy [36]. Results from these works suggest that the brain microenvironment might offer clues to the resistance of brain metastasis to radiation. Interestingly, when WBRT was applied to a naive brain before inoculation of cancer cells, tumor cells inoculated afterward experienced superior growth ability [37].

Similarly, breast cancer cells obtained from brains treated with radiation that were later cultured ex vivo did not reproduce their initial resistance in vivo [34]. Furthermore, upon reinjection into mice, the resistance of cancer cells to WBRT reappeared [34]. Mathematical models predicted that response of brain metastases to radiation could be improved by doses more than 20 Gy [35]. However, an experimental protocol of 30 Gy fractionated in ten doses of 3 Gy is enough to disrupt the generation of Dcx+ immature neurons from neural stem cells [34], discarding the possibility of providing higher doses, given the associated neurotoxicity. Alternative approaches to minimize the impact of radiation on neurocognition have been validated experimentally. Using metastasis-free mice subjected to WBRT or WBRT with hippocampal sparing (HSI, hippocampal sparing irradiation), radiation-induced toxicity was studied at both cellular and behavioral levels [38]. All mice (control, WBRT, WBRT + HSI) did well in non-specific neurocognitive tests, while differed in those involving the hippocampus. Specifically, an increased deficit in spatial memory was detected given that 40% of mice receiving WBRT failed the object placement task, while only 14% do so in the non-irradiated and HSI groups. If more time is given to perform the analysis, further challenging memory, 70% of the animals that received WBRT failed versus 45% of those receiving HSI and 33% of controls. Interestingly, hippocampal tests that do not involve neurogenesis were not altered upon WBRT [38]. Behavioral tests correlated with cellular findings, including increased cell death and absence of proliferation in the dentate gyrus, which has increased levels of microglia [38].

Experimental models recapitulate the lack of major benefit with WBRT reported by recent clinical studies and suggest that alternative approaches to deliver radiation could be better, as confirmed by the application of stereotactic radiosurgery (SRS) [39]. Nonetheless, identification of the molecular mediators of radio resistance associated with WBRT in vivo and the development of radio sensitizers will facilitate a more personalized approach to its application based on potential biomarkers.

Systemic Therapy in Experimental Models of Brain Metastasis: Chemotherapy and Targeted Therapies

The penetration of many systemic chemotherapeutic agents into the brain has been proved to be limited despite the assumption that the BBB is disrupted in brain metastasis and modified into a blood-tumor barrier (BTB). Paclitaxel and doxorubicin, two potent chemotherapies used in cancer, did not reach therapeutic levels in two experimental breast cancer brain metastasis models and were ineffective in treating brain metastases, despite higher accumulation of these two agents in the lesions compared to normal brain tissue [40]. This increased permeability of the BTB has been associated with alterations in pericyte subpopulations, specifically an increase of pericytes expressing desmin, as shown in different experimental brain metastases derived from breast cancer, including triple-negative, HER2+ and inflammatory breast cancer [41]. However, these drug concentrations remain insufficient to exert cytotoxic effects compared to that observed in peripheral metastases derived from the same model [40], proving that BBB-permeable agents are needed to target cancer cells in this secondary organ. In this regard, temozolomide, a well-known alkylating agent used for the treatment of primary brain tumors that penetrates the BBB, has been shown to be effective in preventing brain metastasis from a TNBC brain metastasis model expressing low levels of MGMT [42]; these results have not been successfully translated into patients [43]. However, these clinical studies have included temozolomide therapy for established macrometastases, so the use of this therapy as a preventive strategy has not been explored yet.

The BBB not only imposes a limitation to chemotherapeutic agents but also other drugs targeting specific molecular alterations from key oncogenic signaling pathways in cancer. Side-by-side assessment of drug efficacy of two PI3K/mTOR inhibitors (brain-permeable GNE-317 and nonpermeable GDC-0980) by in vivo two-photon microscopy in an experimen-

tal melanoma brain metastasis model showed effective targeting of brain metastases only by the brain-penetrating inhibitor [44]. BKM120, another selective PI3K inhibitor shown to be BBB-permeable, was effective in reducing brain metastasis incidence in 50% of the sample population when several HER2+ human breast cancer cell lines were implanted orthotopically or injected intravenously [45], suggesting that targeting the PI3K-AKT-mTOR pathway with brain-penetrating small molecules could be an effective treatment for brain metastasis (Table 3.1).

Around 18% of patients diagnosed with brain metastasis are eligible for targeted therapies, specifically those harboring molecular alterations in their primary tumor: HER2+ breast cancer, EGFR-mutant and ALK-translocated lung cancer, and BRAF-mutant melanomas, all of which have shown positive intracranial response to different targeted agents that are both under clinical development or Food and Drug Administration (FDA)-approved [46]. Preclinically, these results have been recapitulated with different experimental mouse models. Lapatinib has been shown to delay brain metastases growth in some HER2+ breast cancer models in a preventive scenario [47]; however, established intracranial lesions from other models are resistant to trastuzumab and lapatinib treatment while orthotopic implantation (i.e. fat pad) of the same cells does respond to both treatments [48]. Efforts to overcome this resistance have resulted in combination therapies of anti-VEGFR2 antibody DC101 together with trastuzumab and/or lapatinib, resulting in more than fourfold survival benefit of the triple combination treatment compared to untreated control mice [48]. In this same line, targeting of other tyrosine kinases related to the pathway like HER3 with the monoclonal antibody LJM716 reduces brain metastases and increases survival significantly in a HER2+ breast cancer model compared to treatment with trastuzumab or pertuzumab alone, which do not give any benefit compared to the untreated control group [49], reflecting the need of targeting oncogenic pathways through several mediators for overcoming treatment-derived drug resistance (Table 3.1).

The use of EGFR tyrosine kinase inhibitors (TKIs) for patients with advanced EGFR-mutant non-small-cell lung cancer (NSCLC) has resulted in positive intracranial response apart from inhib-

Table 3.1 Use of preclinical models to test targeted therapies

Compound	Target	BBB permeability	Preclinical model	Setting	Result	Ref
GNE317/GDC-0980	PI3K/mTOR	Yes/No	Melanoma (A2058)	Interventive	+/–	[44]
BKM120	PI3K	Yes	HER2+ breast cancer (MDA-MB-453/BT474)	Preventive	+	[45]
Lapatinib	HER2	Yes	HER2+ breast cancer (MDA-MB-231-BR-HER2)	Preventive	+	[47]
Lapatinib + trastuzumab	HER2	Yes/?	HER2+ breast cancer (BT474)	Interventive	–/–	[48]
Trastuzumab/pertuzumab	HER2	?/?	HER2+ breast cancer (BT474)	Interventive	–	[48]
Lapatinib/trastuzumab + DC101	HER2/ VEGFR2	Yes/?/?	HER2+ breast cancer (BT474)	Interventive	+	[48]
Trastuzumab/pertuzumab + LJM716	HER2/HER3	Yes/?/?	HER2+ breast cancer (BT474)	Interventive	+	[49]
Rociletinib/osimertinib	$EGFR^{MUT}$	No/Yes	$EGFR^{MUT}$ lung cancer (PC9)	Interventive	–/+	[51]
Crizotinib/alectinib	ALK	No/yes	EML4-ALK variant 5a lung cancer (A925LPE3)	Interventive	–/+	[55]
Entrectinib	ALK/ROS1/ TRK	Yes	EML4-ALK (NCI-H2228)	Interventive	+	[56]

iting extracranial disease thus increasing overall survival [50]. However, preclinical studies, including therapies for brain metastases from this particular primary tumor, are scarce. Osimertinib, a third-generation EGFR TKI selective for EGFR-TKI-sensitizing mutation (EGFRm) and T790M resistance mutations approved in 2017 for clinical use, showed greater penetration of the BBB than gefitinib, rociletinib, or afatinib [51]. It induced sustained tumor regression in an EGFRm-NSCLC brain metastasis experimental model at clinically relevant therapeutic doses while rociletinib did not (Table 3.1), and could potentially overcome resistance to previous treatment with EGFR-TKIs as shown by patients included in the AURA phase I/II study (NCT01802632) [51].

ALK-translocated lung cancer patients have shown positive responses to the first-generation TKI crizotinib, although intracranial response was only achieved with BBB-permeable next-generation TKIs like ceritinib, brigatinib, and alectinib due to suboptimal accumulation of crizotinib in the brain [52–54]. These responses have been faithfully recapitulated preclinically with an EML4-ALK variant 5a lung adenocarcinoma brain metastasis model sensitive to both crizotinib and alectinib at the primary tumor site, but resistant to crizotinib and sensitive to alectinib in the brain [55] (Table 3.1). In spite of these advances, progression-free survival (PFS) of patients receiving these TKIs does not exceed 15 months. Drug resistance developed through prolonged treatment thus remains as an unmet need and novel small molecule inhibitors targeting resistant ALK-dependent brain metastases are necessary. Studies with next-generation ALK inhibitors such as lorlatinib and brigatinib are promising. Entrectinib, an orally bioavailable potent inhibitor of ALK, ROS1 and TRK family kinases, has been reported to induce significant reduction of intracranially implanted tumors from EML4-ALK rearranged NSCLC increasing mice survival in more than 70% [56] (Table 3.1). Future clinical trials could open the way to a drug potentially suited to treat brain metastases from several molecularly defined primary tumors.

Melanoma brain metastasis patients also benefit from targeted therapies, mainly BRAF V600E TKIs dabrafenib and vemurafenib [57–59]. Preclinical models of brain metastasis, including these therapies, are limited. Several BRAF V600E mutated melanoma human melanoma cells have been shown to generate experimental brain metastases [60]. Vemurafenib-resistant melanoma cells generated in vitro show distinct expression profile to vemurafenib-sensitive cells but do not change their ability to colonize the brain despite their increased ability to metastasize to the lung and the liver [60]. Since 50% of melanoma brain metastasis results from BRAF-V600E-mutated primaries, new experimental models incorporating this molecular alteration and targeted therapies are needed to study metastatic spread to the brain in the skin cancer with highest death rates.

Unbiased Screens for Brain Metastasis Mediators

In Vitro Transcriptomics

Metastatic colonization is a multistep process that enriches disseminated cancer cells through positive and negative selection from an initial cellular pool derived from the primary tumor. Consequently, metastatic lesions will be richer in cancer cells with all the attributes required to reach and colonize the target organ. This has been the rationale for the development of organotropic metastatic derivatives that are established through multiple rounds of in vivo selection (Fig. 3.1a).

In order to dissect brain tropism at the molecular level, comparisons between P cell lines, without the ability to target the brain, and BrM cells were performed. This approach has been applied to breast cancer [1] and lung cancer models of brain metastasis [5] (Fig. 3.2a). Transcriptomic analysis of P versus BrM cells growing in vitro reflects significant differences between them. Although the overlap of differentially expressed genes among different models is more limited [4], upregulated genes, potential mediators of brain metastasis tro-

pism, or downregulated genes, potential brain metastasis suppressors, were successfully validated in functional experiments using in vivo brain metastasis assays and in human samples, where their increased levels at the primary tumor correlate with a higher risk of brain metastasis incidence. Many of the genes found with this approach mediated the ability to cross the BBB [1, 12, 13, 15] or interactions with the brain microenvironment [4, 10, 11] (Fig. 3.2a).

For instance, a 17-gene signature named brain metastasis signature (BrMS), obtained by comparing two different ER⁻/HER2⁻ breast adenocarcinoma models tropic to the brain (MDA231-BrM and CN34-BrM) respect to their parental cell lines, was sufficient to predict brain relapse when applied to three independent patient cohorts [1]. Among BrMS genes present in cancer cells, the α2,6-sialyltransferase encoded by *ST6GALNAC5* was selected. Mechanistic studies

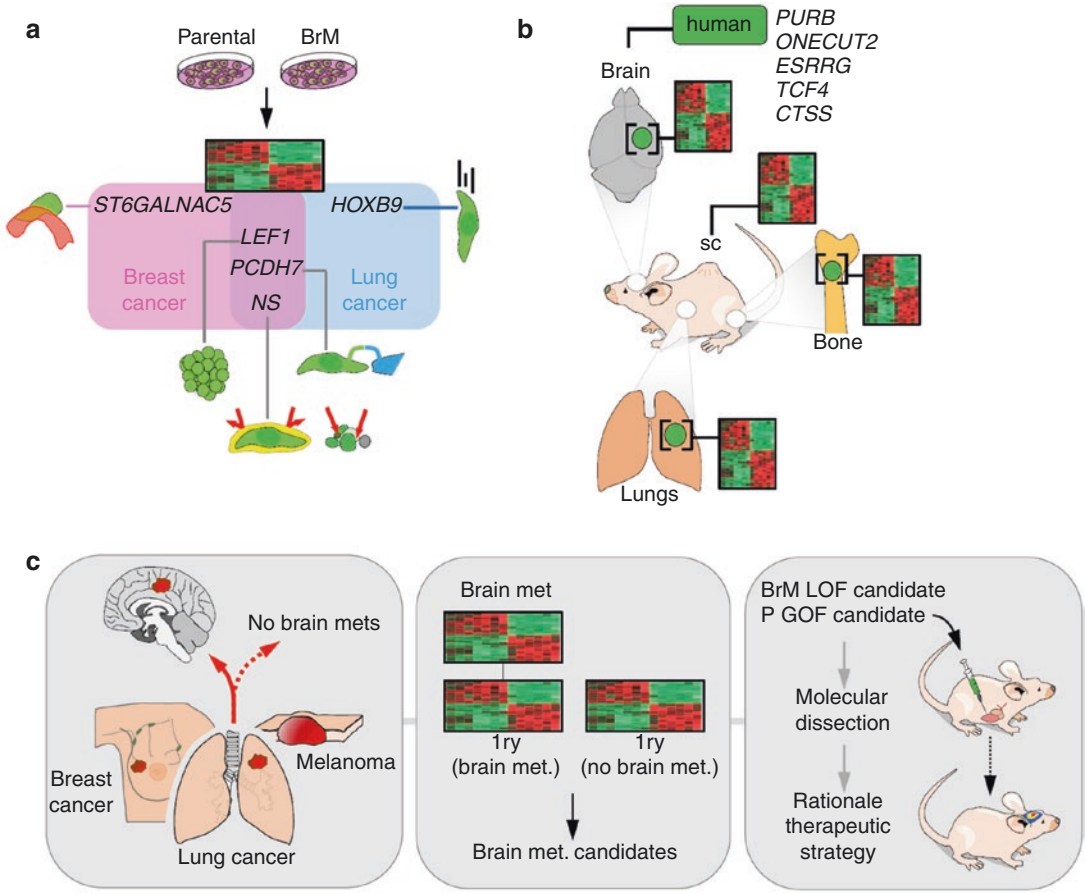

Fig. 3.2 Use of preclinical models to dissect the molecular regulation of brain metastasis. (**a**) Parental and brain metastatic derivatives (BrM) have been interrogated in vitro. Analysis of differentially expressed genes shows not only cancer-type specific but also commonly deregulated mediators of the disease (LEF1, PCDH7, NS) involved in a variety of mechanisms required for brain colonization. (**b**) Brain metastases have been interrogated in situ and compared with orthotopic and subcutaneous tumors and metastases growing in other organs. These studies not only identified potential mediators of brain metastases when human cancer cells were analyzed but also allowed evaluating the tumor microenvironment by analyzing mouse genes. (**c**) Evaluation of human samples, including primary tumors and brain metastasis, can allow identification of candidate genes that may contribute to brain metastasis formation. In order to functionally validate candidate genes, loss of function (LOF) and gain of function (GOF) approaches can be applied using preclinical models. These mechanistic assays in experimental models will help improve therapeutic strategies

proved that cancer cell surface decoration with 2–6 sialyl groups was required to increase the ability to cross the BBB [1].

In contrast to breast cancer, lung cancer usually disseminates fast. A Wnt-dependent program is responsible for facilitating the aggressive dissemination of lung cancer to multiple organs including the brain [5]. Two lung adenocarcinoma models (H2030-BrM and PC9-BrM) tropic to the brain were used to identify key components of the Wnt pathway. LEF1 increases the ability of BrM cells to grow in spheres, which is a surrogate of metastasis-initiating capabilities, while HOXB9 is required for a superior migratory behavior that is necessary for brain colonization [5] (Fig. 3.2a). Although both requirements are critical for brain metastasis, they are equally important for bone metastasis [5].

In Situ Transcriptomics

In vitro unbiased screens to identify mediators of brain metastasis have been complemented with the analysis of transcriptomes in situ [15, 61–63] (Fig. 3.2b). The rationale of this alternative approach is that there may be important mediators of brain metastasis not permanently but transiently induced in cancer cells tropic to the brain. In fact, these analyses confirm that there are transcriptomic modifications only manifested when the cancer cell is studied in a given organ. Breast, lung, melanoma, and colon cancer cells were grown as either subcutaneous tumors, at the orthotopic location according to the origin of the cancer cell, or in the brain after intracarotid injection [61]. Differentially expressed genes show that the transcriptome of cancer cells does not change significantly when grown at the subcutaneous location or in the orthotopic location. However, when the same cancer cells are grown in the brain, their transcriptomic profile diverges from those obtained at other locations (in vitro, subcutaneous, orthotopic) and become more similar to other cancer cell lines from different tumor types also obtained from the brain. Changes in gene expression correlate with altered methylome patterns. Since the methylome obtained from cancer cells growing in the brain also differs from the one obtained from orthotopic tumors [61], epigenetic mechanisms may play a critical role in reprogramming cancer cells during the adaptation to the brain microenvironment. Reprogramming of cancer cells growing in the brain involves the upregulation of neuronal genes [61]. This emerging expression pattern was suggested to be regulated by various transcription factors, including *PURB*, *ONECUT2*, *ESRRG*, and *TCF4*, that show reduced promoter methylation in brain metastatic lesions.

A similar approach comparing different organotropic cell lines including a lung metastatic (LM) derivative, a bone metastatic derivative (BoM), and a BrM one derived from the same parental $ER^{-}/HER2^{-}$ breast cancer cell line (MDA231) was used to evaluate in situ differential expression patterns of proteases and their inhibitors specifically [15]. Transcriptomic differences among metastatic cells in different organs are amplified along the process of organ colonization, suggesting that the transcriptome of cancer cells reflects organ adaptation [15]. These approaches also allow scoring the microenvironment by excluding human genes derived from human cancer cells. Attending to the expression of mouse genes, the three organs evaluated (brain, bones, and lungs) cluster independently. However, the brain differs significantly more from lungs or bones than these two organs among themselves. When cancer cells initiate organ colonization to form micrometastases, they do not significantly alter the expression pattern of the organ compared to the naive one without metastasis. In contrast, at late stages (macrometastases), the organ transcriptome is significantly altered in the lungs, bones, and brain. Again, the degree of transcriptomic changes in lungs and bones is more discrete than that in the brain [15]. This could reflect the abundance of specific barriers in the brain that limit the growth of incoming metastatic cells compared to other secondary organs more similar to the primary tumor that may only require a limited adaptation of cancer cells to thrive.

Although the main findings of unbiased transcriptomic screens applied to brain metastasis

experimental models have been validated in patient samples [1, 5, 15], the inverse approach has not been equally investigated. Evaluating candidates obtained from unbiased screens in human samples using experimental models would allow testing their functional contribution to brain colonization as well as to dissect the underlying molecular regulation (Fig. 3.2c). Both considerations are key to rationalize more specific and effective therapies. Although the limited number of studies that have compared human and experimental transcriptomic screens found reduced overlap in terms of specific genes, pathways were partially conserved. This suggests that experimental brain metastasis models are valuable platforms for the identification of novel mediators of the disease and to test them functionally.

Noncoding RNA

In parallel to transcriptomic analyses, expression profiles of small noncoding RNAs, mainly miRNAs, have been developed to identify mediators of brain metastasis. Unbiased screens comparing organotropic cell lines in vitro [64, 65], their exosome content [66], and human samples have been performed [67–70]. Differentially regulated miRNAs between primary tumors with or without brain relapse or directly at brain metastases [67, 68], as well as liquid biopsies from the cerebrospinal fluid (CSF) [70], have been evaluated to validate the importance of selected candidates.

miRNAs functionally validated in experimental models include modulators of extravasation through the BBB. High levels of miR-181c contained in extracellular vesicles (EVs) from breast cancer cell lines metastatic to the brain are responsible for downregulating the expression of *PDPK1*, which is an essential factor for actin dynamics by mediating the phosphorylation of cofilin. Defective actin dynamics impairs intracellular trafficking of multiple proteins required for the maintenance of brain endothelial cell intercellular junctions such as tight junction proteins and N-cadherin [66]. This finding confirms that miRNA enriched in EVs secreted from primary tumors could influence vascular barriers to facilitate extravasation of cancer cells [71]. In addition, miR-509 downregulation in human brain metastasis as well as experimental brain organotropic breast cancer cell lines allows maintenance of high expression levels of RhoC, which is required to produce MMP9, an enzyme targeting endothelial cell-junctions of the BBB, and TNFα [72], which plays an important role for increased BBB-permeability in sepsis [73].

miRNAs continue to be required once metastatic cells have crossed the BBB. Re-initiation of the secondary tumor requires stem cell-like properties [74], which could be provided by the expression of pluripotency factors. Among them KLF4 is required for the initiation of breast cancer brain metastasis. To maintain high expression levels of *KLF4*, $CD24^{-}/CD44^{+}/ESA^{+}$ brain metastasis cancer stem cells downregulate miR-7 [64]. In addition, miRNAs from the microenvironment also play an important role in colonization. Reactive astrocytes, which closely interact with cancer cells, are highly secretory cells known to produce EVs [75]. miR-19a-containing EVs produced by astrocytes are transferred to cancer cells. miR-19a downregulates *PTEN* expression leading to the attraction of $CCR2^{+}$ macrophages/microglia as a consequence of the increased production of CCL2 from $PTEN^{low}$ cancer cells [76].

The brain microenvironment could be also modulated by cancer cells residing at the primary tumor through the production of miR-122-contained EVs. miR-122 targets enzymes involved in glucose metabolism. Decreased levels of *PKM2* and *GLUT1* induced by miR-122 lead to the reduction of glucose uptake and consumption by brain astrocytes, which increases the available extracellular pool of this nutrient, thus benefiting incoming cancer cells [77].

Although mesenchymal traits are required at various steps of the metastatic process, some experimental models show an additional step that takes place upon organ colonization. The process of mesenchymal to epithelial transition (MET) is regulated by miR-200s family [78]. Liquid biop-

sies from the CSF of patients with parenchymal or leptomeningeal metastases could be separated from noncancerous biopsies by a combination of several miRNAs contained in this family, including miR-10b, miR-21, miR-200a/c, and miR-141 [70]. miR-141 is required to mediate MET in breast cancer brain metastasis [65].

These transcriptomic screens should be complemented with others that have interrogated the epigenome [79–81] and the proteome [82–90]. Comparative analysis of omic approaches will offer a more accurate view of the regulatory mechanisms and pathways that are key in experimental models, where investigational therapies can be tested, and in humans.

Advanced Modeling of Brain Metastasis in Mice

Preclinical models extensively used for studying brain metastasis include cell line-derived xenotransplants, generally based on organotropic human cell lines that preferentially target the brain and are implanted intracardiac or intracranially in immunodeficient mice. Syngeneic mouse cell lines with brain tropism have been used to address the interaction of cancer cells with the brain microenvironment or the immune system [1, 4–7, 10, 15, 41, 76, 91, 92]. However, these models of induced brain metastasis have limitations when recapitulating the course of the human disease, where brain metastases are spontaneously generated in the presence of a primary tumor and generally other extracranial metastases.

Spontaneous Models of Brain Metastasis

Genetically engineered mouse models (GEMMs) that result in spontaneous brain metastases are limited. Two genetic mouse models of melanoma based on different oncogenic drivers have been reported (Fig. 3.1f). The MT/ret transgenic mouse model resembles the process of malignant transformation in human melanoma, resulting in metastases to distant organs including the brain. This process is accompanied by a progressive increase in expression and activity of the *ret* transgene, leading to hyperactivation of the MAPK-related pathway [16]. The PI3K-AKT-mTOR pathway has been shown as a viable therapeutic target in several brain metastasis preclinical models pharmacologically [44, 45]. Genetically, a melanoma mouse model with activated AKT1 in the context of BRAF V600E and silenced *INK4A-ARF*, generated spontaneous brain metastases recapitulating the human disease, and this metastatic capacity was augmented by additional *PTEN* silencing [17] (Fig. 3.1f). This model allows functional validation and characterization of PI3K-AKT-mTOR pathway as key in brain metastasis biology. Although lung cancer is the most common source of brain metastases, GEMMs of lung cancer scoring incidence of metastatic spread to this secondary organ are scarce. A GEMM of small-cell lung cancer (SCLC), a subtype of lung cancer with high incidence of brain metastasis, has been reported to generate spontaneous intracranial lesions from neuroendocrine lung tumors that were engineered by conditional somatic inactivation of *Rb1* and *Trp53* in lung epithelial cells [18]. These tumors gave rise to extrapulmonary metastases including the brain and resembled human SCLC both morphologically and immunophenotypically [18] (Fig. 3.1f), which allows more reliable translation of preclinical results into clinical approaches. GEMMs that faithfully recapitulate the human disease will open new scenarios for brain metastasis research such as the study of prevention. Mouse models representing primary tumors with high incidence of brain metastasis like non-small-cell lung cancer, HER2+ and triple-negative breast cancer are urgently needed.

Patient-Derived Xenografts

The use of patient-derived xenografts (PDXs) for modeling brain metastasis during the past few years [19, 20, 23, 93] has opened new possibilities for personalized medicine to be applied to patients with cancer dissemination to the brain

(Fig. 3.1g). PDXs from patients' brain metastases from different primary sources (non-small-cell lung cancer (NSCLC) [20], several subtypes of breast cancer [19, 23], and melanoma [93]) have been used to establish preclinical mouse models by engraftment of cells derived from fresh surgical samples in immunodeficient mice. In all studies, PDXs show highly similar histopathological features, genetic or functional properties when compared to the parental human brain metastasis, thus proving that PDXs are a reliable resource for recapitulating the human disease. Based on these similarities, PDXs have been used for evaluating the efficacy of targeted therapies or to perform low-throughput drug screenings. In vitro tumor spheres from PDXs from NSCLC brain metastases that maintain their in vivo brain metastatic potential have been established for this purpose [20]. Five PDX-derived tumor spheres were screened for 20 agents targeting commonly altered oncogenic pathways in NSCLC such as EGFR, MET, Mtor, and VEGFR. Efficacy of these agents varied among the different samples, indicating that each one relies on different oncogenic alterations and that personalized approaches based on PDXs will improve current therapies by predicting drug responses. In vivo, inhibition of the PI3K/mTOR pathway using a combined treatment with the PI3K inhibitor BKM120 and the mTOR inhibitor RAD001 (both able to penetrate the brain) resulted in durable tumor regressions in 3/5 PDXs of HER2+ breast cancer brain metastases [23], suggesting the potential efficacy of this combined therapy in the respective donor patients. In this same study, whole-exome sequencing of the PDXs and matched tumor samples from the donor patients showed that each PDX and its matched patient sample shared almost identical genetic alterations regarding copy-number variations and somatic mutation rate. Interestingly, the two non-responding PDXs and their matched patient specimens showed hypermutated genomes with enriched mutation frequencies in DNA-repair genes, suggesting that genomic instability is correlated with therapy resistance. Based on these observations, PDXs are not only a useful tool for drug testing, but also a valuable resource for evaluating biomarkers that predict response to therapy in the context of brain metastasis.

Future Challenges

Despite the efforts in improving currently available experimental models for brain metastasis, whether these models faithfully recapitulate the human disease is a matter of continuous debate. Intracardiac, intracarotid, or intracranial injection of brain tropic human or syngeneic cell lines are still the most commonly used preclinical models for studying the biology of the disease and developing novel therapeutic strategies for brain metastasis patients. Spontaneous brain metastases from GEMMs are still limited. Available GEMMs [16–18] generate aggressive primary or extracranial metastases, thus imposing an additional limitation since brain macrometastases are rare and clinically relevant stages of the disease cannot be easily observed in these models. Most PDXs maintain pathological features of the parental tumor—their increased heterogeneity clinically allows more personalized approaches. CRISPR/Cas9 technology will improve available models by introducing specific genomic alterations detected in human brain metastasis to dissect their functional contribution and test their importance as a therapeutic target. On the other hand, since most patients have been treated with multiple lines of therapy before brain metastases occur, experimental models that incorporate them will allow developing more realistic experimental studies, which will be further improved by the addition of local therapies such as neurosurgery and radiotherapy.

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Pathology of Brain Metastases

4

David J. Pisapia

Neuropathological assessment of brain metastases first and foremost establishes that a given intraparenchymal or meningeal lesion in fact represents metastatic disease and that all potential histological mimics have been ruled out. Second, determining the site of origin is paramount, not only if a primary site of disease has yet to be clinically or radiologically identified, but also in order to rule out a second malignancy in a patient with a known primary. Finally, the pathologist must ensure that appropriate molecular characterization of the metastasis is performed, when necessary, following guidelines that have been established for the relevant primary tumor type. We will consider each of these components to pathological assessment in this chapter.

Identifying Metastatic Disease

Intraoperative Consultation

Initial histological assessment of potential metastatic disease often first occurs during intraoperative consultation. The neuropathologist is typically guided by preoperative MRI findings suggesting that a metastasis is within the differential diagnosis. Metastases tend to be well circumscribed rather than infiltrative lesions, and they are usually T1-hypo to isointense and enhancing [1]. While multiplicity may also be a clue, up to 72% of patients with metastatic disease to the brain may present with a solitary mass [2]. Metastases overall are more common within the supratentorial compartment, in watershed areas, and at the gray-white junction [3]. Approximately 80% are located in the cerebral hemispheres and 15% in the cerebellum [4]. Certain tumor types may demonstrate anatomical predilection within the brain; for example, evidence suggests that renal cell carcinoma has a proclivity to involve the intraventricular compartment and choroid plexus [5]. Associations between particular primary tumor types and the vascular territory in which metastases are more likely to be found have been noted. For example, melanoma is relatively less common in the cerebellum and breast cancer is less common in the posterior cerebral arterial vascular distribution [6].

Once it is established that metastatic disease lies within the radiological differential diagnosis, imaging of the chest, abdomen, and pelvis may be performed prior to a brain biopsy or resection in an effort to identify the primary malignancy and/or a more readily accessible metastatic deposit for biopsy. Among patients with metastatic cancer, cancers with higher rates of brain involvement include melanoma (28%),

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small-cell carcinoma of the lung, lung adenocarcinoma, and non-small-cell carcinoma of the lung (not otherwise specified), each with approximately 25% of patients developing brain metastases [7]. Other cancers with a relatively high proportion of patients experiencing dissemination to the brain include squamous cell carcinoma of the lung (15%), renal cell carcinoma (11%), carcinoma of the breast (8%), testicular cancer (7%), and esophageal carcinoma (5%, among patients with metastatic disease) [7].

With routine intraoperative squash preparation and frozen section analysis, the histological distinction between metastatic carcinoma and primary glial neoplasms is usually trivial (Fig. 4.1). On squash preparation, carcinoma cells tend to cluster, display distinct cytoplasmic borders and may show prominent nucleoli (Fig. 4.1a, b). In the case of adenocarcinomas, intracellular vacuoles with mucin production may be seen. In contrast, most primary gliomas demonstrate spindled nuclei with fibrillar processes (Fig. 4.1f). On frozen section, the architectural features are valuable in distinguishing between the often pushing border between native brain parenchyma and carcinoma cells and the insidiously infiltrative nature of neoplastic glial cells (Fig. 4.2). Moreover, gland formation, squamous nests, or other epithelial characteristics are usually apparent on frozen sections. Challenges arise in the case of glial neoplasms, which may on occasion display epithelioid characteristics (Figs. 4.1e and 4.3). In particular, epithelioid glioblastoma and pleomorphic xanthoastrocytoma may sometimes mimic carcinoma, with dyshesive, plump cells predominating on squash preparation (Fig. 4.3a) or frozen section. At the same time, on occasion a seemingly diffusely infiltrative, perivascular distribution of markedly atypical carcinoma cells, such as those seen in pleomorphic carcinoma of the lung, can appear similar to an epithelioid glial malignancy (Fig. 4.3c). Immunohistochemical staining for GFAP (e.g., Fig. 4.3b) or TTF1 (e.g., Fig. 4.3d) may help resolve the differential (see also caveat with respect to TTF1 staining discussed below).

Additional histological ambiguity may be present in several circumstances. Tumors with a high nuclear to cytoplasmic ratio and small blue cell morphology present a diagnostic challenge at the time of frozen section with a differential diagnosis that includes metastatic small-cell carcinoma, lymphoma, glioblastoma with small cell features, central nervous system (CNS) embryonal tumors, and metastatic primitive neuroectodermal tumors derived from extracranial sites (Fig. 4.2). Complicating the picture for dural-based metastases is the possibility of atypical or anaplastic meningioma, which may also demonstrate epithelioid characteristics. Moreover, the rare phenomenon of meningiomas secondarily harboring metastases has been well documented, and neuropathologists should be alert to the possibility of two distinct cell populations appearing on the slide [8, 9]. Complicating the picture for patients with tumor predisposition syndromes such as von Hippel-Lindau syndrome (VHL) is an increased pretest probability for both metastatic disease and intracranial primaries. For VHL patients with a cerebellar lesion, the differential diagnosis may include both hemangioblastoma and metastatic renal cell carcinoma. Moreover, there may exist histological overlap on frozen section between the stromal cells of hemangioblastoma and the cytoplasmic clearing of renal cell carcinoma, clear cell type.

Metastatic melanoma deserves special mention in this discussion. While some of these tumors may demonstrate melanin pigment as a clue to the frozen section pathologist (Fig. 4.1c), melanin production is by no means specific for metastatic melanoma. In particular, for lesions arising within the extra-axial, meningeal compartment one must also consider primary melanocytic lesions of the CNS. As discussed later, with the advent of next generation sequencing techniques it is becoming easier to resolve this differential in difficult cases. Finally, for paraspinal tumors, or those mass lesions associated with cranial nerves, melanotic schwannoma may also enter into the differential diagnosis of pigmented lesions. The distinction between metastasis and

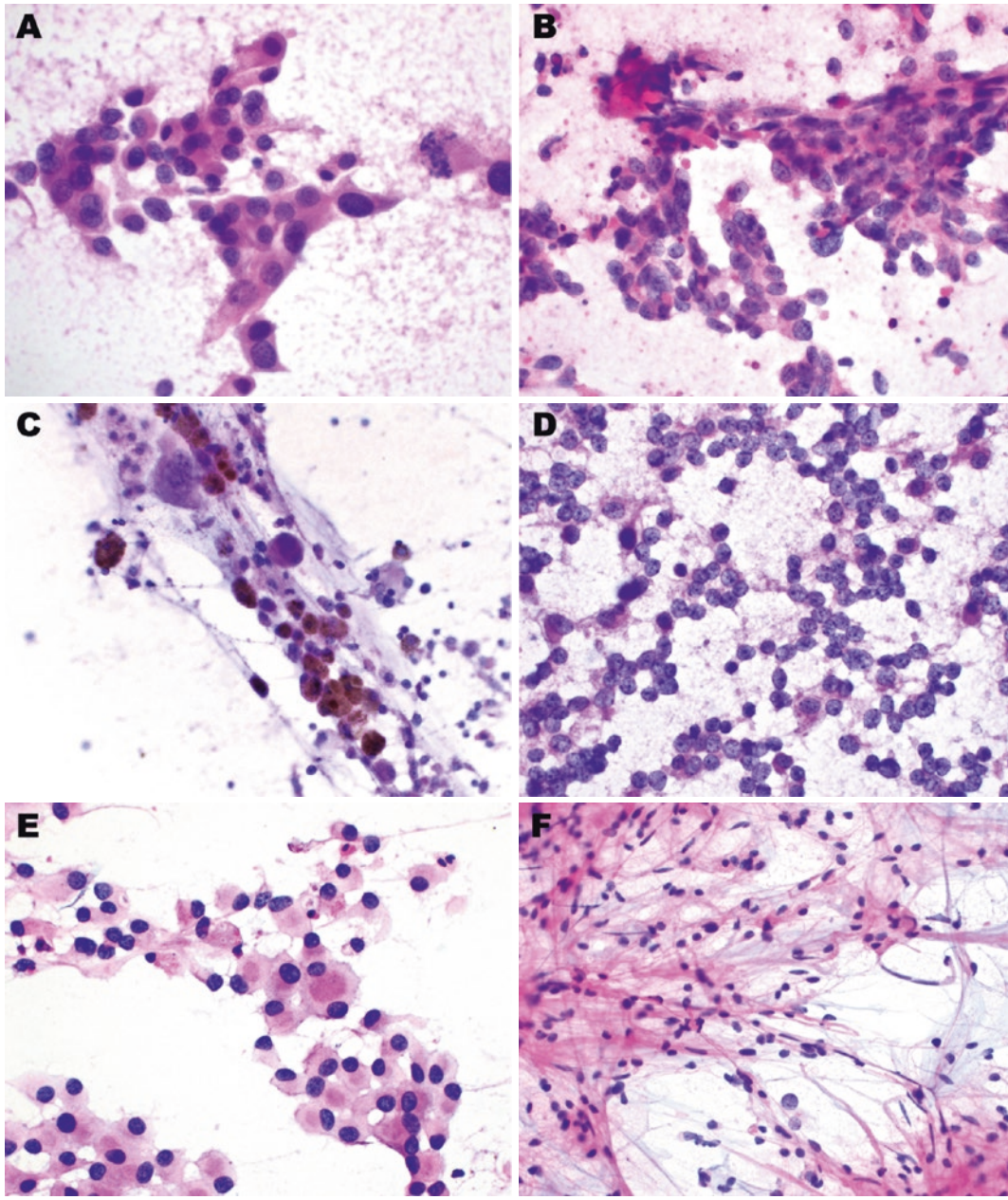


Fig. 4.1 Intraoperative squash preparation of lesional tissue often represents the first histological encounter with potential metastases. (**a**) H&E-stained squash prep of fresh tissue reveals clusters of polygonal epithelial cells with a clumped and cohesive smearing pattern. Cells may also demonstrate prominent nucleoli and intracytoplasmic vacuolization. This case represents metastatic adenocarcinoma of the lung. (**b**) A case of squamous cell carcinoma of lung origin, also demonstrating cellular cohesion. (**c**) Melanin pigment is clearly visible on this squash prep placing metastatic melanoma at the top of the differential diagnosis for intraparenchymal lesions, as well as primary melanocytic neoplasms of the CNS if the lesion is associated with the meningeal compartment. (**d**) The round regular nuclei and stippled chromatin pattern seen here is characteristic of neuroendocrine neoplasms, particularly pituitary adenoma for the neuropathologists; however, metastatic neuroendocrine neoplasms may also enter the differential here. (**e**) In this case of an astrocytoma with epithelioid and gemistocytic features, the histological distinction with metastasis may become more challenging. (**f**) Compare the rounded cytoplasmic features of panel E with the more characteristic fibrillar processes of less unusual neoplastic glial cells, seen here in a pilocytic astrocytoma. *All panels show H&E-stained squash preparations*

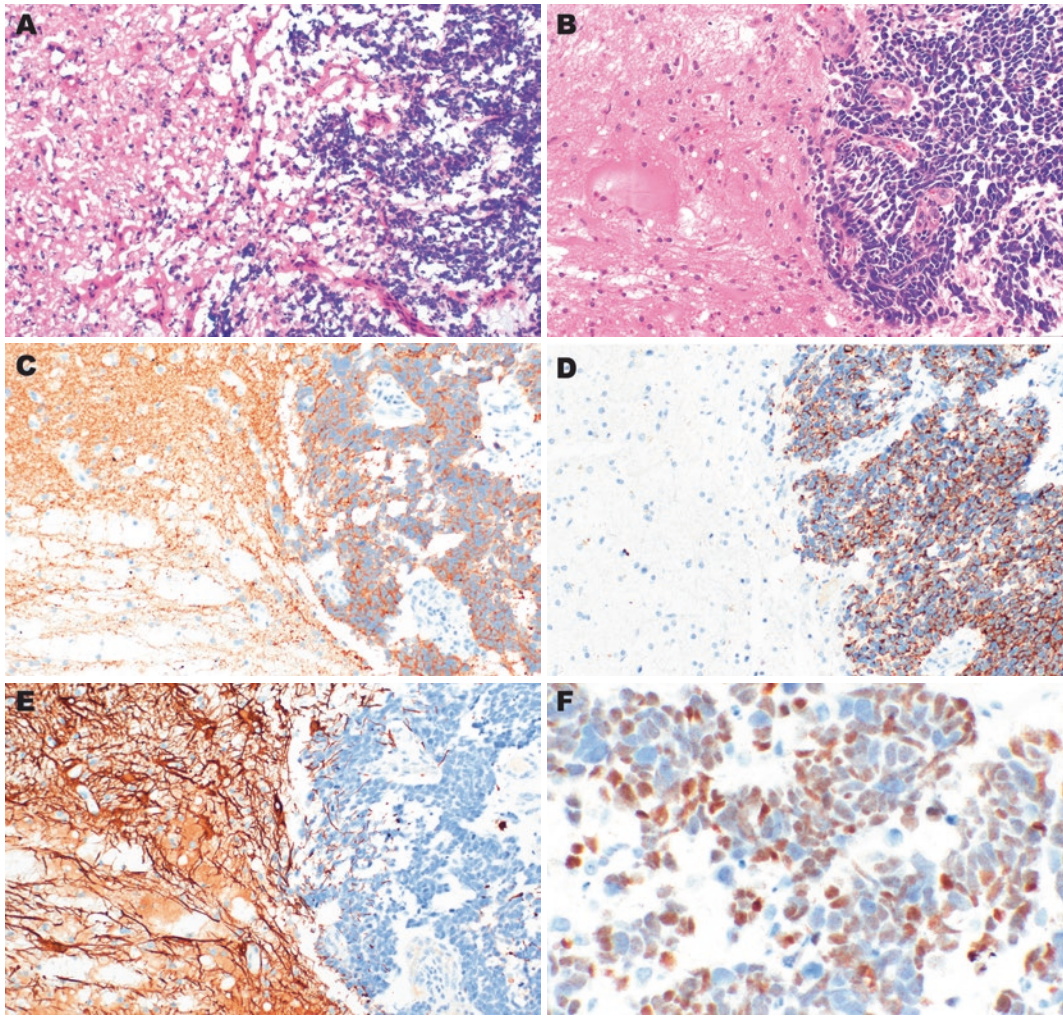


Fig. 4.2 Intraoperative frozen section of small-cell carcinoma of lung. (**a**) H&E-stained frozen section demonstrates a population of small blue cells with scant cytoplasm forming a well-demarcated border with adjacent brain parenchyma. The architectural features including the border itself is helpful since the cytologic differential may be broad on frozen section and could include lymphoma as well as glioblastoma with small cell features. (**b**) Cytologic features, such as the nuclear molding characteristic of small-cell carcinoma, are better appreciated here on an H&E-stained permanent section. (**c**–**f**) Immunohistochemical staining confirms the diagnosis with tumor cells showing labeling for synaptophysin (**c**) and cytokeratin 7 (**d**), an absence of labeling for glial fibrillary acidic protein (GFAP), which highlights the adjacent reactive brain parenchyma (**e**). TTF1 staining is also positive in tumor cells (**f**)

primary peripheral nerve sheath tumors or primary meningeal melanocytic lesions is obviously crucial to properly stage the patient's disease and determine further clinical management.

Rarer, but certainly relevant to the discussion, are de facto epithelial malignancies that arise as primaries within the intracranial compartment. For example, epidermoid cysts may undergo malignant transformation to squamous cell carcinoma, and primary intracranial teratomas can harbor secondary malignant carcinomas [10, 11].

Finally, in the sellar and suprasellar region, the neuropathologist is occasionally confronted with a differential diagnosis of pituitary adenoma versus metastatic carcinoma (Fig. 4.1d); assessment for metastatic neuroendocrine carcinomas often necessitates immunohistochemical stains.

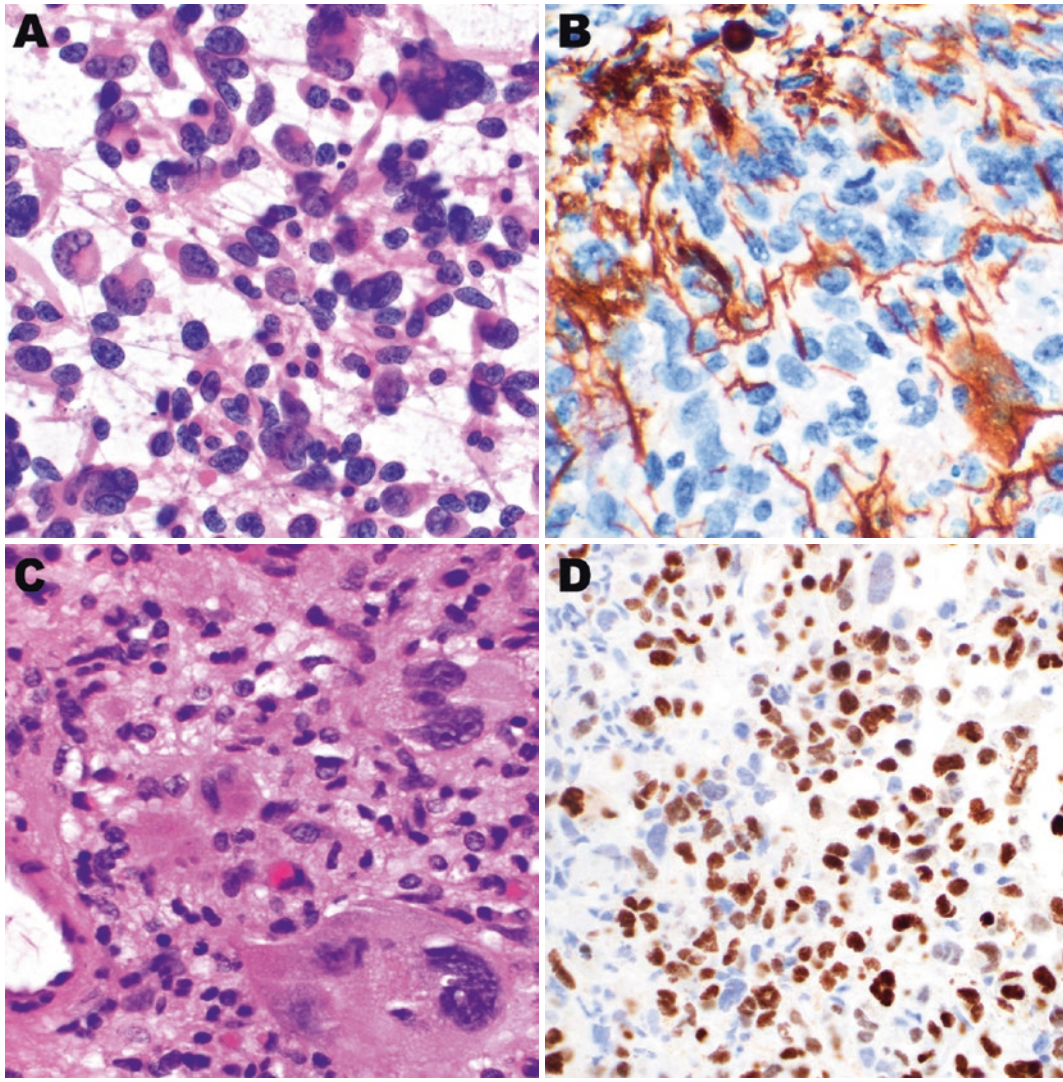


Fig. 4.3 Histological mimics of carcinoma such as epithelioid glioblastoma may present diagnostic challenges. (**a**) Intraoperative squash preparation of glioblastoma often includes highly pleomorphic cells. In this example, some cells demonstrate epithelioid features. Occasional glial processes are also present. (**b**) Immunohistochemical staining for glial acidic fibrillary protein (GFAP) reveals positive labeling in only some tumor cells, with others appearing to be negative. What are likely reactive astrocytic processes additionally can be seen in the background. (**c**) Occasionally, highly pleomorphic carcinoma cells may mimic glioma cells. Here, in a case of pleomorphic adenocarcinoma of lung origin, some cells appear to be diffusely infiltrating the brain. (**d**) Immunohistochemical staining demonstrates TTF-1 immunoreactivity in these cells, corroborating their origin from the lung

As an example from our own practice, a pituitary tumor histologically compatible with pituitary adenoma on hematoxylin and eosin (H&E)-stained sections demonstrated strong nuclear expression for Nkx3.1, confirming a prostatic metastasis in a man with known prostate cancer with neuroendocrine features.

Permanent Histology and Immunohistochemical Assessment of Brain Metastases

While a history of known primary malignancy is often provided to the pathologist, it is essential to confirm that the metastatic lesion is consistent

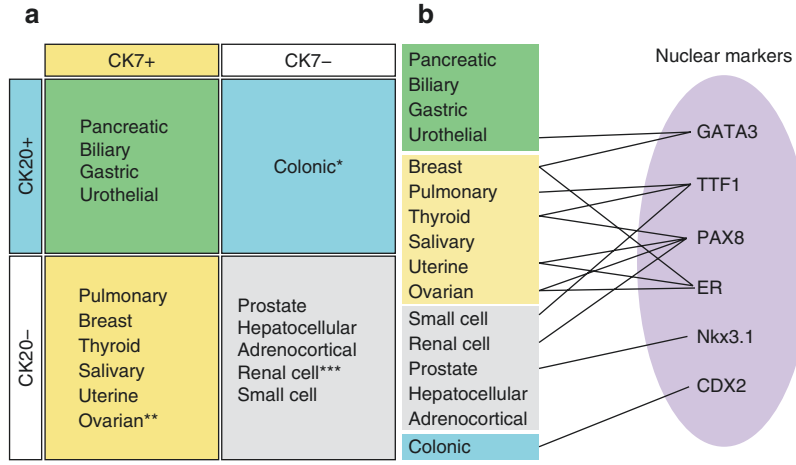


Fig. 4.4 Immunohistochemical workup of metastases to determine site of origin. (**a**) The cytokeratin profile of epithelial tumor cells can inform the likely site of origin. In particular, the pattern of CK7 and CK20 reactivity is often used to narrow down the differential diagnosis. (**b**) Further immunostaining with more specific markers such as transcription factors that show specificity for different cell types is now routinely used for diagnostic purposes. TTF1, thyroid transcription factor one (while TTF1 is the term commonly used for this protein, the encoding gene is properly referred to as Nkx2.1 or NK2 homeobox 1), GATA3 GATA binding protein 3, PAX8 paired box 8, ER estrogen receptor, encoded by ESR1, Nkx3.1 NK3 homeobox 1, CDX2 caudal type homeobox 2. *Higher stage and/or rectal location may correlate with increased CK7 expression. **Whereas ovarian serous adenocarcinoma is negative for CK20, mucinous ovarian neoplasms may exhibit CK20 labeling. ***Reactivity for CK7 is typically negative in clear cell renal cell carcinoma, but positive in chromophobe renal cell carcinoma

with the known primary or whether it represents a manifestation of a distinct primary neoplasm. In one study, the percentage of cancer patients ultimately demonstrating synchronous distinct neoplasms was shown to be 15–17% [12].

If hematoxylin and eosin (H&E)-stained slides are available from a prior biopsy or resection at the primary site, the histological features of the tumor may be directly compared to the metastasis, and in some cases morphological similarity serves as the gold standard to confirm the suspected site of origin. Even if a tumor is determined to be originating from a particular organ by immunohistochemical means (as discussed below), morphological assessment is important to determine which primary lesion seeded the metastasis in a patient with multiple primary lesions in that organ (e.g., in a patient with multiple lung or breast primaries).

Immunohistochemistry

Most pathology laboratories employ a battery of immunohistochemical stains, each with variable degrees of sensitivity and specificity to confirm a site of origin. Antibodies recognizing cytokeratin (CK) intermediate filaments of differing molecular weights are typically applied since many carcinomas demonstrate characteristic patterns of CK reactivity (Fig. 4.4a). For example, while colon adenocarcinoma typically labels for CK20, pulmonary adenocarcinoma demonstrates predominant staining for CK7. Those carcinomas arising from a peri-diaphragmatic location, for example, pancreatic carcinoma or gastric carcinoma, often display reactivity for both CK7 and CK20. A host of transcription factors with protein expression localized to the nucleus are also used to characterize the likely site of origin. Examples include Nkx3.1 (prostate) [13], TTF-1 (lung, thyroid) [14], CDX-2 (colon) [15], and PAX-8 (renal, Mullerian malignancies, and thyroid) [16] (Fig. 4.4b).

The utility of GATA binding protein 3 (GATA3) illustrates a few important principles regarding clinical use of transcription factor immunohistochemistry. While GATA3 had been identified as playing a role in T-cell lymphocyte development since the early 1990s [17] and its association with ER-positive breast cancer cell

lines was demonstrated as early as 1999 [18], its emergence as a clinically useful marker with routine and widespread use in pathology laboratories is much more recent (within the last 5 years) [19–21]. It is now recognized that GATA3 is a sensitive marker for most breast and urothelial carcinomas. However, iterative reevaluation of its specificity is subject to comprehensive tissue studies (evaluation over large numbers of tumor samples using tissue microarrays) or simply through close attention to clinical findings in unusual circumstances. Indeed, in addition to breast and urothelial malignancies, robust GATA3 expression is detected in a majority of paragangliomas (including pheochromocytoma), basal cell, adnexal, and squamous carcinomas of this skin, chromophobe renal cell carcinoma, choriocarcinoma, and mesothelioma, as well as less commonly in many other tumor types [21].

In an educational example from our own neuropathology service, a patient with a history of breast cancer and an intrasellar tumor was found to have a GATA3-postive epithelial neoplasm upon resection that was concerning for breast metastasis. Further investigation revealed that GATA3 labeling is in fact characteristic of gonadotroph-lineage pituitary adenomas as in this case (possibly due to cross reactivity with GATA2 protein), a finding that was later corroborated by other investigators [22]. Thus, as new "markers" are incorporated into the lab, it is essential to consider each case within its proper clinical context and to refrain from making assumptions about specificity or expected staining patterns in poorly characterized tumor types.

Other commonly used markers for the workup of metastatic disease include S100, HMB45, A103, and SOX10 (melanoma) [23], p40 (squamous cell carcinoma (SqCC), including SqCC of the lung) [24], and HepPar1, arginase-1, and glypican-3 (hepatocellular carcinoma) [25].

Again, because any one particular antibody may not demonstrate sufficient specificity, antibody panels may be required to confirm a site of origin. Finally, antibodies may be necessary to exclude the histological mimics mentioned above. For example, epithelioid astrocytic tumors typically display labeling for glial fibrillary acidic protein (GFAP; Fig. 4.3a, b) while meningiomas are classically positive for epithelial membrane antigen (EMA) and SSTR2 but negative for CK.

Stains must be interpreted in the appropriate context and pathologists must have familiarity with the limitations, cross-reactivities, and staining characteristics of each antibody clone used, including its performance characteristics in a particular laboratory. For example, CK AE1/AE3 antibody cocktails (commonly referred to as pan cytokeratin) may show extensive cross reactivity to astroglial antigens [26]. In rare cases, it may therefore be necessary to employ an antibody such as Cam5.2 to reliably distinguish between carcinoma and glioma. The morphological features in combination with immunohistochemical staining are usually sufficient to resolve aberrant pan-cytokeratin staining. It should be noted that certain antibody clones for TTF1 are known to react more promiscuously in glial tumors [27], and bona fide TTF1 expression is increasingly recognized in a range of mostly midline primary intracranial neoplasms, including pituicytomas, other neoplastic processes of the posterior pituitary gland [28], and chordoid glioma of the third ventricle, a lesion potentially associated with the organum vasculosum of the stria terminalis [29].

Beyond strict identification of a site of origin, ancillary immunohistochemical staining may be necessary for additional diagnostic, prognostic, or theragnostic purposes. In breast metastases, it is standard to assess the hormone receptor status for estrogen receptor (ER) and progesterone receptor (PR) as well as for the status of HER2 expression. These staining patterns are associated with recognized molecular subtypes of breast cancer including luminal (typically hormone receptor positive and HER2 negative), HER2-enriched (hormone receptor negative and HER2 positive), and triple negative breast carcinoma including basal-like tumors (hormone receptor and HER2 negative) [30]. In cases with ambiguous HER2 immunohistochemical labeling, FISH is employed to resolve the amplification status of this gene. At our institution, we employ guidelines developed by the American Society of Clinical Oncology and the College of American Pathologists for the reporting of ER, PR, and HER2 stains (Fig. 4.5e–h) [31, 32]. In prostatic adenocarcinomas, we also

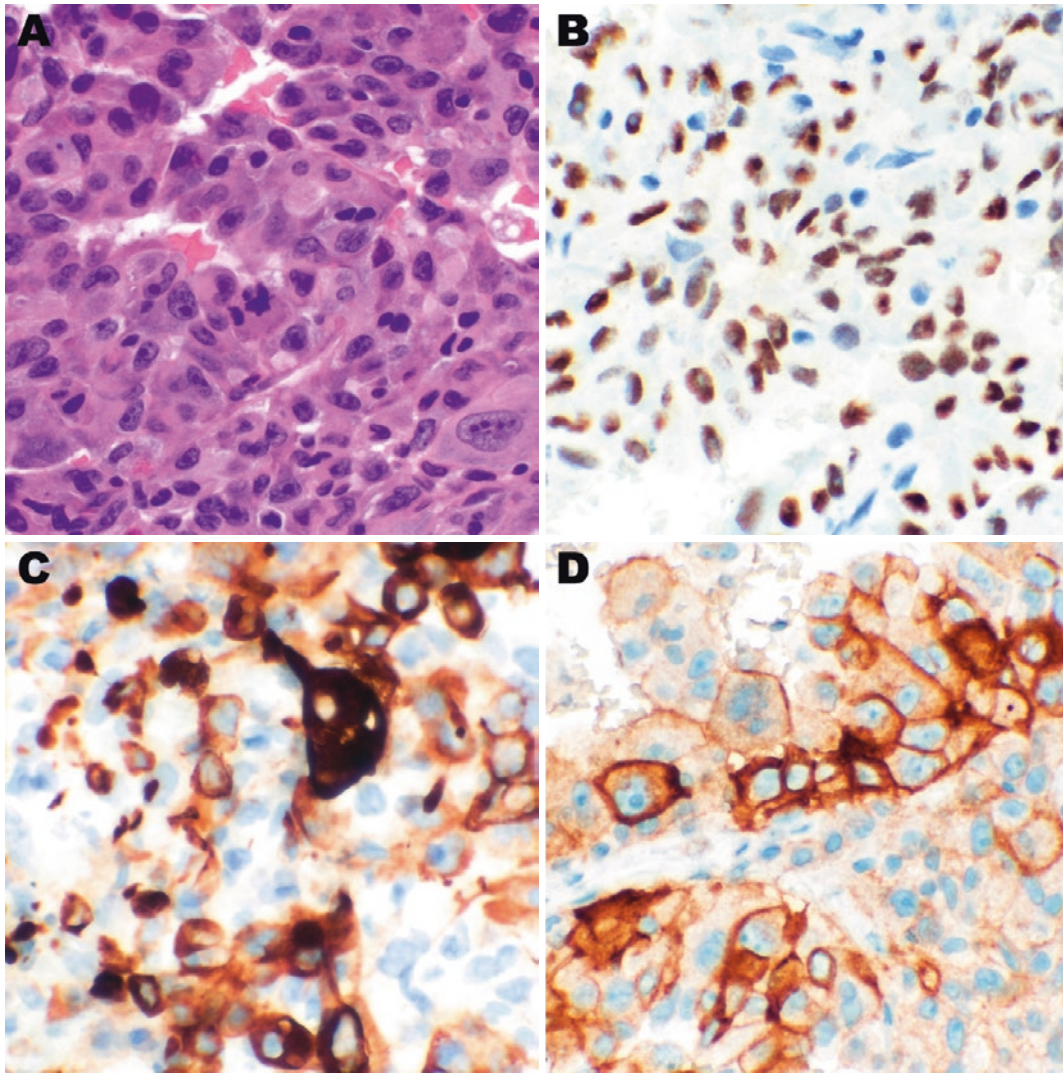


Fig. 4.5 Sample immunohistochemical workup including diagnostic and treatment-relevant biomarkers. (**a**–**d**) A case of metastatic adenocarcinoma of the lung. In this case, the H&E stained section demonstrates highly pleomorphic epithelial cells with abundant cytoplasm and prominent nucleoli (**a**). The immunohistochemical profile supports a diagnosis of lung adenocarcinoma with positive nuclear staining for TTF1 (**b**) and cytoplasmic staining for CK7 (**c**). Moreover, the tumor demonstrates significant labeling for PDL1 (**d**), making this patient a candidate for checkpoint inhibitor therapy with antibodies directed against the PD1/PDL1 T cell signaling mechanism. (**e**–**h**) In this case of metastatic ductal adenocarcinoma of the breast, the H&E again demonstrates a nest of pleomorphic epithelial cells, this time with an area of central tumor necrosis (**e**). The immunohistochemical profile indicates positive labeling for estrogen receptor (ER) in the vast majority of cells (**f**) and progesterone receptor (PR) in a minority of cells (**g**). Because the threshold for considering a tumor to be positive for PR is low (≥1%), this tumor is considered positive for both ER and PR. The tumor also demonstrates strong circumferential membrane staining that is complete, intense and within >10% of tumor cells, and it is therefore considered positive for HER2 by immunohistochemistry (**h**). An equivocal result by IHC would be followed up with assessment using fluorescent in situ hybridization (FISH)

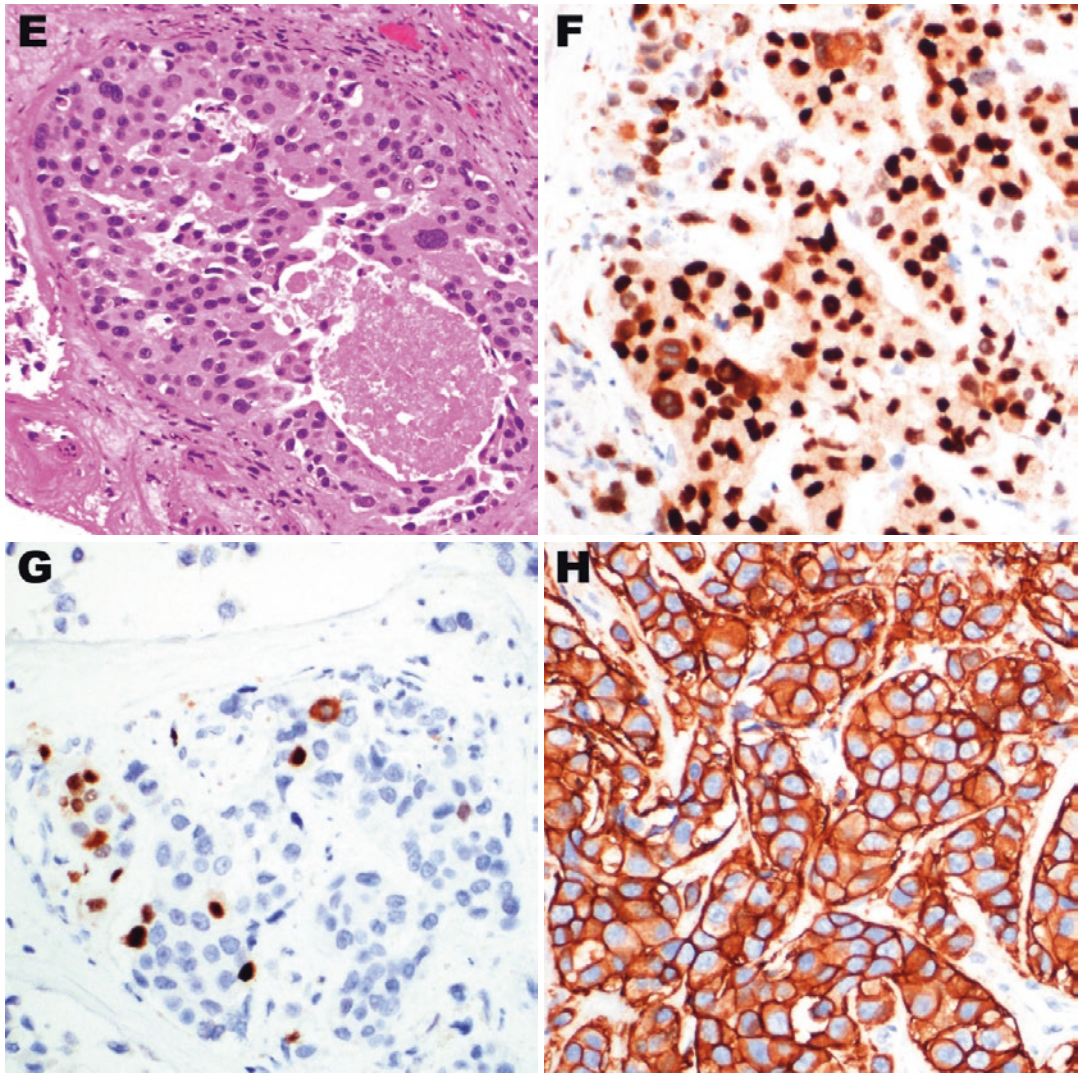


Fig. 4.5 (continued)

routinely assess for neuroendocrine differentiation using antibodies for synaptophysin and chromogranin, which may alter treatment strategies [33]. Immunostaining for MLH1, PSM2, MSH2, and MSH6 may be used to assess for the expression of mismatch repair proteins in colorectal carcinomas and other tumors [34].

Finally, immunohistochemical assessment of PD-L1 as a marker of potential therapeutic susceptibility to immune checkpoint inhibitors is likely to be increasingly incorporated into the routine antigen characterization of brain metastases (e.g., Fig. 4.5a–d). Indeed, it has been demonstrated that there may be significant discordance between the PD-L1 labeling characteristics between primary and metastatic lesions, arguing for the de novo assessment of this biomarker in metastatic foci [35].

Molecular Assessment of Brain Metastases

The molecular characterization of neoplastic disease, including in metastatic lesions, has increased dramatically over the last decade. As recurrent alterations become incorporated into diagnostic schema as entity-defining parameters for tumor subtypes, especially to guide targeted therapies, multiple clinical assays have been developed to interrogate molecular alterations in tumor tissue; most of these are readily applied to formalin fixed paraffin embedded samples.

While many laboratories at academic medical centers offer a comprehensive menu of molecular tests, some clinical care settings may use commercial laboratories. The advent of next generation sequencing technologies with massively parallel strategies has enabled the assessment of larger panels of genes with relatively low input tissue requirements. At our institution, we offer single gene assays (utilizing immunohistochemical proxies, FISH, or PCR-based assays), a 50-gene targeted sequencing panel, and a larger targeted panel that interrogates 143 genes. This latter assay assesses oncogenic hotspot loci, whole exon assessment of a set of tumor suppressors, copy number alteration status for a subset of genes, and also features an RNA-based component for the detection of selected fusion transcripts (e.g., for the detection of *ROS1* and *ALK* rearrangements). We additionally offer a clinically validated whole exome sequencing test that interrogates 22,000 genes and reports somatic alteration calls relative to coincident germline sequencing derived from a peripheral blood sample; a targeted solid tumor gene panel that interrogates 500 genes is also currently under validation.

Examples of immunohistochemical proxies for molecular alterations include antibodies directed against mutated epitopes (e.g., BRAF V600E). Antibodies may also be used to detect aberrant localization of protein epitopes that result from fusion gene products (e.g., STAT6 localization to the nucleus in the setting of STAT6-NAB2 fusions as seen in solitary fibrous tumor, also referred to as solitary fibrous tumor/hemangiopericytoma in the central nervous system). Finally, immunohistochemistry can assess for overexpression of particular protein products, such as in the setting of *ERBB2* (HER2) amplification in breast cancer and *ALK* rearrangement in lung adenocarcinomas.

Molecular assessment is essential, particularly if the metastatic lesion represents the first tissue sampling of a neoplastic process. For lung adenocarcinomas in such circumstances, we routinely assess for *EGFR*, *KRAS*, *ALK*, and *ROS1* alterations using a combination of immunohistochemistry, FISH, and targeted sequencing assays. In particular, the 143-gene NGS assay employed in our Clinical Genomics Laboratory can detect all of these alterations in a single assay—*EGFR* and *KRAS* hotspot mutations are detected in the deoxyribonucleic acid (DNA)-based portion of the assay while *ROS1*, *ALK*, and *MET* exon 14 skipping are found by the RNA-based component. In addition to MMR protein assessment with immunohistochemistry for adenocarcinoma of the colon, microsatellite instability may be assessed via molecular means. Moreover, we can identify *KRAS* and *NRAS* alterations via our targeted sequencing panel.

Rarely, molecular assays are used to resolve diagnoses in cases with ambiguous histological and/or immunohistochemical features. For example, returning to the differential diagnosis of melanocytic lesions, while *BRAF* and *NRAS* mutations are enriched in melanomas derived from cutaneous sites, *GNAQ* and *GNA11* mutations are much more common in primary melanocytic lesions of the CNS as well as in uveal melanoma [36]. In contrast, melanotic schwannomas, which occasionally enter into this differential diagnosis in paraspinal locations, are characterized by *PRKAR1A* mutations (akin to those seen in the context of Carney syndrome) and may additionally show loss of heterozygosity at this locus [37]. Finally, even if a mutation characteristic of primary melanocytic CNS tumors is identified, a comprehensive dermatologic and

ophthalmologic examination as well as PET/CT evaluation should be performed.

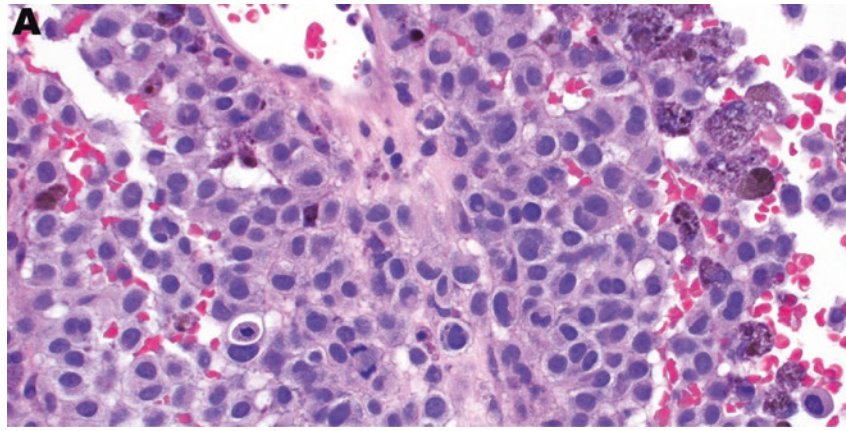
In a second example of molecular diagnostics, poorly differentiated neoplasms with ambiguous histological features or poorly sampled lesions may occasionally prompt consideration of both primary CNS tumors as well as metastases from distant sites. For example, if a tumor were found to harbor loss of chromosome 10, gain of chromosome 7, deletion of *CDKN2A/B*, *TERT* promoter mutation, and *EGFR* amplification (all of which are alterations characteristic of glioblastoma), the molecular results would suggest glioblastoma over a metastatic carcinoma or sarcoma. If the molecular profile of a primary tumor is known, it can be compared to the profile of a putative metastasis in an effort to molecularly prove derivation from the primary.

Indeed, it is likely that molecular testing will be increasingly used to detect the clonal relationship between a given metastasis and its presumed primary. In one study that matched 86 paired primary tumors with brain metastases, four metastases were found to be clonally unrelated to the sampled primary tumor and were hypothesized to have arisen from a clonally distinct neoplasm within the same primary organ due to a high-risk oncogenic field effect (three of these were lung carcinomas that occurred in the setting of smoking exposure, and one was a breast cancer arising in the setting of a germline *BRCA1* mutation) [38].

Just as epigenetic profiling of primary neoplasms of the CNS has recently demonstrated great promise as a diagnostic aide [39], there have been improved outcomes using methylation profiling for the identification of metastases of unknown primary and applying cancer-specific treatments, rather than more generalized empirical treatment strategies [40]. In one study, therapeutically relevant subtypes of melanoma, breast, and lung cancers metastatic to brain were successfully classified on the basis of methylation profiling [41]. The robustness of epigenetic profiling in classifying both primary and secondary malignancies of the brain is likely attributable to the fact that the epigenetic footprint of a tumor encodes information concerning both developmental as well as oncogenic pathways for a particular cell population [42, 43].

Since the presence of brain metastases de facto represents advanced stage disease, clinicians are more frequently using larger sequencing panels in an effort to detect targetable alterations that may not have been present (or may not have been assessed) in the patient's primary site of disease. Targetable alterations may be identified using next generation sequencing of brain metastatic tissue in patients without significant molecular information regarding their primary site of disease. Salient examples from our own service include a patient with metastatic melanoma whose tumor was found to harbor a *BRAF* V600E mutation (Fig. 4.6a, b), and a second patient with metastatic adenocarcinoma of the colon that was found to have *ERBB2* (HER2) amplification in addition to several additional nontargetable but characteristic alterations, namely, *KRAS*, *APC, and TP53* mutations (Fig. 4.6c–e). In the study of matched primary and brain metastatic samples referenced earlier, 53% (46/86) of cases harbored at least one potentially actionable alteration in brain metastatic samples that was not identified in the paired primary tumor sample. These alterations included those affecting the PI3K/AKT/mTOR pathway, such as *PTEN* and *PIK3CA*, as well as *ERBB2* (HER2) and *EGFR* alterations, indicating susceptibility to tyrosine kinase inhibition [38]. In addition to individual molecular alterations, the overall tumor mutational burden (TMB) may alter clinical management [44]. A tumor's TMB can be gleaned from broader NGS panels—its relationship to predicted neoantigen production, immune system regulation, and response to immunotherapy (such as checkpoint inhibitors) remains to be fully elucidated [45, 46].

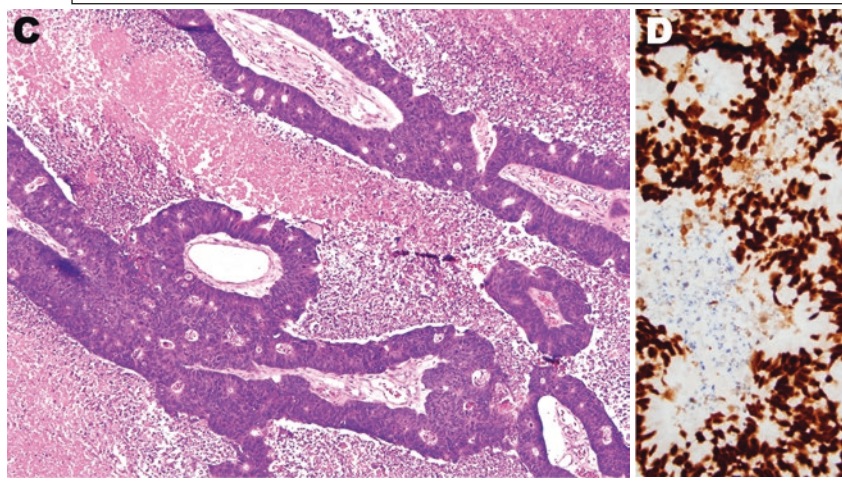
In addition to DNA-based and epigenetic assessment of metastases, other modalities including RNA-sequencing paradigms, metabolomic



B

Tier 1 Variants

Variant	Type	VAF	CN
BRAF c.1799T>A, p.Val600Glu	missense	43.0%	N/A



E

Tier 1 Variants

Variant	Type	VAF	CN
KRAS c.35G>T, p.Gly12Val	Missense	57.4%	N/A

Tier 2 Variants

Variant	Type	VAF	CN
APC c.4242_4245delAAGT, p.Ser1415fs	Frameshift deletion	89.9%	N/A
TP53 c.560-1G>A, p.?	Splice site	63.7%	N/A
ERBB2	Amplification	N/A	42.9

Fig. 4.6 Sample molecular workup of metastatic disease using next generation sequencing. (**a**) In this case of metastatic melanoma, the H&E depicts sheets of epithelioid cells with large nuclei, abundant cytoplasm, and focal dark melanin pigment. (**b**) Next generation sequencing revealed a BRAF V600E point mutation. (**c**) H&E-staining shows islands of carcinoma cell surrounded by areas of necrosis. Immunostaining demonstrated CDX2 and CK20 positivity (not shown), corroborating the site of origin as colon. (**d**) Next generation sequencing demonstrated several mutations that are characteristic of colonic adenocarcinoma including *KRAS*, *APC*, and *TP53* mutations. In addition, the sequencing panel is able to detect a subset of copy number alterations and in this case showed amplification of *ERBB2* (HER2), a potentially targetable alteration

Table 4.1 Commonly assessed biomarkers in brain metastases

Primary site	Commonly assessed proteins	Commonly assessed genes
Breast	GATA3, GCDFP-15, Mammaglobin, ER, PR, HER2, CK7	*ERBB2/HER2, BRCA1, BRCA2*
Lung, adenocarcinoma	TTF1, Napsin-A, CK7, PDL1	*EGFR, KRAS, ALK, ROS1*
Melanoma	HMB45, S100, SOX10, Melan-A	*BRAF, NRAS, TERT*
Colon, adenocarcinoma	CK20, CDX2, MMR proteins (MLH1, PMS2, MSH2, and MSH6)	*APC, BRAF, RAS*
Renal cell carcinoma, clear cell type	PAX8, CD10, CAIX	*VHL, BAP1, PBRM1*

assessment, and exosomal assessment of brain tumors have the potential to reveal new clinically useful biomarkers and/or therapeutic targets. For example, recent evidence indicates that patients with BRAF-mutated melanoma may benefit from inhibition of mitochondrial respiration in combination with BRAF inhibitors; a hypothesis generated using a combination of RNA sequencing, metabolomic, and pharmacogenetic data [47, 48]. Better understanding of the biology underlying tumor derived exosomes has identified mechanisms of metastatic spread as well as potential use of exosomes for diagnosis (e.g., in liquid biopsies), novel therapeutic targets, and potentially improved drug delivery [49, 50].

Conclusion

The management of patients with brain metastases inherently begins with diagnostic assessment. While clinicoradiological information is sometimes sufficiently diagnostic (or the goals of care do not necessitate a tissue diagnosis), tissue assessment is usually crucial not only to exclude other neoplastic etiologies, but to define the primary site of origin and to further refine the molecular assessment of the metastasis, even in cases when the primary lesion has already been extensively characterized. Increasingly, immunohistochemical and molecular testing algorithms are being employed to identify subtypes of cancer (e.g., ALK-rearranged lung adenocarcinoma or HER2-enriched breast carcinoma) and characterize potential therapeutically relevant proteins (e.g., PD-L1) or targetable molecular alterations (e.g., BRAF V600E) (also see Table 4.1). Interestingly, as the sampling of brain metastases becomes more clinically relevant for therapeutic planning (even when the basic diagnosis and primary organ of origin are already known) the use of less invasive strategies to interrogate metastases such as cell-free DNA or CSF-based sequencing techniques will likely become more prevalent. Looking ahead, the pathological evaluation of brain metastases is rapidly changing, driven primarily by the ongoing revolution in molecular genetics, high throughout sequencing technologies, and multiparametric "omic" assessment of tissue samples.

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5 Role of Precision Medicine in Patients with CNS Metastasis

Albert Eusik Kim and Priscilla K. Brastianos

Introduction

Brain metastases (BMs) are the most common central nervous system (CNS) malignancy, and are widely felt to represent a grim prognosis. Progression of intracranial disease is the cause of death in up to 50% of patients with clinically significant BM [1]. The reported incidence of BM is 10–30% in all adults with cancer, and up to 40% of patients with metastatic cancer [1]. However, these estimates likely underestimate the true incidence in the current era of modern cancer therapies. Over the past decade, the incidence of BM has risen due to improved diagnostic testing that facilitates detection of asymptomatic BM and increased patient survival through better tolerated and more effective treatment strategies [1]. Lung cancer (39–56%), breast cancer (13–30%), and melanoma (6–11%) are among the most likely systemic cancers to cross into the CNS [2]. Less common, but still reported, are gastrointestinal cancers (3–8%) and renal cell carcinoma (2–4%) [2].

Prognosis for BM is poor, with a median survival ranging from 3 to 27 months after detection, depending on the primary malignancy [1]. Treatment options are limited and involve a multidisciplinary approach including surgical resection, radiotherapy, and systemic treatment. Historically, patients with BM were treated with whole brain radiotherapy (WBRT); however, recent data in specific clinical scenarios where there are effective systemic treatment options suggest that deferring WBRT may be reasonable due to a lack of overall survival benefit and the associated neurotoxicity. At present, treatment for BM is often case-specific and dependent on many factors, such as performance status of the patient, as well as the number, location of, and primary tumor type of BM [3]. Surgical resection followed by radiotherapy is generally the standard of care for solitary or large (>3 cm) symptomatic lesions [1, 3]. Stereotactic radiosurgery (SRS) alone is frequently used for oligometastatic disease, which is commonly defined as up to four BMs [1, 3]. Hippocampal-sparing WBRT, which may have a lower risk of neurocognitive side effects [1], can be considered in patients with multiple disseminated BMs and leptomeningeal spread of disease.

It is generally recommended that patients with active extracranial disease receive systemic therapy after local brain therapy, as surgery and radiation alone are not curative. Differential responses to these treatments for intracranial and extracranial disease are often observed, where systemic disease is adequately controlled with progression of

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intracranial tumor burden [4]. The reasons behind this differential response are multifactorial and not completely understood. One reason may be inadequate penetration of these systemic therapies [4]. However, even with the use of new agents with known intracranial efficacy, the majority of patients progress in the brain. This issue illustrates an incomplete understanding of BM tumor biology and the drivers that mediate blood-brain barrier (BBB) penetration and CNS proliferation. This is due, in part, to a relative paucity of clinical trials evaluating systemic therapies in BM, due largely to the exclusion of patients with BM from clinical trials due to perceived poor prognosis. Another barrier is the lack of understanding of the genomic drivers behind development of BM and longitudinal changes in tumor genomics and physiology during treatment. Direct tissue analysis to understand these changes can be challenging due to the surgical risk associated with tissue sampling or inoperable location within the brain. Noninvasive methods of genomic profiling of BM are currently under development and detailed in this review.

In the current era of precision medicine, choice of treatment for many systemic cancers has become increasingly personalized and dependent on the molecular or genomic characterization of systemic cancer. To this end, improved control of both intracranial and extracranial tumor burden has been observed with targeted therapy and immunotherapy. In this review, we present current efforts to characterize the genomic drivers and heterogeneity of BM, as compared to the primary tumor, using modern sequencing techniques. A better understanding of these genomic alterations will lead to more precise tailoring of current treatments and new therapeutic approaches. Additionally, we will present current knowledge of targeted therapies for BM of systemic cancers of different histologies.

Genetic Heterogeneity in Brain Metastases

Selection of targeted therapy for BM has traditionally relied on genomic analysis of the initial primary tumor resection to identify actionable mutations. Recent studies, however, have demonstrated significant genomic heterogeneity between BM and the paired primary tumor [5]. In a study of 86 patients in which BM, primary tumors, and normal tissue were analyzed by whole exome sequencing, 46 (53%) patients had distinct, potentially actionable mutations in the BM not detected in the paired primary tumor [5]. The vast majority of BMs, however, are clonally related to the primary tumor, as only 4/86 (4.6%) specimens were shown to be unrelated to the primary lesion [5]. Similarly, distal extracranial and regional lymph node metastases were also found to be clonally related to the primary tumor, but highly divergent from BM [5]. These findings suggest that branched evolution, or the divergent propagation of multiple subclonal populations arising from a common ancestor [6, 7], likely explains genomic differences between the primary tumor and different metastases as well as the phenomenon of locoregional genomic heterogeneity. During branched evolution, tumors will acquire hundreds, if not thousands, of genetic alterations, a minority of which is driver mutations that confer a selective growth advantage to clones harboring the mutation [7]. These advantageous mutations allow for the development and proliferation of subclonal populations.

The exact genomic signatures required for CNS metastases and proliferation are still unclear. Interestingly, spatially and temporally separated BM from the same patient possess a more homogenous genomic signature when compared to each other as opposed to the primary tumor [5], suggesting that specific genomic alterations may be integral for the brain metastatic process. To this end, several studies have shown that upregulation of specific pathways such as phosphatidylinositol-4,5-bisphosphate 3-kinase (Pi3K) [8], epidermal growth factor receptor (EGFR) [8], or human EGFR 2 (HER2) [9] is associated with cancer cells crossing into the blood-brain barrier (BBB) and proliferating within the CNS. Furthermore, alterations in the cyclin-dependent kinase (CDK) pathways, such as *CDKN2A* loss and *CDK4/6* amplification, have also been implicated in CNS metastases [5]. The exact role that these genomic alterations play in BM pathogenesis is not known

at this time, and remains an active area of research. For example, are these genetic alterations simply related to the underlying histology of the primary tumor, or is dysregulation of these pathways necessary for CNS spread and proliferation? In support of the latter, a recent study demonstrated loss of phosphatase and tensin homolog (PTEN), a tumor suppressor gene, expression in human tumor cells with normal PTEN expression after dissemination to the brain but not to other organs [10]. Furthermore, the PTEN deficient level in BM tumor cells was restored after leaving the brain microenvironment. This finding seems to indicate that certain genomic changes are needed for CNS proliferation, a topic worthy of further prospective study for confirmation.

Divergent evolution of BM has important therapeutic implications. This genomic heterogeneity likely explains the divergent response seen in intracranial and extracranial disease burden in response to targeted therapies. In many cases, actionable mutations for CNS metastases may only be present in BM. As BMs are not always resected for diagnostic purposes due to the morbidity associated with tissue sampling, CNS therapeutic strategies are often made from analysis of the primary tumor or extracranial metastasis. This assumption can result in sampling bias, given frequent BM genomic divergence from extracranial tissue samples. If available, actionable targetable alterations for BM purposes should be assessed from BM tissue analysis. It should be noted that whether specific systemic targeted therapies hold prophylactic or durable therapeutic efficacy for BM is unknown at this time. It is possible that reprogramming of the cancer cell transcriptome by the CNS microenvironment may impact efficacy of systemic therapies in BM. This question requires further study to fully answer.

As BM tissue analysis or serial brain biopsies are not always feasible, continued development of noninvasive techniques that shed light on genomic and physiologic changes as a result of treatment are critical. Several such methods, such as liquid biopsies, circulating tumor cells, or cell-free deoxyribonucleic acid (DNA), are described further below. Such techniques may help us better understand the breadth of genomic heterogeneity in BM and will result in further refinement of current treatment strategies.

Genomic Profiling of Brain Metastases

The recent introduction of targeted therapies and checkpoint inhibitors has resulted in unprecedented durable responses for many systemic cancers, including those with a high propensity for BMs, such as melanoma, non-small-cell lung cancer, and breast cancer. As such, cancer treatment has become increasingly personalized and dependent on the molecular and genomic traits of each patient's cancer. Similarly, identification of these actionable mutations within BM holds great potential to drastically alter outcomes. Unfortunately, determining the exact genomic signature for BM can be unwieldy as this frequently entails direct tissue analysis. As BM often possesses targetable mutations not present in the primary tumor or distal extracranial metastases [5], genomic analysis of these extracranial sites can miss these genomic alterations and thus targeted therapy opportunities for BM. This clinical conundrum illustrates a critical need for noninvasive and clinically practical methods to capture intracranial molecular profiling. Such a biomarker would provide a better understanding of temporal evolution of BM, inform choice of treatment, and aid in early identification of drug-resistant mutations.

Molecular analysis of circulating tumor DNA (ctDNA) in plasma is currently used for several systemic cancers as a noninvasive tool for genomic profiling and monitoring treatment response [11–13]. However, tumor DNA was found to be either absent or only present in small amounts in the plasma of patients with primary brain tumors or solid tumor BM [12]. In such cases, molecular analysis of ctDNA isolated from cerebrospinal fluid (CSF) is emerging as a promising biomarker. The fraction of cell-free ctDNA in the CSF is higher than in plasma due to the relative absence of background normal DNA in CSF [13]. This allows for the detection of somatic mutations in the CSF with moderate sequence

coverage, whereas plasma ctDNA sequencing requires very deep sequence coverage to achieve similar sensitivities for detecting mutations occurring at low allele frequencies. Additionally, mutations present only in BM and not in the extracranial tumors were represented in CSF ctDNA [12]. Lastly, tumor DNA burden in CSF ctDNA was observed to change during treatment [12]. Mutant allelic frequency of CSF ctDNA decreased with tumor response to treatments and increased with progression. While current methods using CSF ctDNA for detection of all types of mutations still require optimization, the above data suggests that CSF ctDNA may soon develop into a clinical tool for BM genomic analysis.

Additional biomarkers that reflect the BM genomic signature are currently under development. One such example is an exosome, an extracellular vesicle released from the cell upon fusion of an intermediate endocytic compartment with the plasma membrane. These vesicles are felt to be a conduit for intercellular communication and may contain genomic data consistent with a tumor's molecular properties. The burgeoning field of radiogenomics, or the relationship between an imaging-derived phenotype and genomic data, may also be a promising way to noninvasively monitor for genomic alterations. Using these correlations with serial imaging may shed light on alterations in tumor biology as a result of treatment. If optimized, radiogenomics may assist in the early detection of drug-resistant mutations and thus inform a change to a more efficacious treatment regimen. Both fields are largely in their infancy, and currently associated with significant limitations.

Non-Small-Cell Lung Cancer

Non-small-cell lung cancer (NSCLC) is the leading cause of cancer mortality worldwide, accounting for 18.2% of total deaths from cancer [14]. Furthermore, NSCLC, adenocarcinoma in particular, is the most common primary malignancy to metastasize to the brain [3]. Approximately 25–30% of NSCLC patients will develop BM during the course of their disease [15]. Larger tumor size, lymphovascular space invasion, and hilar lymph node involvement are associated with an increased risk of BMs [16]. Unfortunately, despite an aggressive multimodality treatment approach combining platinum-based chemotherapy, radiation, and surgery, prognosis remains poor. The reported 1-year mortality rate after developing BM ranges from 81% to 90% [14]. In addition, approximately 40–50% of patients with complete initial responses to therapy will develop BM [17]. Over the past decade, NSCLC management has been revolutionized by the identification of oncogenic driver mutations in anaplastic lymphoma kinase (*ALK*) and epidermal growth factor receptor (*EGFR*) and the development of targeted therapies, resulting in unprecedented response rates.

NSCLC: EGFR Tyrosine Kinase Inhibitor

Activating mutations in *EGFR* are generally found in NSCLC patients with the following characteristics: female gender, age <35 years, Asian descent (in about 40%), history of never or light-smoking and adenomatous histology [18]. In such patients, *EGFR* mutation testing is recommended. *EGFR* mutations render these tumors sensitive to EGFR tyrosine kinase inhibitors (TKIs), which results in significantly improved outcomes when compared to platinum-based combination chemotherapy [19]. For patients without a non-squamous histology *EGFR* mutation testing is not recommended due to extremely low likelihood of positivity, unless they are non-smokers [18].

First- and second-generation EGFR TKIs selectively target the *EGFR* receptor through competitive, reversible binding at the tyrosine kinase domain, and are currently first-line therapy for *EGFR*-mutant NSCLC [19, 20]. Erlotinib and gefitinib are among the most commonly used EGFR first-generation TKIs. However, the majority of patients with initial response to EGFR TKIs had disease progression due to an acquired resistance within 1–2 years [21]. The development of an additional *EGFR* mutation, most com-

monly the threonine-to-methionine substitution at position 790 on exon 20 (T790M), is responsible for approximately 60% of this acquired resistance [22]. Third generation TKIs, such as osimertinib and rociletinib, have shown promising activity for these resistant *EGFR*-mutant types [23].

Presently, data on the efficacy of *EGFR* TKIs in treating NSCLC BMs is hopeful, but limited. Barriers to an accurate evaluation are the lack of clinical trials studying targeted therapies in BM, and regional genomic heterogeneity—as an *EGFR*-mutant status in the primary tumor is not always present in BM. Nonetheless, available data suggests that these agents likely have some CNS activity. Recent preclinical data demonstrates intracranial activity of afatinib, a second-generation *EGFR* TKI and an irreversible ErbB family inhibitor [24]. Post-hoc subgroup analysis from the LUX-Lung 3 and LUX-Lung 6 studies, which allowed patients with asymptomatic BM to be enrolled, showed survival benefit from treatment with afatinib compared to platinum-based chemotherapy. Progression free survival (PFS) (8.2 vs. 5.4 months) and objective response rate (ORR) (70–75% vs. 20–28%) were significantly better with afatinib than platinum-based chemotherapy [25]. Another small phase II prospective trial exploring *EGFR* TKIs in BM reported an 83% ORR with first-generation TKIs [26]; however, other studies have reported more modest responses [27]. For acquired resistance, a recent study demonstrated superior BBB penetration with osimertinib than with gefitinib or afatinib, as well as sustained BM regression in an *EGFR*-mutant mouse model [28].

Taken together, EGFR TKIs, especially osimertinib, appear to have positive CNS activity. How to apply these findings in the context of surgical resection and radiotherapy still remains unclear. It seems reasonable to incorporate EGFR TKIs up front in asymptomatic BMs and to consider delaying surgery or radiation until BM progression to minimize adverse effects. Further prospective trials evaluating EGFR TKIs and sequential approaches with brain radiotherapy to optimize CNS efficacy and minimize radiation-induced neurotoxicity are needed.

NSCLC: Anaplastic Lymphoma Kinase (ALK) Tyrosine Kinase Inhibitors

The discovery of the *ALK* gene rearrangement and development of genetically driven therapies targeting this aberration have led to tremendous progress in treating NSCLC. The most common rearrangement arises from a fusion between *ALK* and the echinoderm microtubule-like protein 4 (*EML4*) gene. This results in an oncogenic tyrosine kinase with constitutive activity, and is found in up to 5% of NSCLC [29]. BM is a relatively common occurrence in *ALK*-rearranged NSCLC, with incidence quoted at 23.8% at time of diagnosis and 58.4% at 3 years [30]. As with EGFR, *ALK* translocations are associated with younger age, history of light or no smoking, and adenocarcinoma histology [31]. Consequently, testing for *ALK* is highly recommended for such patients [2], as the presence of an *ALK*-mutation is correlated with response to ALK TKIs.

Crizotinib, a first-generation ALK TKI that also has activity against *MET* and *ROS1* [31], is superior to standard-of-care chemotherapy for management of systemic ALK-rearranged NSCLC [32]. While assessing ALK TKIs for CNS efficacy is limited due to exclusion of BMs from many randomized clinical trials, crizotinib likely holds some CNS efficacy. In the PROFILE 1005 and 1007 studies, patients with untreated asymptomatic BMs were included in a pooled retrospective analysis. For these patients, intracranial disease control rate was noted to be 56% at 12 weeks, with a median time to CNS progression of 7 months [31]. In PROFILE 1014, a randomized phase III trial of crizotinib versus platinum-based chemotherapy, patients with stable treated BMs were allowed to enroll with CNS efficacy as a secondary endpoint. In this cohort, CNS disease control rate for patients with BM was significantly higher with crizotinib at 12 weeks (85% vs. 45%) and median PFS was significantly longer (9 vs. 4 months) [33].

Second-generation ALK TKIs are promising options for *ALK*-rearranged NSCLC patients who develop resistance to crizotinib, and are also felt to have improved CNS efficacy. Of these agents, alectinib and ceritinib are among those

with the strongest evidence for BM. Preliminary findings from the J-ALEX study, a Japanese phase III trial that recruited ALK-inhibitor naïve patients with *ALK*-rearranged NSCLC, reported that the alectinib cohort had yet to reach median PFS, while the crizotinib cohort's median PFS was 10.2 months [34]. Two other phase II studies with alectinib demonstrated CNS response rates up to 75% and median CNS disease response durations of 10–11 months [35, 36]. In the ASCEND-1 study, 94 patients with *ALK*-rearranged NSCLC BM were retrospectively analyzed. Of this cohort, 79% of ALK TKI-naïve and 65% of ALK TKI-pretreated patients had intracranial response to ceritinib [37]. Newer ALK TKIs such as lorlatinib and brigatinib likely have even better brain efficacy. As with first-generation ALK TKIs, further work is needed to determine utility of these treatments in combination with radiotherapy with the intent of maximizing CNS efficacy.

NSCLC: Immunotherapy

Immune checkpoint inhibitors have emerged as an option for patients with advanced NSCLC without an actionable driver mutation (i.e., EGFR and ALK), or for those with actionable mutations that have progressed on next-generation targeted agents [38]. Immune checkpoints, which refer to inhibitory pathways that modulate the physiologic immune response to minimize collateral damage and thus maintain self-tolerance, are co-opted by tumors. For example, the interaction of programmed death 1 (PD-1) receptor on activated T cells with programmed death ligand 1 (PD-L1) on tumor cells leads to T-cell inactivation, which prevents the immune system from attacking the tumor cell [38]. Nivolumab and pembrolizumab are anti-PD1 monoclonal antibodies that have been shown to improve survival outcomes in patients with metastatic NSCLC without actionable mutations, as compared to docetaxel-based chemotherapy [39, 40]. Furthermore, pembrolizumab demonstrated PFS and overall survival (OS) superiority to platinum-based chemotherapy as first-line therapy in patients with NSCLC with greater than 50% PD-L1 expression, suggesting that PD-L1 expression may be a predictive biomarker for response [41].

Many immunotherapy trials for NSCLC, to date, have excluded patients with active brain metastases. However, a recent early analysis of a phase II trial investigating activity and safety of pembrolizumab in NSCLC and melanoma patients with untreated or progressive BMs showed encouraging results. Patients with NSCLC had tumor tissue positive for PD-L1 expression. In this study, 33% (6 of 18) of NSCLC patients had durable intracranial response without high-grade adverse events [42]. Further randomized prospective studies are needed to investigate these promising options for brain metastases.

Breast Cancer

Breast cancer is the most common cancer in women and the second-leading cause of cancer-related death in women [3]. It is also the second most common cancer to metastasize to the brain, after NSCLC [1]. The exact incidence of BM from breast cancer in the current era of modern therapies is not clearly defined; however, it is estimated that between 10% and 45% of breast cancer patients will be affected by BM during their disease course, depending on breast tumor subtype [43]. This number will likely increase as overall survival improves with newer, more durable, therapies.

As expected, prognosis for BM in breast cancer remains poor. A large retrospective study identified older age, Karnofsky Performance Status (KPS), and tumor subtype as prognostic factors [44]. Within breast cancer, there are four main tumor subtypes. Basal subtype [estrogen receptor (ER), progesterone receptor (PR), and HER2 negative; also referred to as "triple negative"] has the worst prognosis, with a median OS of 5 months after developing BM [44]. Luminal A (ER- and/or PR-positive, HER2-negative, low levels of Ki-67) are generally low-grade tumors with the best prognosis [44]. Other subtypes include luminal B (ER- and/or PR-positive, and

either HER2-positive or HER2-negative with high levels of Ki-67) and HER2-enriched (ER/PR-negative and HER2-positive). Patients with triple-negative and HER2-enriched breast cancer are at highest risk of CNS metastases [44]. Current management of BM from breast cancer is similar to those of other primary cancers, and includes consideration of systemic therapies in addition to surgical resection and radiation.

In this section, we describe current targeted therapies for breast cancer. Triple negative breast cancer (TNBC) is especially challenging to treat due to lack of clinically actionable genomic alterations and nondurable response to systemic chemotherapy [45]. For this cohort, there has been a growing pool of novel targets as gene sequencing has become more readily accessible. One promising target for TNBC is poly ADP-ribose polymerase (PARP), a family of proteins involved in DNA repair and genomic stability. Histologic studies have shown similarities between the pathological and clinical features of TNBC- and BRCA-associated cancers [45]. Interestingly, BRCA-1 and BRCA-2 mutant cell lines have been shown to be exquisitely sensitive to PARP inhibition [46]. Several PARP inhibitors (i.e., olaparib and veliparib) are currently being evaluated in the adjuvant, neoadjuvant, and metastatic setting for the subset of TNBC with BRCA-1 or BRCA-2 mutations.

Breast Cancer: HER2 Antibodies and TKIs

HER2 is a member of the human epidermal growth factor receptor family, which consists of four membrane-bound receptor tyrosine kinase implicated in multiple signaling cascades that mediate cell proliferation and apoptosis. This protein is overexpressed in 20% of all breast cancer patients [47]. HER2-directed therapies, such as trastuzumab, lapatinib, pertuzumab, and T-DM1 (ado-trastuzumab emtansine, an antibody-drug conjugate consisting of trastuzumab linked to the cytotoxic agent DM1), significantly improve PFS and OS of patients with HER2-positive metastatic breast cancer. Furthermore, HER2-overexpression is associated with an increased risk of BM, as approximately 30–50% of patients with HER2-positive breast cancer will develop BM during their disease course [48]. The propensity of HER2-positive breast cancer for CNS relapse may be related to improved survival of patients with HER2-directed therapy, the limited CNS penetration of HER2-directed agents, and perhaps the neurotropism of HER2-positive breast cancer [48]. As with other types of primary tumors, temporal and spatial genomic heterogeneity are seen with breast cancer BM. A retrospective study showed that 24% of 182 patients with HER2-positive primary breast cancer had HER2-negative metastatic disease [49]. There is also evidence to suggest that BM commonly occurs in patients with HER2-positive breast cancer that is otherwise systemically well controlled with HER2-directed therapy [48]. As with other types of systemic cancers, these findings illustrate the necessity of repeat genomic analysis on BM tissue if clinically feasible.

Like most other monoclonal antibodies, trastuzumab, which targets the HER2 receptor, has limited CNS activity due to its inability to cross the intact BBB [48]. Consequently, adjuvant radiation with trastuzumab, pertuzumab, and T-DM1 are all being investigated as options for HER2-positive BM. A recent pharmacokinetic study demonstrated improved CNS penetration of trastuzumab after BBB disruption by radiation. The ratio of the CSF to plasma levels of trastuzumab improved significantly from 1:420 before radiotherapy to 1:76 after radiotherapy [50]. Pertuzumab, another monoclonal antibody against the HER2 receptor, likely has some synergistic CNS antitumor efficacy in combination with trastuzumab and docetaxel, as shown in the CLEOPATRA trial, a randomized phase III placebo-controlled trial of pertuzumab in metastatic HER2-positive breast cancer. The median time to development of BMs as first site of disease progression was significantly longer in the pertuzumab arm compared to the placebo arm (15.0 vs. 11.9 months), and the median OS was 56.5 months in the pertuzumab arm, compared to 40.8 months in the placebo arm [51]. Other small case series have also demonstrated

some efficacy for pertuzumab-containing regimens in BM from HER2-positive breast cancer BM [52, 53]. Finally, several retrospective studies indicate some potential activity for the antibody-cytotoxin conjugate T-DM1 in CNS disease [54], but clear prospective evidence is lacking.

Lapatinib is a dual small-molecule HER2 and EGFR TKI that has shown some ability to cross a disrupted BBB. A novel PET imaging study using radiolabeled lapatinib demonstrated increased levels of lapatinib in brain metastases as compared to normal brain tissue [55]. Lapatinib has demonstrated partial response of CNS disease to a modest degree as adjuvant monotherapy (CNS ORR 6% [56]) and in combination with capecitabine (CNS ORR 20–38% in pretreated patients [57, 58]). This CNS antitumor efficacy is augmented in treatment-naïve patients with HER2-positive breast cancer (CNS ORR 65% [59]). Neratinib, an irreversible HER1, HER2, and HER4 TKI, also may have CNS efficacy in HER2-positive metastatic disease. The NEfERTT trial, a randomized phase III trial of patients with metastatic HER2-positive breast cancer, noted significantly lower rates of CNS progression and delayed time to CNS metastases with the neratinib-paclitaxel combination than with trastuzumab-paclitaxel, although the two groups had similar OS [60]. Further studies evaluating these regimens are ongoing.

Breast Cancer: Additional Mutations

Sequencing studies of BM from breast cancer demonstrated that actionable mutations in the phosphoinositide 3-kinase/protein kinase B/rapamycin (Pi3K/AKT/mTOR) pathways are common [5]. This pathway regulates several cellular functions in cancer, most notably cell growth and proliferation. Increased activation of this pathway is one hypothesized mechanism of resistance to hormonal therapy. Everolimus, an mTOR inhibitor, is currently being studied for breast cancer BM. The breast cancer trials of OraL EveROlimus-3 (BOLERO-3) trial showed that triple therapy with everolimus, trastuzumab, and vinorelbine was superior to placebo, trastuzumab, and vinorelbine in trastuzumab-resistant advanced HER2+ breast cancer [61]. Another large phase III trial showed that everolimus combined with an aromatase inhibitor improved PFS in heavily pretreated hormone receptor-positive advanced breast cancer [62]. While these trials excluded brain metastases, these results may perhaps be generalized to BM as everolimus has been demonstrated to possess CNS penetration in patients with primary brain tumors [63]. Clinical trials evaluating the role of everolimus and other therapies targeting the Pi3K and mTOR signaling pathways in management of breast cancer BM are ongoing.

Alterations in the CDK pathway are common in breast cancer brain metastases [5]. Activation of CDK4 and CDK6 by cyclin D results in cell proliferation by facilitating G1 phase progression and transition from G1 to S phase in the cell cycle [48]. CDK inhibitors, such as ribociclib, palbociclib, and abemaciclib, have demonstrated success in hormone-receptor positive breast cancer [64]. Recent preclinical studies have shown good CNS penetration of abemaciclib, and some efficacy for breast cancer BM as demonstrated by several case series [65]. Current trials are further investigating the efficacy of these agents.

Melanoma

Melanoma is the third most common systemic cancer to metastasize to the brain [3]. Approximately 50% of patients with stage IV melanoma will develop BM during the course of their disease [1, 3]. As with other systemic malignancies, prognosis of BM in metastatic melanoma is poor due to significant neurologic morbidity. Median OS after the diagnosis of BM has historically been about 4.7 months, although a recent retrospective analysis reported improvement of median OS to 7.7 months with the recent use of targeted therapies [66].

Melanoma: Mitogen-Activated Protein Kinase (MAPK) Pathway

Approximately 50% of patients with metastatic melanoma will have an activating mutation in *BRAF*, a serine/threonine protein kinase within the MAPK signaling pathway [67]. BRAF is a key regulator of cell growth, division, and differentiation, and when inactive can result in downstream constitutive activation of the MAPK pathway. This provides a basis for the mutational activation and uncontrolled tumor growth for multiple cancers, and thus a potential target for selective inhibition.

In melanoma, the most common *BRAF* mutation is the substitution of valine for glutamic acid (V600E), comprising nearly 90% of all BRAF mutations in melanoma [67]. The second most common *BRAF* alteration is the valine for lysine substitution (V600K), which represents 5–6% of cases. *BRAF*-mutant melanomas are generally more aggressive and may confer a higher risk of developing BM [67]. There are currently two FDA-approved BRAF inhibitors for systemic melanoma: vemurafenib and dabrafenib [67]. BRAF inhibitors have markedly improved OS for patients with *BRAF*-mutant metastatic melanoma. This response, however, is not usually durable [66]. As with other systemic tumors, current BM genomic sequencing studies indicate that the development of treatment-resistant genomic alterations contributes to treatment failure.

Evidence for dabrafenib and vemurafenib in BM efficacy is limited, as many large phase III trials excluded CNS disease. Nonetheless, these agents likely hold some CNS efficacy. The BREAK-MB trial, a multicenter phase II trial with 172 patients with *BRAF*-mutant melanoma with at least one asymptomatic brain metastasis, showed that dabrafenib had activity for patients with either untreated or pretreated BM. For both groups, there was a response rate of >30% with improvement in OS and PFS [68]. In a retrospective study of 27 patients, vemurafenib resulted in an intracranial response rate of 71%. The median intracranial PFS was 4.6 months and median OS was 7.5 months [69]. Interestingly, genomic sequencing analysis of BRAF-inhibitor resistant BM revealed genomic alterations resulting in activation of the Pi3K/AKT pathway [70].

Mitogen-activated protein (MEK) kinase is downstream of *BRAF* in the MAPK pathway, and is frequently activated by members of the Pi3K pathway as a resistance mechanism from BRAF inhibition. To prevent resistance, BRAF inhibitors are frequently combined with MEK inhibitors, such as trametinib and cobimetinib, in metastatic melanoma. When BRAF inhibitors were combined with MEK inhibitors, treatment efficacy was further potentiated in patients with *BRAF* mutant extracranial metastatic melanoma, as evidenced by improved PFS (2 years) and OS (3 years) [71–73]. Dual BRAF and MEK inhibitions for brain metastases are currently being evaluated in clinical trials.

Melanoma: Pi3K/AKT/mTOR Pathway

Genomic analysis of 16 pairs of patient-matched melanoma brain metastases and extracranial metastases demonstrated increased activation of the Pi3K/AKT/mTOR pathway specific to BM [8]. Preclinical and animal studies using a Pi3K inhibitor, BKM120, demonstrate growth inhibition rates of up to 80% and induced apoptosis in vitro and inhibition of tumor growth of human brain metastatic melanoma cells within brains of nude mice [74]. These findings suggest that an alteration in the Pi3K pathway, for reasons unknown at present, may make a tumor more at risk for CNS spread and proliferation. Furthermore, Pi3K inhibitors may be a potential therapeutic option worthy of prospective clinical trials for metastatic melanoma.

Melanoma: Immunotherapy

Unprecedented treatment advances for patients with advanced-stage melanoma have occurred recently with the advent of immunotherapy. High-dose interleukin-2 had early success [75],

but was frequently associated with severe toxicities and was consequently limited only to patients with excellent performance status. Ipilimumab, an anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody, received FDA approval in 2011 after a landmark study in 2010 demonstrated improved patient outcomes in unresectable stage III or IV melanoma [76]. Systemic response rates for ipilimumab have ranged from 10% to 15%, with improved response in those with BRAF-wild type melanoma [77, 78]. About 20% of patients with response to ipilimumab were long-term survivors, measured on the order of years [79, 80]. Soon afterward, two anti-PD-1 antibodies, nivolumab and pembrolizumab, were approved by the FDA for metastatic melanoma. Subsequent clinical testing with PD-1 checkpoint blockade demonstrated improved outcomes with less toxicity as compared to ipilimumab [81]. Nivolumab, with a PFS of 6.9 months, was more effective than ipilimumab monotherapy, which displayed a median PFS of 2.9 months [81]. Additionally, pembrolizumab or nivolumab monotherapy were associated with ORR ranging from 33% to 57%, with the majority of responses being durable [77, 82]. In a recent phase III trial of patients with advanced melanoma without BM, the combination of nivolumab and ipilimumab achieved a median PFS of 11.5 months, superior to either monotherapy, but was also associated with more high-grade toxicity (59% for combination ipilimumab/nivolumab vs. 21% with nivolumab) [77].

More data are emerging that checkpoint inhibitors likely possess some efficacy within the CNS. In a phase II study of ipilimumab in 72 melanoma patients with BM, the disease control rate was 24% in patients who were neurologically asymptomatic and not on corticosteroids. One- and two-year survival rates were 31% and 26% in this cohort [80]. Furthermore, there is increasing data that suggests improved OS when SRS is used with checkpoint inhibitors. One retrospective analysis found that the 2-year survival rate of those receiving SRS plus ipilimumab was 47.2%, compared with 19.7% in those who received SRS alone [83]. Another retrospective study of 26 patients with melanoma BM noted an 85% local BM control and a median OS of 11.8 months with nivolumab and SRS to BM [84]. Two recent phase II studies, specifically tailored for patients with melanoma BM, provide even stronger evidence of checkpoint inhibitor efficacy. One study tested ipilimumab and nivolumab in 74 patients with at least one measurable, nonirradiated, asymptomatic BM. Here, the rate of intracranial clinical benefit (57%) was concordant to that of extracranial benefit (56%) with a 20% complete response rate and 30% partial response rate intracranially [85]. Another study with a similar cohort found that combination ipilimumab and nivolumab had an intracranial response rate of 46% (16 of 35) and single-agent nivolumab resulted in an intracranial response rate of 20% (5 of 25) [86]. Similar to prior trials, the combination of ipilimumab and nivolumab was associated with more high-grade adverse events (54% vs. 16% for nivolumab monotherapy) [86].

Despite these promising results, predictive biomarkers of response are desperately needed for more precise tailoring of existing therapies, especially given the high risk of adverse events. Genomic sequencing of melanoma BMs are being analyzed with the hope of identifying mutational profiles associated with better prognoses.

Conclusion

Brain metastases represent an understudied and underserved area within oncology. This entity is associated with poor prognosis, due to significant neurologic morbidity and current lack of durable CNS-directed therapies. Consequently, better treatments for brain metastases are critically necessary, as incidence is rising as therapies for systemic cancer improve. One major reason for current treatment difficulties is the paucity of clinical trials evaluating systemic treatments for brain metastases, due largely to exclusion of patients with CNS disease. Recently, next-generation targeted agents and immunotherapies have demonstrated improved tolerability and promising response rates for CNS disease.

Current trials evaluating these therapeutic strategies specifically for brain metastases are underway and desperately needed to optimize treatment.

Another breakthrough for brain metastases has been the recognition of spatial and temporal genomic heterogeneity across different metastatic sites. Recent genomic analyses have demonstrated the presence of actionable driver mutations within brain metastases not present in the paired primary tumor. This genomic heterogeneity likely contributes to the clinically observed divergent response seen between intracranial and extracranial disease burden. As brain metastasis tissue analysis is not always feasible, noninvasive methods to obtain genomic information are necessary to guide personalized genomic-directed therapy for brain metastases. Novel approaches such as cell-free circulating tumor DNA in the CSF and radiogenomics are under development and promising. These methods, if optimized for clinical use, may be repeated during a treatment course to help determine response and to assist in the early detection of drug-resistant mutations. Such biomarkers would be a critical step forward in better understanding the temporal evolution of brain metastases and informing choice of treatment.

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Classification of Brain Metastases

6

Paul W. Sperduto

Introduction

Brain metastases are a common and complex conundrum for cancer care. An estimated 300,000 patients are diagnosed each year with brain metastases in the United States [1] and that incidence is growing due to advances in treatment that result in patients living longer and thus at prolonged risk for development of brain metastases [2]. It is a complex problem because of the marked heterogeneity of this patient population: brain metastases may arise from a wide variety of tumor types and subtypes. Furthermore, these patients may have already received a plethora of different treatments for their cancer or may present with brain metastases at the time of initial diagnosis. This heterogeneity has long plagued interpretation of clinical trials involving this patient population because it was essentially impossible to sufficiently stratify studies to verify similar groups of patients were being compared [3]. Interpretation of clinical trials and efforts to estimate prognosis are further complicated by the plethora of possible combinations of currently available treatment options [surgery, stereotactic radiosurgery (SRS), whole brain radiation therapy (WBRT), chemotherapy, targeted drug therapies, and immunotherapies]. Furthermore, four prospective randomized trials have shown WBRT adds no survival benefit over SRS alone in SRS-eligible patients [4–7] and, on the other end of the prognostic spectrum, there is evidence that supportive care may be as effective as WBRT [8]. Accordingly, WBRT is used less commonly than in the past.

Classification Systems

These concerns led to efforts to better understand prognosis. The purpose of a prognostic index is to predict outcome before, not after, treatment. It is important to distinguish prognostic from predictive factors. A prognostic factor identifies good versus bad outcome irrespective of the treatment used, whereas a predictive factor identifies good versus bad outcome for a specific treatment. Gaspar et al. published the Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis for brain metastases (Table 6.1) in 1997 [9]. This prognostic index consisted of three classes: I (age < 65, Karnofsky performance score (KPS) ≥70, controlled primary tumor, no extracranial metastases), II (all patients not in class I or III), and III (KPS < 70), which correlated with median survival of 7.7, 4.5, and 2.3 months, respectively, at that time. Weltman et al. published the score index for

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Table 6.1 Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) for patients with brain metastases

Class	Criteria	Median survival
Class I	Age < 65 yrs, KPS ≥ 70, controlled primary tumor, and no extracranial metastases	7.1 mo
Class II	All patients not in Class I or III	4.2 mo
Class III	KPS < 70	2.1 mo

Data from Ref. [9]
KPS Karnofsky performance status

Table 6.2 Score index for radiosurgery (SIR)

	Score		
	0	1	2
Age (years)	≥60	51–59	≤50
KPS	≤50	60–70	80–100
Systemic disease	Progressive	Stable	CR or NED
Number of lesions	≥3	2	1
Volume of largest lesion (mL)	>13	5–13	<5

Data from Ref. [10]
Median survival (MS) by SIR score: SIR 1–3 (MS 2.91 mo), SIR 4–7 (MS 7.00 mo), SIR 8–10 (MS 31.38 mo)
KPS Karnofsky performance status, *CR* complete response, *NED* no evidence of disease

radiosurgery (SIR) (Table 6.2) in 2000 [10]. This index used the sum of scores (0–2) for each of five prognostic factors (age, KPS, status of systemic disease, number of brain metastases, and the volume of the largest metastasis). Lorenzoni et al. published the basic score for brain metastases (BSBM) (Table 6.3) in 2004 [11]. This index is based on the sum of scores (0–1) for three prognostic factors (KPS, control of primary tumor, and extracranial metastases). In 2012, Sloan-Barnholtz published a nomogram (Fig. 6.1) in an effort to further individualize prognosis [12]. In 2014, Kondziolka published an interesting survey study in which experts in the field were asked to estimate survival for a series of patients given all relevant clinical parameters. This study showed that even experts cannot predict outcomes with certainty for all patients [13]. All prognostic indices have limitations but can provide guidance for clinical decision-making and are essential for stratification of clinical trials so that those trials are comparing comparable

Table 6.3 Basic score for brain metastases (BSBM)

	Score	
	0	1
KPS	50–70	80–100
Control of primary tumor	No	Yes
Extracranial metastases	Yes	No

Data from Ref. [11]
Median survival (MS) by BSBM: BSBM 3 (MS >32 mo), BSBM 2 (MS 13.1 mo), BSBM 1 (MS 3.3 mo), BSBM 0 (MS 1.9 mo)
KPS Karnofsky performance status

patients, thus making the results of those trials worthwhile, relevant, and interpretable.

Our group has published a series of articles developing and refining a diagnosis-specific prognostic index, the graded prognostic assessment (GPA), for patients with brain metastases. The GPA was first published in 2008 [14] based on 1960 patients from five randomized Radiation Therapy Oncology Group (RTOG) trials (7916, 8528, 8905, 9104, and 9508). Analysis showed four prognostic factors (age, KPS, extracranial metastases, and number of brain metastases) were significant for survival. Those prognostic factors were weighted in proportion to their regression coefficients and scaled such that patients with the best/worst prognosis would have a GPA of 4.0/0.0, respectively. In 2010, we refined the GPA based on an analysis of a retrospective multi-institutional database of 4259 patients. That study found survival varies by diagnosis and diagnosis-specific prognostic factors [15]. The Breast-GPA was then further refined using tumor subtype [16] and a summary report was published [17]. More recently, the GPA indices for lung cancer, melanoma, and renal cell carcinoma have been updated using molecular and other clinical factors with new data from patients (2,186 lung cancer and 823 melanoma patients) diagnosed since 2005 including molecular factors. The Lung-molGPA incorporates EGFR and ALK gene status [18, 19] and similarly the melanoma-molGPA incorporates *BRAF* status [20, 21]. The original melanoma-GPA found only two factors to be significant (KPS and the number of brain metastases), whereas the updated melanoma-molGPA found five factors (BRAF

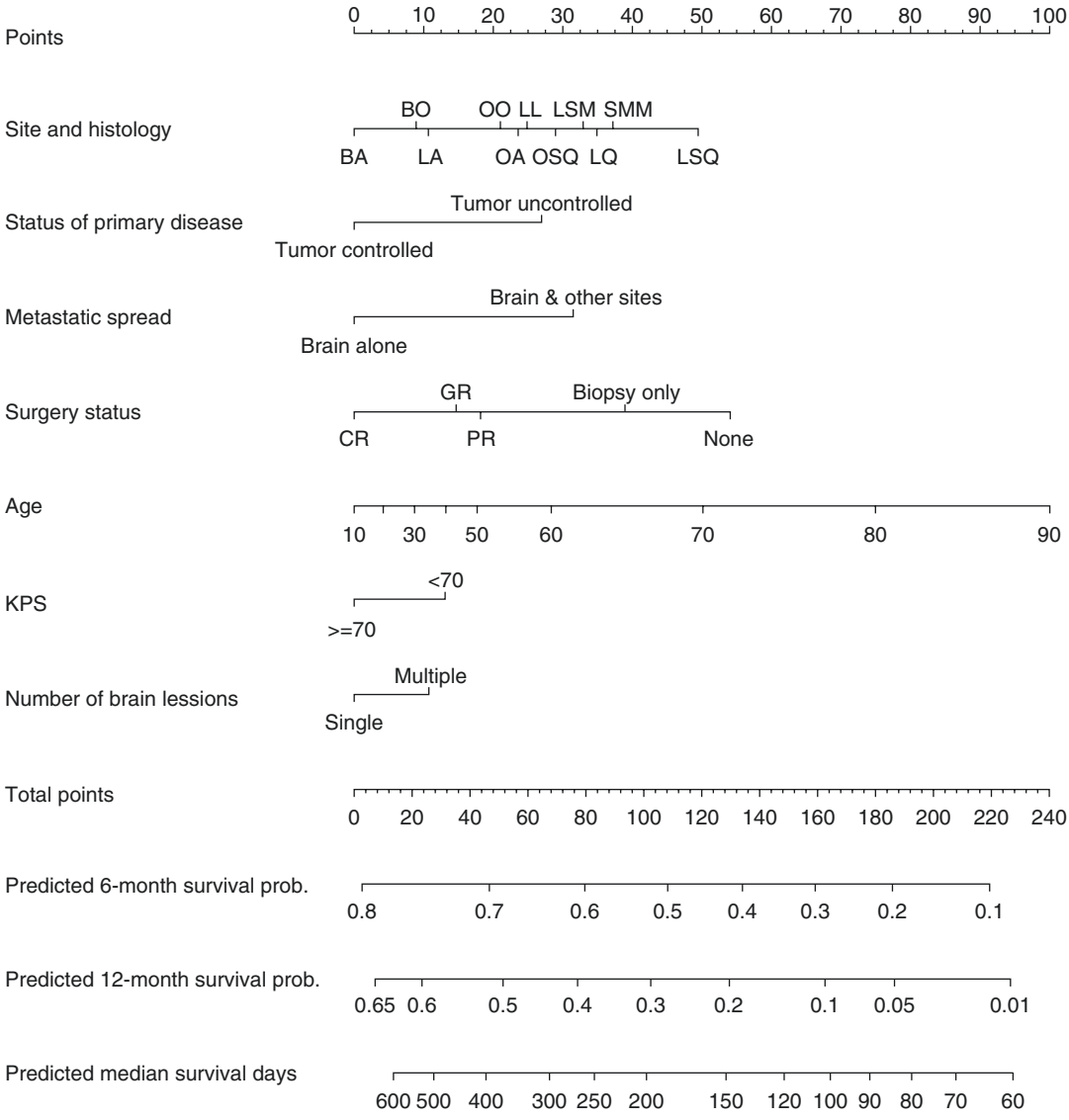

Fig. 6.1 Nomogram for 6-month and 12-month survival probability and median survival prediction for RTOG brain metastases patients. Abbreviations for site and histology: BA breast and adenocarcinoma, BO breast and other, LA lung and adenocarcinoma, LL lung and large cell, LO lung and other, LSM lung and small cell, LSQ lung and squamous cell, OA other and adenocarcinoma, OSQ other and squamous cell, SMM skin-melanoma, OO other and other. Surgery: PR partial resection, CR complete resection, GR gross resection. (Reprinted from Sloan-Barnholtz-Sloan et al. [12], with permission from Oxford University Press)

status, KPS, age, extracranial metastases, and number of brain metastases) to be significant. The renal GPA has also been updated. Data from 711 renal cell carcinoma patients with brain metastases, diagnosed between 2006 and 2016, showed four prognostic factors to be significant for survival: KPS, hemoglobin, extracranial metastases, and the number of brain metastases [22, 23].

Table 6.4 shows the median survival time for patients with brain metastases by diagnosis-specific GPA. Table 6.5 shows the diagnosis-specific definition of the updated GPA indices and a user-friendly worksheet to facilitate cal-

Table 6.4 Median survival time for patients with brain metastases by diagnosis specific—graded prognostic assessment score

		DS-GPA				
Diagnosis	Overall MST (95% CI) *N*	0–1.0 MST (95% CI) *n* (%)	1.5–2.0 MST (95% CI) *n* (%)	2.5–3.0 MST (95% CI) *n* (%)	3.5–4.0 MST (95% CI) *n* (%)	*p* (log-rank)
NSCLC	15 (14–17) 1521	7 (6–9) 337 (22%)	14 (12–15) 664 (44%)	26 (23–31) 455 (30%)	47 (37-NE) 65 (4%)	<0.001
SCLC	5 (4–6) 281	3 (2–3) 65 (23%)	5 (4–7) 119 (42%)	8 (6–9) 84 (30%)	17 (5–27) 13 (5%)	<0.001
Melanoma	10 (9–11) 823	5 (4–7) 136 (17%)	8 (7–9) 386 (47%)	16 (13–19) 256 (31%)	34 (24–50) 45 (5%)	<0.001
RCC	12 (11–13) 669	4 (3–5) 170 (25%)	12 (9–14) 178 (27%)	17 (13–21) 204 (30%)	35 (20–41) 117 (17%)	<0.001
Breast cancer	14 (12–16) 400	3 (3–4) 23 (6%)	8 (6–9) 104 (26%)	15 (13–16) 140 (35%)	25 (23–27) 133 (33%)	<0.001
GI cancer	5 (4–6) 209	3 (2–5) 76 (36%)	4 (3–7) 65 (31%)	7 (5–12) 50 (24%)	14 (10–27) 18 (9%)	<0.001
Other	6 (5–7) 450	–	–	–	–	–

The top row in each cell is the median survival time (MST) in months and its associated 95% CI. The bottom row is the frequency and percentage of patients with the corresponding DS-GPA category for a given diagnosis. Abbreviations: *DS-GPA* Diagnosis specific-graded prognostic assessment, *NSCLC* non-small cell lung cancer (adenocarcinoma), *SCLC* small cell lung cancer, *RCC* renal cell carcinoma, *GI* gastrointestinal, *NE* not estimable

Table 6.5 GPA worksheet to estimate survival from brain metastases by diagnosis

Non-small cell/small cell lung cancer	GPA scoring criteria				Patient
		0	0.5	1.0	Score
	Age	≥70	<70	n/a	–
	KPS	≤70	80	90–100	–
	ECM	Present		Absent	–
	#BM	>4	1–4	n/a	–
	Gene status	EGFR neg/unk and ALK neg/unk	n/a	EGFR pos or ALK pos	–
				Sum total =	–
Adenocarcinoma MS by GPA: GPA 0–1.0 = 6.9; 1.5–2.0 = 13.7; 2.5–3.0 = 26.5; 3.5–4.0 = 46.8					
Non-adenocarcinoma MS by GPA: GPA 0–1.0 = 5.3; 1.5–2.0 = 9.8; 2.5–3.0 = 12.8					
Melanoma		0	0.5	1.0	Score
	Age	≥70	<70	n/a	–
	KPS	<70	80	90–100	–
	ECM	Present	n/a	Absent	–
	#BM	>4	2–4	1	–
	Gene status	BRAF neg/unk	BRAF pos	n/a	–
				Sum total =	–
MS (mo) by GPA: 0–1.0 = 4.9, 1.5–2.0 = 8.3, 2.5–3.0 = 15.8, 3.5–4.0 = 34.1					

Breast cancer		0	0.5	1.0	1.5	2.0	Score
	KPS	≤50	60	70–80	90–100	n/a	–
	Subtype	Basal	n/a	LumA	HER2	LumB	–
	Age	≥60	<60	n/a	n/a	n/a	–
						Sum total =	–
Subtype:	Basal = triple negative (ER/PR/HER2-neg) LumA = Luminal A (ER/PR-pos, HER2-neg) LumB = Luminal B (triple positive, ER/PR/HER2-pos) HER2 = HER2-pos, ER/PR-neg						

Table 6.5 (continued)

Non-small cell/small cell lung cancer	GPA scoring criteria						Patient
MS (mo) by GPA: 0–1.0 = 3.4, 1.5–2.0 = 7.7, 2.5–3.0 = 15.1, 3.5–4.0 = 25.3							
Renal cell carcinoma			0	0.5	1.0	2.0	Score
	KPS		<80		80	90–100	–
	ECM		Present	Absent			–
	Hgb		≤11	11.1–12.5	>12.5		–
	#BM		>4	1–4			–
						Sum Total =	–
MS (mo) by GPA: 0–1.0 = 3.3, 1.5–2.0 = 7.3, 2.5–3.0 = 11.3, 3.5–4.0 = 14.8							
GI cancers		0	1	2	3	4	Score
	KPS	<70	70	80	90	100	–
MS (mo) by GPA: 0–1.0 = 3.1, 2.0 = 4.4, 3.0 = 6.9, 4.0 = 13.5							

Data from Refs. [17, 19, 21]

Abbreviations: *GPA* graded prognostic assessment, *KPS* Karnofsky performance score, *ECM* extracranial metastases, *#BM* number of brain metastases, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *MS* median survival in months, *neg/unk* negative or unknown

culation of the graded prognostic assessment by diagnosis and estimate survival for patients with brain metastases. A free online/smart phone application is available at brainmetgpa.com, which further simplifies the calculation of the GPA.

Table 6.6 shows a multivariate analysis of risk of death and median survival by treatment (excluding drug therapies) and diagnosis. It is important to understand these data are retrospective in nature with the selection bias inherent in all retrospective studies so one should not conclude that one treatment is better than another based on these data. Figure 6.2 shows Kaplan–Meier curves for survival for six diagnoses by GPA, demonstrating excellent separation between groups.

The diagnosis-specific GPA indices presented here define how survival has improved for brain metastasis patients over the past four decades. This progress mirrors the progress seen in survival for patients with the same diagnoses who do not have brain metastases. These data hold several implications for clinical management and research involving patients with brain metastases: (1) There is marked heterogeneity in outcomes for patients with brain metastases and these outcomes vary not only by diagnosis but also by diagnosis-specific prognostic factors, as detailed herein. Because of this heterogeneity, we should not treat all patients with brain metastases the same way—treatment should be individualized and the past philosophy of fatalistic futility should be abandoned. (2) On the other hand, as shown in Table 6.4, if a patient has a GPA of 0–1.0, regardless of diagnosis, their expected survival is poor. For these patients, supportive care, as suggested by the QUARTZ Trial [8], may be the best option. (3) For patients with GPA scores above 1.0, the median survival time (Table 6.4) varies more by diagnosis and more aggressive treatment strategies may be appropriate, but these retrospective data do not provide a basis for assuming that longer survival is a consequence of more aggressive treatment. Indeed, the survival by treatment data shown in Table 6.4 is certainly fraught with selection bias and should not be blindly applied or expected. Nonetheless, these data reflect patterns of care for patients with brain metastases. (4) Performance status is prognostic in every diagnosis. Clinicians should take the time to accurately assess and document their patients' performance status. (5) Table 6.5 shows the number of brain metastases is a significant prognostic factor for lung cancer, melanoma, and renal cell carcinoma, but not for breast or gastrointestinal cancers. Patients should not be denied treatment because of the number of brain metastases. (6) Extracranial metastases are only prognostic in lung cancer and melanoma but not in breast cancer, renal cell carcinoma, or gastrointestinal cancers. The implication here is that those patients with nonlung, nonmelanoma malignancies should not be denied aggressive

Table 6.6 Multivariable analysis of risk of death and median survival[a] by treatment and diagnosis

		Treatment					
		WBRT	SRS	WBRT + SRS	S + SRS	S + WBRT	S + WBRT + SRS
Diagnosis	Statistics						
NSCLC *n* = 1,521	Risk of death (HR)	1.0	1.08	1.20	0.66[b]	0.78	0.79
	95% CI		0.92–1.27	0.94–1.54	0.50–0.88	0.58–1.06	0.40–1.58
	p-value		0.35	0.15	<0.01	0.11	0.51
	Median survival[a]	13	14	10	32	20	20
	n (%)	342 (22%)	767 (50%)	139 (9%)	114 (7%)	76 (5%)	13 (1%)
SCLC *n* = 281	Risk of death (HR)	1.0	0.97	0.24[b]	0.00	0.42[b]	0.00
	95% CI		0.41–2.26	0.10–0.59	NA	0.25–0.73	NA
	p-value		0.94	0.002	0.99	0.002	0.98
	Median survival[a]	4	7	15	12	15	15
	n (%)	229 (81%)	13 (5%)	21 (7%)	1 (0.4%)	16 (6%)	1 (0.4%)
Melanoma *n* = 823	Risk of death (HR)	1.0	0.69[b]	0.62[b]	0.50[b]	0.54[b]	0.70
	95% CI		0.54–0.89	0.45–0.86	0.36–0.69	0.35–0.84	0.36–1.36
	p-value		< 0.01	<0.01	<0.01	<0.01	0.29
	Median survival[a]	6	10	9	13	11	11
	n (%)	91 (11%)	464 (56%)	73 (9%)	95 (12%)	34 (4%)	12 (1%)
Renal cell *n* = 711	Risk of death (HR)	1.00	0.84	0.78	0.38	0.64	1.29
	95% CI		0.62–1.12	0.51–1.19	0.25–0.59	0.38–1.08	0.45–3.68
	p-value		0.23	0.25	<0.01	0.09	0.64
	Median survival[a]	5	11	11	24	16	11
	n (%)	90 (12%)	410 (58%)	41 (6%)	70 (10%)	23 (3%)	4 (1%)
Breast cancer *n* = 400	Risk of death (HR)	1.0	1.07	0.74	0.59	0.72	0.47[b]
	95% CI		0.66–1.73	0.47–1.16	0.28–1.23	0.43–1.21	0.23–0.96
	p-value		0.80	0.18	0.16	0.72	0.04
	Median survival[a]	7	13	15	24	18	30
	n (%)	131 (33%)	115 (29%)	86 (22%)	19 (5%)	28 (7%)	20 (5%)
GI cancer *n* = 209	Risk of death (HR)	1.0	0.72	0.69	2.30	0.33[b]	0.39[b]
	95% CI		0.40–1.28	0.39–1.22	0.43–12.4	0.19–0.56	0.17–0.90
	p-value		0.26	0.21	0.33	<0.001	0.03
	Median survival[a]	3	7	7	9	10	8
	n (%)	95 (45%)	35 (17%)	35 (17%)	2 (1%)	34 (16%)	8 (4%)

Data from Refs. [17, 19, 21]

Diagnoses: *NSCLC* non-small-cell lung cancer (adenocarcinoma), *SCLC* small-cell lung cancer, *GI* gastrointestinal

Treatments: *S* surgery, *WBRT* whole brain radiation therapy, *SRS* stereotactic radiosurgery

Statistics: Risk of death: hazard ratio (HR) normalized to patients treated with whole brain radiation therapy alone (HR = 1.0) and calculated by multivariable Cox regression, adjusted for DS-GPA and stratified by institution

[a]Median survival in months based on one-sample Kaplan–Meier method

[b]Statistically significantly better than WBRT alone; 95% confidence interval

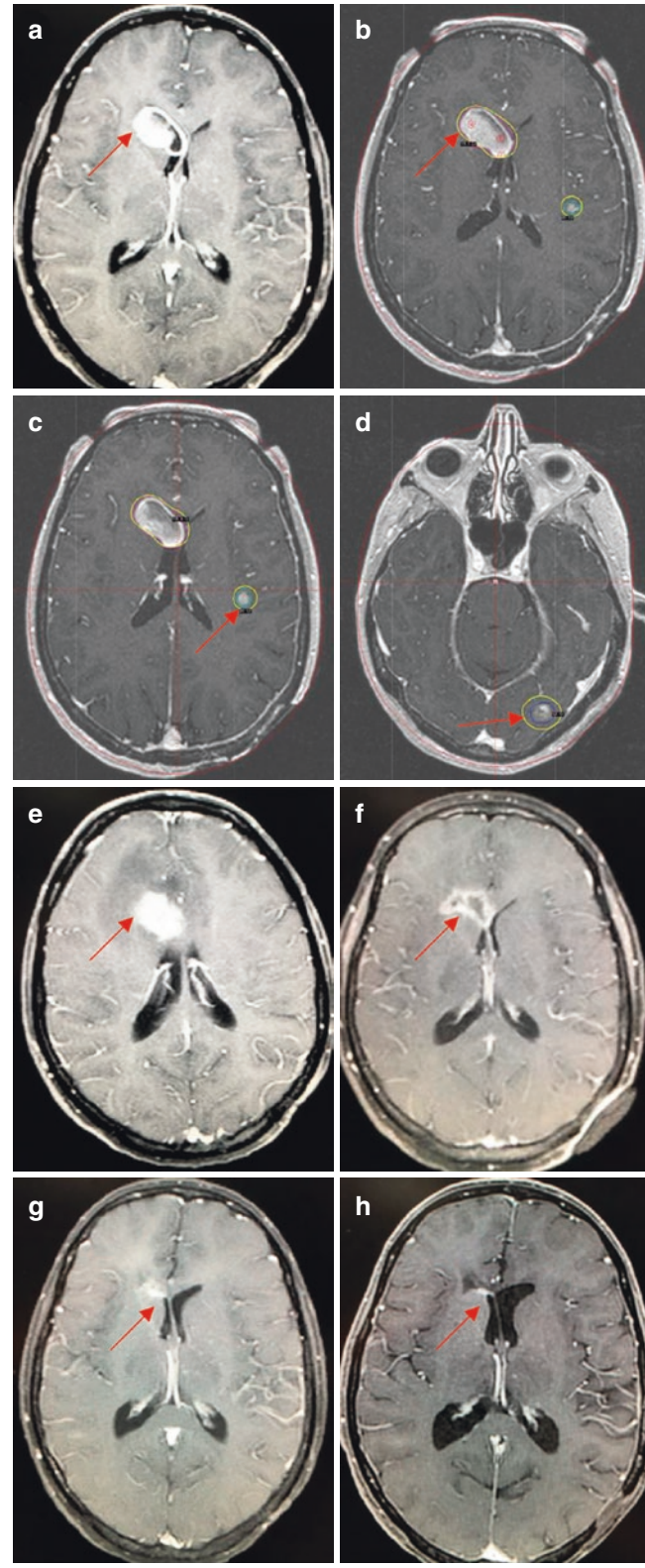

Fig. 6.2 Kaplan–Meier curves for survival by GPA for six diagnoses: breast cancer, non-–small-cell lung cancer, small-cell lung cancer, melanoma, renal cell carcinoma, gastrointestinal cancers. (**a**) Initial MRI shows largest of three brain metastases, December 06, 2006. (**b**) Gamma Knife plan for right frontal brain metastasis, December 13, 2006. (**c**) Gamma Knife plan for left frontal brain metastasis, December 13, 2006. (**d**) Gamma Knife plan for left occipital brain metastasis, December 13, 2006. (**e**) MRI 9 months after GK shows marked radiation necrosis and edema, September 26, 2007. (**f**) MRI 18 months after GK shows resolving radiation necrosis, May 23, 2008. (**g**) MRI 21 months after GK shows minimal residual enhancement, October 23, 2008. (**h**) MRI 10.7 years after GK shows no evidence of disease, August 02, 2017. (From Sperduto et al. [24]. Creative Commons Attribution License CC-BY 3.0)

treatment for their brain metastases because they have extracranial metastases. (7) Age is strongly prognostic in lung cancer and weakly prognostic in breast cancer and melanoma but not prognostic in renal cell carcinoma or gastrointestinal cancers. Thus, age should not be used as a rationale to withhold aggressive treatment for nonlung malignancies. (8) Because lung cancer and brain metastases from lung cancer are so common, those patients have masked our understanding of the distinct course for patients with nonlung malignancies and brain metastases, as demonstrated by points 5, 6, and 7 above. (9) Tumor subtype in breast cancer is of paramount importance and prognostic significance but it is not as prognostic as the Breast-GPA index. (10) A disproportionate number of patients with gastrointestinal cancers present with GPA of 0–1.0. Whether this is due to lack of screening MRI in these patients versus other biological reasons remains unclear but the finding should serve as a reminder that brain metastases are not uncommon in GI cancer patients. On-going research will better elucidate prognosis for these patients and the GI-GPA will be updated accordingly. (11) Clinicians may use the worksheet in Table 6.5 or go to brainmetgpa.com, a free user-friendly smart-phone application to calculate their patient's GPA score and estimate survival [12]. The GPA may be used for purposes of stratification in clinical trials dealing with patients with brain metastases.

All prognostic indices are imperfect and cannot always predict the outcome for an individual patient. The following case study is remarkable for the patient's outcome because it demonstrates not only the application of the GPA in a clinical setting but also the potential pitfalls of prognostic indices for such a heterogeneous patient population.

Case Study

A 36-year-old white female marathon runner presented in August 2005 with a right neck mass. Fine needle aspiration initially confirmed a malignancy, later confirmed as a malignant melanoma by excisional biopsy of a posterior scalp lesion on September 15, 2005. This malignant melanoma was histopathologically staged as Clark's Level IV, Breslow depth at least 6 mm, with angiolymphatic invasion and positive deep and peripheral margins. Brain MRI for initial radiologic staging on September 27, 2005, showed multiple scalp lesions but no evidence of parenchymal brain metastases. PET scan on September 27, 2005, showed hypermetabolic activity only in the left neck. On October 11, 2005, she underwent a left modified radical neck dissection and wide local excision of the scalp lesion. Pathology confirmed metastatic melanoma in 3 of 28 lymph nodes with extension into the adjacent soft tissues in two areas. Pathology from the scalp excision showed a maximum tumor depth of 1.9 cm and the deep margin remained positive. She underwent two additional scalp excisions and the deep margin remained positive. Her stage was T4bN2bM0, stage IIIC. She received 64 Gy radiation therapy to the left neck and scalp, completed on January 20, 2006. She then received three cycles of cisplatinum, interferon, and vinblastine followed by interleukin-2, completed in March 2006. She did well without evidence of recurrence until November 2006 when she underwent a debridement of necrotic tissue in the scalp lesion. PET scan on December 5, 2006, showed a 0.7 cm hypermetabolic nodule in the retroperitoneum consistent with metastatic recurrence. Brain MRI on December 6, 2006, showed three brain metastases (2.5 cm right caudate, 1.1 cm left parieto-occipital, and 0.7 cm left posterior frontal) (Fig. 6.2a), which were not present on the prior scan performed on June 22, 2006.

Whole brain radiation therapy was not given (and has not been given) due to the prior scalp radiation. She underwent SRS (Gamma Knife) on December 13, 2006, to all three lesions: right caudate, 20 Gy to a volume 8.4 cm^3 (Fig. 6.2b); left posterior frontal 24 Gy to a volume of 0.47 cm^3 (Fig. 6.2c); and left parieto-occipital, 24 Gy to a volume of 1.6 cm^3 (Fig. 6.2d). She underwent SABR to the pelvic soft tissue metastasis (25 Gy × 5 over two weeks, completed

on February 23, 2007). Between March and June 2007, she received four cycles of carboplatin, paclitaxel, and temozolomide treatment. In September 2007, she developed headaches, nausea, vomiting, and confusion. MRI on September 26, 2007, showed a marked increase in enhancement and edema in the right frontal lobe consistent with radiation necrosis (Fig. 6.2e). Due to increased headaches and possible radiation necrosis, the temozolomide was discontinued. She has received no treatment since September 2007. The edema was treated with steroids, which were gradually tapered off over four months. Brain MRI on May 23, 2008, showed improvement with central necrosis of the previously solid-appearing lesion (Fig. 6.2f). Brain MRI on October 23, 2008, showed further resolution of the enhancement/necrosis with minimal residual enhancement (Fig. 6.2g). Serial imaging since that time has shown no evidence of recurrent tumor or necrosis.

She remains clinically and radiographically free of disease 13 years after the diagnosis of multiple brain metastases and more than 10 years after completion of treatment. Brain MRI on August 2, 2017, showed no change in the minimal residual enhancement/scar tissue (Fig. 6.2h) and PET scan on August 2, 2017, showed no evidence of disease. She has remained asymptomatic for over a decade and continues to run marathons, as recently as October 14, 2017. In November 2017, she completed the FACT-Brain questionnaire, a patient-reported QOL tool to reassess brain cognition. Her FACT-BR score was perfect (200 on a scale of 200), 11 years after diagnosis of her brain metastases. Notably, this patient never underwent craniotomy or whole brain radiation therapy and thus avoided the related long-term neurocognitive toxicity of these interventions.

To fully appreciate this patient's remarkable outcome, it is appropriate to review how her outcome compares to the best available evidence of survival for melanoma patients with brain metastases. We recently updated and published the melanoma-molGPA [20, 21] based on a multi-institutional retrospective study of 483 melanoma patients with brain metastases diagnosed between January 1, 2006, and December 31, 2015. Notably, the patient presented here was diagnosed in 2006, so she is a contemporary of the patients in the melanoma-molGPA update study. The study showed five prognostic factors significant for survival (Table 6.5).

Overall median survival for melanoma patients with brain metastases has improved from 6 to 10 months since the 1980s, and the median survival by melanoma-molGPA groups for GPA of 0–1.0, 1.5–2.0, 2.5–3.0, and 3.5–4.0 was 4.9, 8.3, 15.8, and 34.1 months, respectively. The patient presented here had a melanoma-GPA of 3.0 on a 4.0 scale on both the original and updated GPA indices, correlating with an estimated survival of 8.8 and 15.8 months, respectively. This patient is disease-free and asymptomatic with a perfect FACT-Brain QOL score 13 years after the diagnosis of multiple brain metastases. Clearly, prognostic indices are imperfect but nonetheless provide our best estimate of survival for these patients.

Summary

Patients with brain metastases are a heterogeneous population and outcomes vary widely by diagnosis and diagnosis-specific prognostic factors. Because of this heterogeneity and the plethora of available treatment options, it is difficult to estimate survival. These problems have complicated clinical decision-making as well as interpretation of clinical trials. The graded prognostic assessment (GPA) is a diagnosis-specific prognostic index that has been updated to reflect the current treatment era by incorporating diagnosis-specific prognostic factors including molecular factors such as tumor subtype and gene status. The GPA is useful for clinical decision-making as physicians determine whether and what treatment is appropriate for these patients. It can also be useful to stratify clinical trials to ensure those trials are comparing comparable patients, which is especially important in such a heterogeneous patient population. Without accurate stratification, the results of clinical trials are uninterpretable and a waste of resources.

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7 The Role of Advanced Imaging in the Management of Brain Metastases

Eaton Lin and Gloria C. Chiang

Introduction

Nearly 20–40% of patients with cancer develop brain metastases [1]. Approximately half of brain metastases are solitary at initial presentation [2], and they can be asymptomatic 25–40% of the time [1]. In the pretreatment period, the primary role of imaging is to detect and diagnose brain metastases, by differentiating them from other neoplastic lesions, including primary brain tumors and nonneoplastic lesions.

Treatment of brain metastases may include a combination of systemic chemotherapy, surgery, and radiotherapy. Multiple forms of radiotherapy exist, including stereotactic radiosurgery (SRS) and whole-brain radiation [3], but stereotactic radiosurgery is often favored due to the risk of cognitive dysfunction following whole-brain radiation. However, SRS leads to a higher risk of radiation injury/necrosis, with a reported relative risk of 19 [4]. Within 6–24 months of SRS, radiation injury occurs in 5–34% of cases [5–7] and can even be seen in patients more than 5 years after radiotherapy [8]. Approximately 10% have symptomatic radiation injury that may require surgery [9].

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In the postradiation period, the primary role of imaging is to differentiate recurrent or progressive metastatic disease in the brain from radiation injury. Radiotherapy leads to breakdown of the blood-brain barrier, which can increase contrast enhancement and vasogenic edema, make treated lesions appear larger, and mimic tumor progression on conventional magnetic resonance (MR) imaging. A study of more than 500 metastases found that almost one-third of metastases treated with radiosurgery showed an apparent increase in tumor volume on postcontrast T1-weighted imaging, typically 6 weeks to 15 months after SRS [10]. Various multimodal imaging techniques, including MR perfusion, MR spectroscopy, diffusion-weighted imaging, and positron emission tomography (PET), have been studied to help differentiate true disease progression from radiation injury.

Recently, there have been exciting advances in the use of systemic immunotherapy to treat brain metastases. A multicenter phase 2 study of combined nivolumab and ipilimumab in metastatic melanoma to the brain found a clinical benefit in 57%, with a complete response in 26% of patients [11]. Pembrolizumab was studied in a small cohort of patients with metastatic non-small-cell lung cancer and was found to show a clinical response in 33% of patients [12]. Patients who receive immunotherapy may develop a transient increase in the size of contrast-enhancing lesions and associated vasogenic edema, which is similar

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to MR imaging findings of patients who undergo radiotherapy. Furthermore, those who receive immunotherapy may have even greater risk of developing radiation-related changes following SRS, with an odds ratio of 2.4 [13]. The immunotherapy response assessment for neuro-oncology (iRANO) guidelines therefore require patients who have apparent tumor progression on imaging, within 6 months of receiving immunotherapy, to undergo repeat imaging in 3 months to confirm tumor progression [14]. Multimodal advanced imaging techniques may play a role in this cohort as well.

The goal of this chapter is to review the advanced imaging techniques used in the management of brain metastases, in both the pretreatment and posttreatment periods.

MR Perfusion

DSC-, DCE-, and ASL-MR Perfusion Techniques

Dynamic susceptibility contrast (DSC) MR perfusion is the most commonly used advanced imaging technique in daily clinical management of brain metastases. This technique involves injecting a bolus of gadolinium contrast intravenously, then monitoring the contrast bolus through a region of brain tissue with dynamic T2∗-weighted MR images. Since gadolinium is paramagnetic, the passage of the contrast bolus decreases the signal intensity in the region of the brain tissue being imaged, and the change in signal intensity over time can be represented on a time-intensity curve. The area under this curve (AUC) is used to derive the cerebral blood volume (CBV), which is a commonly used measure of tumor vascularity or angiogenesis. The relative CBV can be obtained by comparing the CBV of the region of the presumed metastasis with the CBV from an area of uninvolved brain, often in the contralateral hemisphere.

T1-weighted dynamic contrast-enhanced (DCE) MR perfusion is similar to DSC-MR, but uses dynamic T1-weighted images to track the gadolinium-based contrast bolus through brain tissue. DCE-MR is widely referred to as "permeability magnetic resonance imaging (MRI)" because the time-intensity curve reflects both tissue perfusion and vessel permeability. The volume transfer coefficient (Ktrans), a measure of gadolinium leakage from the intravascular to the extravascular space, is commonly used to reflect permeability. The advantages of DCE-MR over DSC-MR are higher spatial resolution and decreased sensitivity to susceptibility effects, due to T1-weighted imaging rather than T2∗-weighted imaging.

Arterial spin labeling (ASL) is a third MR perfusion technique, which has the advantage of not requiring injection of an exogenous contrast agent. Rather, ASL-MRI uses radiofrequency pulses to "label" endogenous arterial blood water, which passes into the capillary bed of the brain tissue of interest. The difference between "labeled" images and unlabeled images is used to derive the cerebral blood flow (CBF). However, ASL-MRI has the main limitation of a low signal-to-noise ratio.

Pretreatment Imaging for Differential Diagnosis

In the pretreatment period, it is important to differentiate brain metastases from a primary brain tumor, such as glioblastoma, since the latter would require more aggressive resection. When there is a solitary brain metastasis, this differentiation can be difficult because both metastases and high-grade gliomas can have avid enhancement and central necrosis. DSC-MRI has been shown to accurately differentiate between the two by using CBV in the peritumoral region; the surrounding T2-hyperintense vasogenic edema of metastases has significantly lower relative CBV than the T2-hyperintense nonenhancing tumor of high-grade gliomas [15, 16]. This method has been shown to have a sensitivity of 77% and specificity of 96% in differentiating metastasis from glioma [17].

Peak height and percentage of signal intensity recovery of the time-intensity curve with DSC-MRI have also been reported to differentiate

solitary metastasis from high-grade glioma [18] (Fig. 7.1). In fact, percent signal recovery was shown to have the higher accuracy than MR spectroscopy (MRS) in differentiating metastasis from lymphoma and high-grade glioma with an area-under-the-curve of 0.97 [19]. Combining percent signal recovery with MRS further increased the area-under-the-curve to 0.99 and increased the specificity from 83% to 100% [19].

Differentiating high-grade gliomas from brain metastases using DCE-MR has also been attempted, although DCE-MR can differentiate only glioblastoma from hypovascular brain metastases, such as non-small-cell lung, breast, and colon cancer; there was no significant difference in permeability parameters between glioblastoma and hypervascular melanoma metastases [20]. In the pretreatment period, when differential diagnosis is key, DSC-MR is believed to have higher diagnostic potential than DCE-MR.

One paper using ASL-MR reported an area-under-the-curve of 0.84 in differentiating metastases from gliomas, finding lower CBF in both the enhancing portion and the surrounding T2 hyperintensity of metastases compared to high-grade gliomas [21]. Although promising, the diagnostic utility of ASL-MRI is still not as high as DSC-MR in the pretreatment setting.

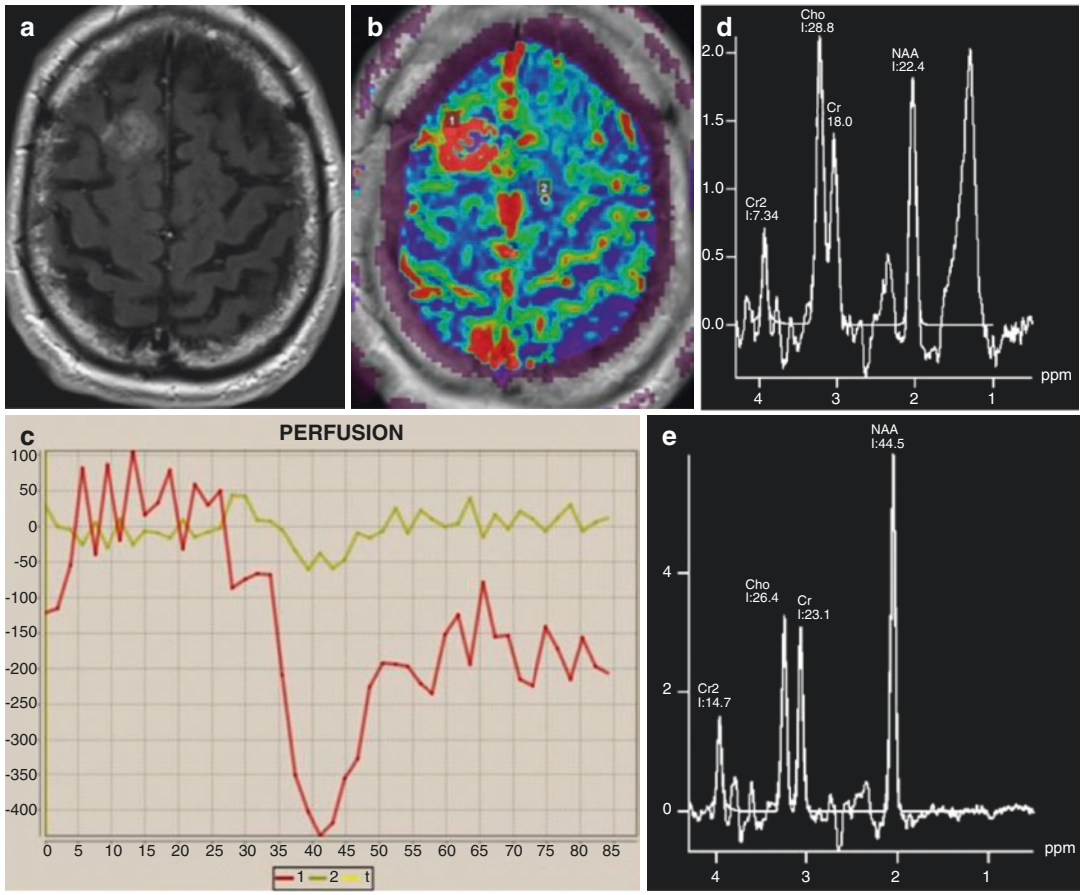

Fig. 7.1 Dynamic susceptibility contrast (DSC) MR perfusion and proton MR spectroscopy to diagnose a solitary brain metastasis in a patient with lung adenocarcinoma. A solitary-enhancing lesion in the right superior frontal gyrus (**a**), seen on postcontrast MRI, demonstrates elevated cerebral blood volume (**b**) and an incomplete return to baseline of the signal-intensity curve (**c**), compatible with a metastasis. Single-voxel proton MR spectroscopy demonstrated an elevated choline-to-NAA ratio (**d**), compared to the unaffected side (**e**), also compatible with a neoplastic lesion, such as a metastasis

Posttreatment

In the posttreatment period, MR perfusion is used to differentiate recurrent brain metastasis from radiation injury, since radiation can break down the blood-brain barrier and result in an apparent increase in contrast enhancement on conventional MRI. A 2009 paper using DSC-MR found that patients with recurrent metastases after gamma knife radiosurgery had a significantly lower percentage of signal intensity recovery, higher relative CBV, and higher relative peak height compared to an area of radiation injury [22]. A study that used both DSC-MR and DCE-MR reported 62% sensitivity and 81% specificity for Ktrans and 74% sensitivity and 82% specificity for CBV in differentiating recurrent metastatic disease and radiation injury [23]. A prospective study in a combined cohort of gliomas and brain metastases found that DCE-MR outperformed 2-(^{18}F) fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) in detecting recurrent metastasis, with plasma volume showing the highest area-under-the-curve of 0.87, resulting in 92% sensitivity and 77% specificity [24]. Another study found that ASL-MR was more accurate than both FDG-PET and thallium single-photon emission computed tomography (SPECT) in differentiating recurrent metastasis from radiation injury, with accuracies of 87, 73, and 53%, respectively, and specificities of 100, 75, and 63%, respectively [25].

MR perfusion has also been found to be prognostic of subsequent treatment response. A longitudinal increase in Ktrans of 15% on DCE-MR showed 78% sensitivity and 85% specificity for predicting progression of metastatic disease 4 weeks after SRS [26]. A decrease in relative CBF on ASL-MR after SRS correctly predicted tumor response [27].

Taken together, MR perfusion is widely used in both the pretreatment and posttreatment management of brain metastases, to both diagnose brain metastases and differentiate recurrent disease from radiation injury. Of the three methods described, DSC-MR is the most widely cited and commonly used technique in daily clinical practice.

MR Spectroscopy

Technique

Proton magnetic resonance spectroscopy (MRS) is another noninvasive imaging technique that can be used to differentiate intracranial metastatic disease from other tumors and radiation-related changes. MRS involves measuring metabolite levels within brain tissue. Typical metabolites assessed include *N*-acetylaspartate (NAA), a marker of neuronal integrity, choline (Cho), a marker of cell membrane turnover, lactate (Lac), a marker of anaerobic metabolism, and lipid, a marker of necrosis. Creatine (Cr), an energy metabolite, is typically used as an internal control against which other metabolite peaks are compared.

Single-voxel MRS methods involve comparing metabolite levels in a prescribed region of interest over the presumed metastasis or peritumoral region with a region of interest over uninvolved brain. Two-dimensional multislice [28] and three-dimensional [29] multivoxel or spectroscopic imaging techniques have also been described. These multivoxel MRS techniques have better spatial resolution, since smaller voxels are used, and cover larger portions of the brain. Since multiple voxels cover the region of interest, tumor heterogeneity can also be better assessed. However, multivoxel MRS has longer acquisition times, due to the millimolar-range concentration of these metabolites, and require additional postprocessing time and expertise. Both techniques require careful voxel placement to avoid contaminating the metabolites of interest with lipid signal from the calvarial marrow, particularly at the skull base, and scalp soft tissues.

Pretreatment

Like MR perfusion, MRS has been studied to differentiate metastases from other brain lesions. There is some evidence that metastases show elevated levels of Cho, Lac, glutamate/glutamine, and myo-inositol, as well as decreased NAA

[30]. One paper reported that MRS, when added to conventional MR sequences, increased the rate of correct diagnosis of intracranial masses, including metastases, from 55% to 71% [31]. Lipid levels, a marker of necrosis, appear to differentiate between high-grade gliomas and metastases [31], with lipid peak-area ratios resulting in 80% sensitivity and specificity [32]. However, another paper reported that MRS could not accurately distinguish metastasis from high-grade glioma, reporting an AUC of 60% [33]. Similar to MR perfusion techniques, MRS may be most effective in assessing the peritumoral region, with lower Cho-to-Cr ratios seen with metastases compared to high-grade gliomas [15, 16]. MRS may even help differentiate among different types of metastases, with higher mobile lipid content in colonic metastases [34] and lower Cho-to-Cr ratios in non-small-cell lung cancer compared to breast and melanoma metastases [35]. Although MRS is available in most tertiary care centers, the additional scanning and postprocessing time required makes this technique less commonly used compared to MR perfusion. Nevertheless, it can often confirm findings seen with MR perfusion or be useful in patients who cannot receive intravenous contrast, such as pregnant patients.

Posttreatment

Since brain metastases treated with radiotherapy often increase in size on conventional postcontrast MR imaging, MRS has also been studied to differentiate recurrent metastases and radiation injury. Weybright et al. reported that Cho-to-NAA, Cho-to-Cr, and NAA-to-Cr ratios on MRS accurately distinguished recurrent metastasis from radiation injury, correctly classifying 96% of patients [36], while Elias et al. reported sensitivities of 86 and 93% and specificities of 90% and 70% using Cho-to-NAA and NAA-to-Cr ratios [37]. In patients with pathologically proven recurrent metastases at surgery after gamma knife radiosurgery, MRS was found to have a positive predictive value of 82% [38]. Chernov et al. reported higher accuracies using multivoxel MRS rather than FDG-PET after gamma knife radiosurgery [39, 40].

Longitudinal MRS can be used to monitor treatment efficacy. A high Cho peak can be seen in viable tumor before treatment, and a decrease in this Cho peak with an increase in the lipid peak after SRS is suggestive of tumor necrosis after treatment [41]. Although a 2016 meta-analysis confirmed that Cho-to-NAA and Cho-to-Cr ratios are useful in differentiating recurrent metastasis from radiation injury [42], the accuracies of these ratios likely decrease when the interrogated lesion includes a combination of tumor and treatment-related changes, as often occurs in clinical practice. Indeed, a paper found that the Cho-to-Cr and lipid/lactate-to-Cho ratios could accurately distinguish lesions that consisted of pure tumor from pure radiation necrosis, but specimens with mixed tumor and radiation necrosis were more difficult to diagnose [43].

Diffusion-Weighted Imaging

Technique

Diffusion-weighted magnetic resonance imaging (DWI) generates image contrast based upon differences in Brownian motion, the random thermal movement of molecules in fluid. A DWI sequence will generate several different images and maps; the most relevant to this discussion are the apparent diffusion coefficient (ADC) and isotropic or trace diffusion maps. Isotropic diffusion maps are the first-line images used for clinical diagnosis, while the ADC images provide a more specific assessment of diffusion characteristics by mathematically removing inherent T2 effects. Areas of relatively free water molecular movement, such as in normal cerebrospinal fluid spaces, will have low signal intensity on isotropic diffusion maps and high signal intensity on ADC, whereas areas of restricted diffusion are hyperintense on isotropic diffusion maps and hypointense on ADC.

A common advanced DWI technique is diffusion tensor imaging (DTI), which employs a

greater number of gradient directions to enable assessment of diffusion directionality; this can convey useful structural information such as white matter tract orientation. The two main parameters derived from DTI data are mean diffusivity (MD), which is analogous to ADC, and fractional anisotropy (FA), which is an index of diffusion asymmetry or directionality within a voxel.

Brownian motion is affected by microenvironmental architecture, temperature, and a variety of other factors, including several pathologic states. The most well-known and common clinical use of DWI is for detection of restricted diffusion in acute infarction. However, restricted diffusion can also be seen in a variety of other pathologic settings, including abscesses, encephalitis, hemorrhage, status epilepticus, demyelinating disease, epidermoid cysts, toxic/metabolic conditions, and hypercellular tumors. The correlation between tumor cellularity and diffusion restriction has generated interest in its utility in tumor diagnosis and management [44–46]. Resulting studies have correlated ADC values to tumor grade, histology, and treatment response [47–51].

Pretreatment

Investigations into the diagnostic role of DWI in the pretreatment setting have largely focused on the differentiation of solitary brain metastases and high-grade gliomas. There is considerable overlap between the signal characteristics and enhancement patterns of these two entities, and conventional imaging alone is often unreliable. Studies investigating DWI characteristics within the area of contrast-enhancing tumor have thus far been incongruous. Numerous studies have shown discordant FA differences for CNS metastases and glioblastomas [52–57]. Similarly, some studies have shown significantly lower MD and ADC values for metastases compared with glioblastomas [58, 59], whereas others have found no statistically significant difference [54, 60].

DWI assessments of peritumoral edema have demonstrated more promising results as a potential differentiating factor. A key histological difference between these two entities is that glioblastomas grow in an infiltrative manner and invade surrounding tissues, whereas metastases are typically expansive and displace surrounding tissues. Given that tumor hypercellularity correlates with diffusion restriction, many authors have postulated that the area of nonenhancing peritumoral edema in glioblastomas may demonstrate greater diffusion restriction—due to infiltration with malignant cells—when compared with peritumoral edema of metastases, which is comprised predominantly of vasogenic edema.

One study supporting this theory demonstrated a gradient of ADC values in the peritumoral edema of glioblastomas, with progressively increasing ADC values further from the enhancing tumor, corresponding to progressively decreased extent of nonenhancing infiltrative tumor [61]. No such gradient was evident within peritumoral edema for brain metastases. Several additional studies have demonstrated significantly increased peritumoral MD for metastases compared with glioblastomas [53, 62, 63] and significantly higher ADC or minimum ADC values for metastases [16, 60, 64], although a few studies still showed inconclusive results [56, 65, 66]. A meta-analysis involving 14 studies with 1143 patients demonstrated moderate performance for DWI and DTI in differentiating metastases from glioblastomas, particularly in analyses of peritumoral edema [67]. This meta-analysis showed a pooled sensitivity of 72.6% and a pooled specificity of 77.0% for studies evaluating enhancing tumor, compared with a pooled sensitivity of 84.7% and pooled specificity of 84.0% for studies evaluating MD and ADC in perienhancing area.

DWI is also helpful for differentiating CNS metastases from many other neoplastic entities. For example, when compared with CNS metastases, ADC values are significantly higher in hemangioblastomas [68] and significantly lower in primary CNS lymphomas [44]. Among CNS

metastases, DWI may have some utility in histologic differentiation. For example, in lung metastases, lower ADC values are associated with poorly differentiated adenocarcinomas and with small-cell carcinomas [69]. DWI also has predictive value for biomarkers in CNS metastases, with lower ADC values in EGFR mutation-positive CNS metastases from lung adenocarcinoma and ER/PR-positive metastases from breast cancer [70–73].

Posttreatment

In the posttreatment setting, DWI is helpful for differentiating progression and pseudoprogression. Pseudoprogression can be seen in up to 33% of metastases treated with stereotactic radiosurgery (SRS) [10, 74, 75]. These subacute posttreatment-related changes may be difficult or impossible to differentiate from true progressive disease based on enhancement patterns and conventional imaging. However, an increase in ADC—presumably reflecting decreased tumor cellularity—when comparing pre- and post-SRS imaging is suggestive of pseudoprogression rather than true progressive disease, although interval decreases in ADC are less reliable for predicting true progression [76–80].

Positron Emission Tomography

Technique and Radiotracers

FDG-PET has been widely used in the imaging of metastatic disease. As a glucose analog, FDG is actively transported into the cell, phosphorylated by hexokinase in the glycolytic pathway, and then trapped within the cell. The FDG that is trapped can then be imaged, and the uptake on PET serves as a proxy for glucose utilization and metabolic activity. Since brain metastases are typically more metabolically active than nontumoral brain regions, they demonstrate greater FDG uptake than normal surrounding brain regions, providing a means for noninvasive tumor diagnosis and monitoring. The commonly used metric to assess metabolic activity is the standardized uptake value (SUV), a ratio of the concentration of radioactivity in tissue to the injected dose per kilogram of the patient's body weight. The SUV within a region-of-interest placed over the tumor can then be compared to a reference region, providing a semiquantitative measure of metabolic activity; either normal-appearing white matter or gray matter is typically used as a reference region.

Since the cortex and deep gray matter of the normal brain is highly metabolically active, it can be difficult to identify tumors, including metastases, which are located in or near these areas on FDG-PET, leading to decreased tumor-to-background ratios. Amino acid tracers, on the other hand, show high tumor-to-background ratios due to low uptake of these tracers in normal brain tissue. Radiolabeled amino acid tracers are taken up by membrane-associated carrier proteins, which are upregulated in tumor cells, and then accumulate inside the tumor cells. Three amino acid tracers that have been widely studied in the setting of brain tumors include ^{11}C-methyl-L-methionine (MET), O-(2-[18F]fluoroethyl)-l-tyrosine (FET), and 3,4-dihydroxy-6-[18F]-fluoro-L-phenylalanine (FDOPA). While MET has a short half-life of 20 minutes, both FET and FDOPA have the added advantage of having a longer half-life of 110 minutes, making it more widely available to clinical practices without their own cyclotron.

Pretreatment

Unlike MR perfusion and MRS, FDG-PET does not play a significant role in the initial diagnosis of brain metastases because the background of normal high cortical metabolism decreases its sensitivity, particularly for lesions less than 1 cm in size [81–83]. Reported sensitivities of FDG-PET for detecting brain metastases range from 27% to 50% [84–86]. Furthermore, some metastases may be hypometabolic, such as mucinous adenocarcinoma and renal cell carcinoma. These may be better detected with amino

acid tracers. One study using MET-PET reported that 80% of the brain metastases that did not show increased uptake on FDG-PET did show increased uptake on MET-PET [87]. MET-PET may also be used for SRS treatment planning because it more accurately delineates the margins of the metastases, resulting in smaller irradiation volumes and longer median survival time [88].

PET also has a limited role in differentiating brain metastases from high-grade gliomas. A study of almost 400 patients using FET-PET found no significant difference between gliomas and metastases [89].

Posttreatment

In the posttreatment period, FDG-PET is widely used to differentiate recurrent metastasis and radiation injury, with a sensitivity and specificity of 71 and 80%, respectively [90] (Fig. 7.2).

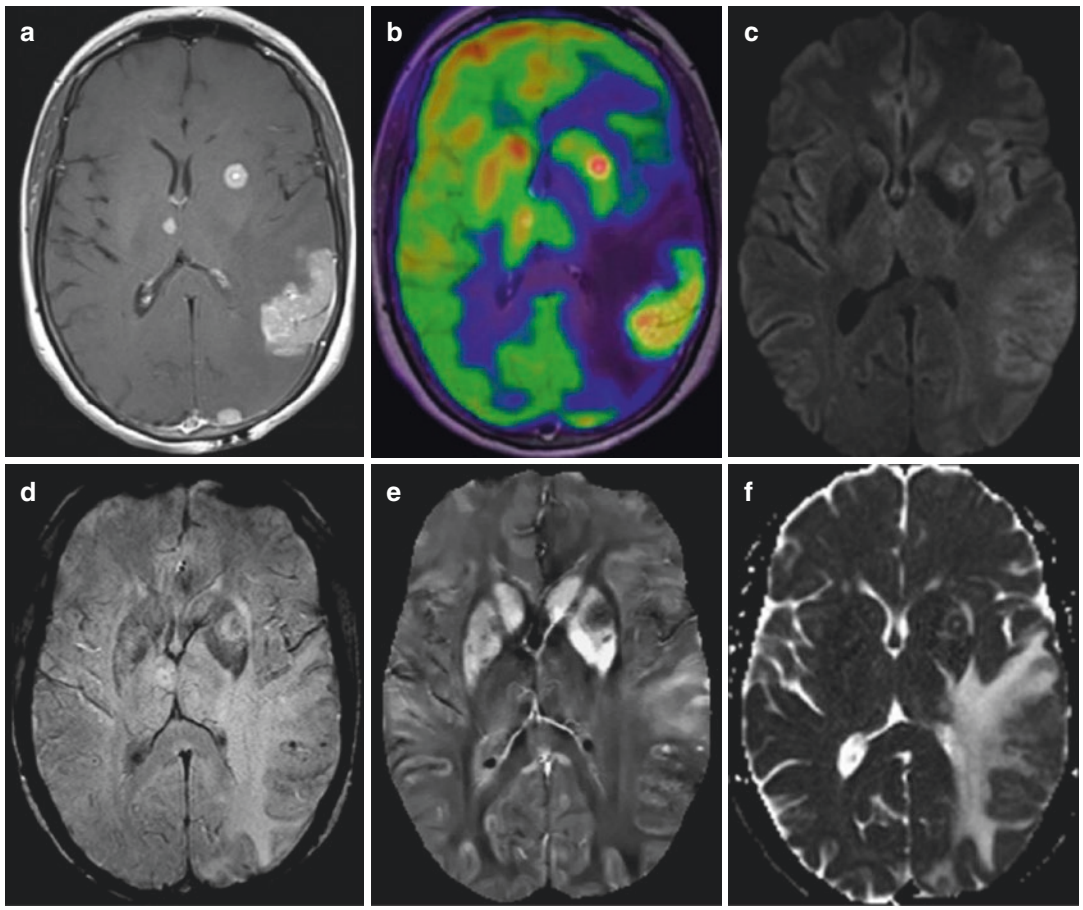

Fig. 7.2 A patient with metastatic breast cancer, who had undergone multiple rounds of systemic chemotherapy and stereotactic radiosurgery to brain metastases, was sent for evaluation after presenting with aphasia. The enhancing lesions seen on postcontrast MRI (**a**) demonstrated marked uptake on FDG-PET (**b**), which were found to represent viable metastatic disease on biopsy. There is also associated reduced diffusion, with signal hyperintensity seen on the b1000 image (**c**) and hypointensity on the ADC map (**f**), likely reflecting hypercellularity. The lesions demonstrated susceptibility hypointensity (**d**), with the lesions predominantly showing hypointensity on quantitative susceptibility mapping (QSM) (**e**), suggest of mineralization posttreatment, but two foci of QSM hyperintensity in the left temporal lobe (**e**), suggestive of intralesional hemorrhage

A decrease in SUV on FDG-PET can also be used to monitor effectiveness of a drug against metastatic disease in clinical trials [91]. Dual-phase FDG-PET, using early and delayed imaging, may increase sensitivity and specificity to 95 and 100%, respectively, with an overall accuracy of 96% [92]. Dual-phase FDG-PET takes advantage of the different time-activity curves between tumor, normal brain tissue and post-treatment inflammatory cells. An increase in the maximum SUV of the lesion relative to normal gray matter suggests tumor rather than inflammatory change. The drawback is that delayed imaging occurs at least 2 hours after initial imaging, which is difficult to maintain in a busy clinical practice.

Amino acid tracers, though used in clinical trials and in research studies, are not yet approved by the Food and Drug Administration (FDA) for clinical use in the United States. Nevertheless, studies have reported high accuracy in differentiating recurrent metastasis from radiation injury with MET-PET, FET-PET, and FDOPA-PET [93–97]. Combined imaging with MET-PET and FET-PET showed sensitivity and specificity of 91 and 100% [95], while FDOPA-PET showed sensitivities and specificities of 81–90% and 84–92% [96, 97], outperforming MR perfusion, which has a specificity of only 68% [96].

Dynamic FET-PET, which allows assessment of parameters such as time-to-peak and slope of the time-activity curves, also found high diagnostic accuracies in the range of 80–90% [98–100], but requires longer acquisition times of 40–50 minutes. In the setting of checkpoint inhibitor therapy for melanoma metastases, dynamic FET has been shown to be particularly useful [101]. With the advent of machine-learning algorithms, a 2018 paper found that FET-PET textural features had slightly higher accuracy than textural analysis of contrast-enhanced MRI in differentiating radiation injury and recurrent brain metastases, 83% versus 81% [102]. This paper found that FET-PET was more sensitive at 88%, and MRI was more specific at 90%, but combined accuracy reached 89%, with 85% sensitivity and 96% specificity.

The main practical limitations of PET in the management of brain metastases are the added cost, time, and radiation exposure. FDG uptake can also be difficult to discern adjacent to areas of normal metabolically active cortex and deep gray matter. Overall, it appears to be less accurate than MR perfusion in the posttreatment setting [24]. The amino acid PET tracers, though higher in accuracy, remain investigational and require access to radiochemistry laboratories and a cyclotron for ^{11}C-compounds.

The use of MRI coregistration with FDG-PET appears to increase sensitivity for detecting recurrent metastasis after SRS from 71% to 86%, but without a significant increase in specificity (80%) [90]. The advent of integrated PET-MRI scanners addresses some of the aforementioned issues by reducing radiation exposure (compared to a PET-CT), reducing imaging time (PET and MRI simultaneously acquired), and improving anatomical resolution for precise localization of metabolic uptake. However, specificity remains lacking.

Susceptibility-Weighted Imaging

Technique

Susceptibility-weighted imaging (SWI) is a high-resolution, velocity-corrected gradient echo MRI sequence. A key feature of this imaging sequence is that it does not refocus spins dephased by magnetic field inhomogeneities. Compounds that have ferromagnetic, paramagnetic, and diamagnetic properties can all interact with the local magnetic field; these field distortions appear hypointense on SWI.

From a clinical standpoint, SWI is markedly sensitive for hemorrhage due to the paramagnetic properties of hemoglobin derivatives such as deoxyhemoglobin, methemoglobin, and hemosiderin. SWI is significantly more sensitive for hemorrhage than other MR sequences such as T2∗- or T1-weighted imaging [103]. SWI is also extremely sensitive for dystrophic calcifications and bone minerals due to their diamagnetic properties. While computed tomography is sometimes used

to further characterize areas of susceptibility identified on SWI, differences in local phase alterations between paramagnetic and diamagnetic compounds will often allow for distinction between calcium and hemoglobin derivates on the filtered phase component of SWI. Newer methods of quantifying these magnetic field distortions—such as quantitative susceptibility mapping—also offer more reliable differentiation between calcium and hemorrhage [104, 105].

Pretreatment

SWI has a mostly supplementary role in the imaging of CNS metastases, primarily being used in the detection of lesional hemorrhage. Classically, CNS metastases from melanoma, renal cell carcinoma, choriocarcinoma, and thyroid carcinoma have a high propensity for hemorrhage, although metastases from many other primaries may also potentially bleed, particularly metastases from lung and breast carcinoma due to their frequency. Presence or absence of hemorrhage is an important feature in imaging characterization of CNS metastases, as the presence of hemorrhage portends poorer prognosis [106].

Given the exquisite sensitivity of SWI for hemorrhage, some authors—particularly of earlier studies on SWI—have hypothesized that early hemorrhagic metastases or micrometastases may be first detectable or better imaged on SWI [107, 108]. However, more recent studies following nonenhancing foci of susceptibility in patients with hemorrhagic brain metastases have not shown these foci to evolve into true metastatic lesions [109], and incidence of hemorrhage has been shown to be significantly lower or absent in micrometastases [110]. The sensitivity of SWI for hemorrhagic metastases also does not rival that of contrast enhanced T1 imaging. A study comparing the sensitivity of SWI with other MR imaging sequences for melanoma metastases demonstrated much higher sensitivity of postcontrast T1 imaging (99.7%) compared with SWI (61.0%) [111]. Nonetheless, 2% of the lesions in this study were more conspicuous on SWI, and 1 out of the 712 lesions was first identified only on SWI. Accordingly, SWI still remains complementary in identification of CNS metastases, in addition to its role in characterizing presence or absence of associated hemorrhage. SWI is also useful for detection of metastases in patients with impaired renal function, contrast allergies, or other contraindications for contrast-enhanced imaging.

Posttreatment

The role of SWI in posttreatment imaging is also largely confined to hemorrhage detection. In particular, radiation-induced cavernous malformations and cerebral microbleeds of other etiologies are relatively common following radiation therapy to the brain [112, 113], and SWI is the most sensitive imaging sequence for identifying these microbleeds [114, 115]. Radiation-induced cavernous malformations have slightly higher prospective hemorrhage risk when compared with nonradiation cavernous malformations [116], and cerebral microbleeds carry important prognostic implications such as an increased risk for cognitive dysfunction [117]. Accordingly, their identification remains an important part of posttreatment imaging characterization. While stereotactic radiosurgery presents no significant additional risk of lesional hemorrhage in CNS metastases [118, 119], smaller series have speculated that radiosurgery may induce breakdown of fragile tumor vessels and contribute to rare hemorrhagic posttreatment complications [120]. Regardless of causal relationships, lesional hemorrhage remains a clinically significant finding in the posttreatment period best assessed with SWI.

Future Directions

The field of neuroimaging continues to undergo rapid development, and many new techniques offer the potential for more detailed characterization of the molecular, cellular, and structural components of brain metastases. The techniques discussed in this section are not yet under widespread clinical use, and further research is necessary. However,

these novel imaging techniques hold promise for future improvements in diagnosis and characterization of brain metastases.

Molecular/Cellular MRI

MR imaging has traditionally been limited to macroscopic anatomical evaluation, which reveals manifestations seen in later stages of disease. For example, contrast-enhanced MRI is the gold standard for imaging brain metastases, with contrast enhancement dependent upon the blood-brain barrier breakdown occurring in later-stage lesions. However, newer techniques enable in vivo imaging of molecular and cellular manifestations that occur earlier in the disease process, such as early inflammation and angiogenesis.

Cellular visualization on MR image requires cell labeling with a detectable agent. Currently, the most commonly used agents are superparamagnetic iron oxide (SPIO) nanoparticles, which are generally composed of an iron core, a polymer coating, and functional moieties. Iron oxide nanoparticles can be administered intravenously, with eventual uptake by phagocytic cells allowing for imaging of inflammation. Alternatively, iron oxide nanoparticles can also be used to label cells in culture prior to injection or transplantation, allowing for cell tracking. A variety of cell types have been labeled and tracked using this technique, including stem cells [121], dendritic cells [122–124], T-lymphocytes [125], and cancer cells [126–128]. Subsequently, imaging with an MR pulse sequence sensitive to iron—such as T2∗ imaging—enables visualization of iron nanoparticle locations.

For imaging brain metastases, one promising avenue within molecular and cellular MRI has been based on the imaging of endothelial vascular cell adhesion molecule-1 (VCAM-1). The vascular endothelium of the brain is profoundly reactive to pathological stimuli, with surface molecules such as VCAM-1 mediating the adhesion and migration of lymphocytes in areas of inflammation [129–131]. Metastatic lesions are closely associated with existing cerebral vasculature [132, 133], and there is evidence of VCAM-1 upregulation during early stages of metastatic lesions [134–137]. The administration of anti-VCAM-1 antibodies conjugated to SPIOs enables highly sensitive in vivo imaging of areas of VCAM-1 upregulation [138]. This technique has demonstrated VCAM-1 upregulation not only in established gadolinium-enhancing brain metastases, but also in nonenhancing micrometastases, with a proportional increase in VCAM-1 expression upon tumor progression [139]. While further research is needed, it is estimated that this technique can already detect brain metastases approximately 300 μm in diameter, allowing diagnosis at substantially earlier stages than with gadolinium-enhanced MRI and opening doors to therapeutic techniques targeting earlier stage disease.

Postcontrast T1 Mapping

The distinction between radiation necrosis and recurrent tumor in the postradiation setting remains a common diagnostic dilemma. While MR perfusion and FDG-PET can be useful differentiating tools, there are limitations to this techniques, including low spatial resolution, degradation by susceptibility artifacts, need for high-velocity bolus injections, and interinstitutional variations in technique and analysis. Based on early research, postcontrast T1 mapping—a technique free of these limitations—shows potential as an alternative for differentiating radionecrosis and recurrent tumor.

T1 mapping enables quantitative evaluation of T1 relaxation times of tissues. Postcontrast T1 mapping can be used to exploit differences in vascularity and contrast enhancement kinetics between radiation necrosis and recurrent tumor. Vasculature in both tumor and radionecrosis exhibits increased permeability, contributing to contrast enhancement on gadolinium-enhanced MRI. However, tumor microvasculature is normally characterized by abundant neoangiogenesis with intact vascular lumens [140–143], contributing to brisk early contrast accumulation and rapid clearance of contrast [144], whereas areas of radionecrosis have damaged vascular lumens and absent neovascularization [140], contributing to

slow accumulation and slow clearance of contrast [145]. Studies of delayed contrast enhanced MRIs (performed greater than 1 hour after contrast injection) have shown contrast clearance in areas of tumor and contrast accumulation in areas of enhancing nontumor tissue [146]. In a study of postcontrast T1 mapping in patients with brain metastases postradiosurgery, T1 values were measured for enhancing lesions 5 and 60 minutes after contrast administration. The authors demonstrated that the difference between these two values could distinguish between recurrent tumor and radionecrosis, with an AUC of 0.97, sensitivity of 81.5%, and specificity of 96.5% [147].

Novel PET Agents

While FDG is the principal oncologic PET imaging agent, new radiotracers continue to expand the diagnostic capabilities of PET for imaging brain metastases. Amino acid radiotracers are the most extensively studied alternative agents (discussed more thoroughly earlier in the chapter). F-18 fluorothymidine (FLT) is another PET agent which—like amino acid tracers—demonstrates lower uptake in normal cerebral parenchyma compared with FDG, allowing for better lesion-to-background contrast [148, 149]. FLT is a thymidine analog retained in proliferating tissue and tumor via thymidine salvage pathways in cellular proliferation [150]. FLT-PET has demonstrated promising results for assessment of treatment response in malignant gliomas and extracranial melanoma [149, 151–154]. There has been less research using FLT-PET for monitoring brain metastases, but preliminary studies have shown potential in FLT-PET response assessment for breast and melanoma brain metastases [155, 156].

Another promising PET agent is 2-(5-fluoropentyl)-2-methyl-malonic acid (^{18}F-ML-10)—a PET probe designed for selective detection of apoptosis. While apoptosis is easily detected in vitro, in vivo assessment is challenging. ^{18}F-ML-10 targets a complex set of cell membrane alterations that occur during the apoptotic process, resulting in selective transmembrane transportation of ^{18}F-ML-10 into apoptotic cells, but not into viable or necrotic cells [157]. The detection of apoptosis posttreatment provides early evidence of response to therapy, at a time when FDG-PET results are often confounded by posttreatment inflammation and persistent tumor cell uptake. In patients undergoing whole brain radiation therapy, significant correlation has been demonstrated between early posttreatment ^{18}F-ML-10 findings and subsequent anatomic changes seen on MR image 6–8 weeks after completion of therapy [158].

There are many additional experimental PET agents with more niche roles; for example, ^{68}Ga-DOTATATE has an affinity for somatostatin receptors, which are highly expressed in neuroendocrine neoplasms and meningiomas, among other tumors. While research with this radiotracer for brain metastases remains minimal, it has been suggested to have greater sensitivity than traditional imaging methods for detecting metastases from neuroendocrine tumors and medullary thyroid carcinoma [159, 160].

In summary, imaging currently plays a major role in the management of brain metastases, both pre- and posttreatment. As more specific MR and PET techniques and tracers continue to be developed, multimodal imaging will serve to detect and monitor the various molecular processes underlying intracranial metastatic disease development.

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Part II

Evaluation of CNS Metastasis

8 Clinical Presentation of Central Nervous System Metastases

Laura E. Donovan and Rajiv S. Magge

Introduction

Central nervous system (CNS) metastases are associated with significant morbidity and mortality and remain one of the most challenging complications of systemic cancer. While intraparenchymal brain metastases represent the most common site of CNS disease, other potential locations in the brain include the pituitary gland, ventricular system and choroid plexus, as well as the spinal cord and leptomeninges [1]. In this chapter we provide an overview of the clinical presentation of CNS metastases including diagnostic workup and initial management.

Brain Metastases

Brain metastases are the most common intracranial malignancy, occurring ten times more frequently than primary brain tumors [2]. The reported incidence of brain metastases varies, ranging from 6% to 30% across various studies [3–6]. The incidence is thought to be increasing, in part due to improved imaging techniques as well as more effective systemic therapies resulting in longer overall survival [3]. The CNS is considered a sanctuary site for disease. While there have been advances in the treatment of certain types of CNS metastases with targeted therapies or checkpoint inhibitors, the majority of chemotherapeutic agents have limited blood-brain barrier penetration [7, 8]. Survival varies greatly depending on the underlying cancer subtype, burden of systemic disease, and other patient-associated factors such as age and performance status [9].

Brain metastases can present at any point along the disease course. The Surveillance, Epidemiology, and End Results (SEER) database recently added information regarding the presence or absence of brain metastases at the time of initial diagnosis. Based on these data, the incidence proportion of brain metastases in all patients with newly diagnosed cancer was calculated to be about 2%. Brain metastases at diagnosis were most common (>10%) in small cell and non-small cell lung cancer regardless of cancer stage. Conversely, among all patients with breast cancer, melanoma, and renal cancer, the incidence at diagnosis was relatively low (0.4%, 0.7%, and 1.5% respectively). Compared to patients with any stage cancer diagnosis, patients with systemic metastases at baseline carried an increased incidence of brain metastases at 12.1%. In this population, the incidence of brain metastases was

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highest in patients with melanoma (28.2%), lung adenocarcinoma (26.8%), small cell lung cancer (23.5%), and renal cancer (10.8%) [10].

The presentation of brain metastases varies dramatically, ranging from incidentally discovered, asymptomatic lesions found during a staging workup to acute neurologic decompensation requiring emergent intervention, particularly in the case of hemorrhagic metastases. Depending on the location, number, size, and degree of surrounding edema, they can present with a diversity of symptoms [11].

Focal Neurologic Deficits

Focal neurologic deficits are the presenting symptom in 20–75% of patients with brain metastases [11, 12]. The specific deficit depends on the location of the tumor. Intraparenchymal metastases are most often found along the grey-white junction or in watershed regions. This is thought to reflect hematogenous dissemination of disease with seeding of distal capillaries by tumor microemboli [13, 14]. While some studies suggest the majority of brain metastases (70–80%) are supratentorial, other autopsy studies have found nearly equal rates of disease in the posterior fossa and cerebellum [15, 16]. Compared to other cancers, breast and lung cancer metastases seem to have a predilection for the cerebellum [17]. Although limited by small sample size, a recent study quantifying the spatial distribution of brain metastases found that metastases were more common along branches of the anterior cerebral artery, particularly in the paracingulate gyrus [18].

Supratentorial metastases can involve any lobe of the brain. Patients with symptomatic tumors in the frontal lobes can present with contralateral hemiparesis as well as personality changes ranging from abulia to disinhibition. When the dominant hemisphere is involved, a Broca's-type aphasia, characterized by difficulty expressing language, can occur. Due to the spatial arrangement of motor function along the homunculus, weakness from cortical lesions may be very specific, such as isolated hand weakness from a metastasis in the hand knob. Lesions in the medial motor cortex often affect the leg, while more lateral lesions tend to involve the arm and face to a larger degree [19].

The temporal lobes include the hippocampus, limbic system, portions of the visual pathways, and Wernicke's area. Temporal lobe metastases, particularly bilateral lesions, can present with short-term memory impairment. If the dominant hemisphere is affected, Wernicke's aphasia, characterized by an inability to comprehend language (also known as receptive aphasia), can result. On exam, a contralateral superior quadrantanopia may be detected if the optic tracts are involved; however, this is not always reported by the patient. Seizures are also very common, particularly with medial temporal lobe lesions [11, 19].

Patients with right parietal lesions often present with visual spatial disturbance, specifically left neglect. This may manifest itself as bumping into things on the left or, in more extreme cases, neglecting the left side completely. Patients may report forgetting to close the car door on the left or improperly clothing the left side of their body. Often there is a lack of awareness of the deficit, or anosognosia, seen with non-dominant parietal lesions. Left parietal lesions can present with acalculia. Contralateral hemisensory loss or visual field deficits, specifically an inferior quadrantanopia, can also be seen. Occipital lesions also present with a contralateral visual field cut, typically involving the entire contralateral hemifield. Complex visual hallucinations have also been reported [11, 19].

Infratentorial disease can present with ataxia or gait impairment. Cerebellar hemispheric lesions can cause ipsilateral dysmetria and incoordination. Lesions affecting the cerebellar vermis are more likely to contribute to truncal instability instead of classic dysmetria. Given the high density of motor and sensory pathways as well as cranial nerve nuclei that run through the brainstem, even small lesions can be highly symptomatic. Brainstem lesions can cause contralateral hemiparesis and hemisensory loss of the face, arm, and leg. If the lower pons (below the facial nucleus) or medulla are affected, patients may present with crossed find-

ings including ipsilateral weakness of the face and contralateral weakness in the body [19].

In the setting of intratumoral hemorrhage, these deficits may be acute in onset; however, in many patients, they progress over the course of days to weeks. Progressive focal neurologic deficits in any patient with known systemic cancer should trigger additional workup for CNS metastases.

Cognitive Impairment

While not often considered a true focal neurologic deficit, cognitive impairment is also common in patients with brain metastases [11]. This can manifest as disorientation, confusion, memory impairment, and/or executive dysfunction. One study evaluating whole brain radiotherapy in patients with lung cancer found that 65% of patients with brain metastases had cognitive dysfunction prior to treatment [20]. In patients with primary brain tumors, cognitive impairment is one of the leading causes of disability and caregiver distress. In caregivers of patients with brain metastases, cognitive impairment was associated with worse coping strategies, which can negatively impact quality of life [21]. While delirium or acute mental status changes are common in cancer patients, this is a less common presentation of brain metastases. In a series of 132 patients requiring neurology consults for altered mental status, brain metastases were the underlying etiology in only 15% of cases [22].

Headaches

Headaches are another common symptom of brain metastases, reported by approximately 25–60% of patients, particularly in the setting of multiple lesions [1, 11]. These can result from increased intracranial pressure (ICP) as well as traction on the dura which contains pain fibers [23]. The classic headache resulting from a brain tumor is focal, worse in the morning, and exacerbated by lying flat or Valsalva maneuvers. These headaches may also be associated with nausea and/or vomiting [24]. However, a prospective study of over 100 patients at Memorial Sloan Kettering Cancer Center with brain tumors (both primary and metastatic) found that the majority (77%) described a tension-type headache that was most often bifrontal or ipsilateral. Unlike classic tension-type headaches, these were more frequently associated with nausea (40%) and worsened with bending over (32%). In this series, the classic morning headache was uncommon [25].

Headaches are also very common in the general population, with an annual prevalence approaching 60% [26]. In a cancer patient with an underlying headache disorder, a change in the frequency, severity, or character of their typical headaches should prompt additional evaluation to exclude brain metastases.

Seizures

Up to one-third of patients with brain metastases present with seizures. In one retrospective study of over 500 patients with surgically resected metastases, multiple lesions, temporal and occipital locations, and bone involvement were all associated with preoperative seizures. Large tumors (>5 cm) and those in locations other than the frontal lobes were associated with uncontrolled seizures preoperatively (defined as requiring more than one antiepileptic drug (AED)). Headaches and cognitive dysfunction were also commonly seen with seizures. In this cohort, subtotal resection, >3 metastatic lesions, temporal lobe location, local recurrence, and no postoperative chemotherapy were all associated with seizures in the postoperative setting [27, 28].

While some studies have suggested the presence or absence of seizures has no impact on overall survival with brain metastases, they can significantly impair quality of life. Each state has laws limiting driving after seizures. Patients also need to be maintained on AEDs, sometimes indefinitely. Poorly controlled seizures are associated with worse outcomes in patients with brain metastases [29].

Numerous studies have demonstrated no benefit to prophylactic AEDs in the primary preven-

tion of seizures, with an increased risk of adverse events [30, 31]. For this reason, the American Academy of Neurology recommends against prophylactic AED use for patients with brain tumors, including metastases [32]. Despite this, prophylactic AED use remains common in practice [33]. Many of the original studies focused on older AEDs with more side effects, while newer drugs such as levetiracetam are often better tolerated with a more favorable risk-benefit profile [34, 35]. There are also data to suggest that primary prophylaxis may be beneficial in a high-risk subset of patients or in the perioperative period to decrease the rate of early postoperative seizures [36, 37]. However, randomized controlled trials are limited and this remains an area of controversy.

Uncommon Intracranial Metastases

Pituitary Metastases

Metastases to the pituitary gland are rare, accounting for 0.14–3.6% of intracranial metastases, although in autopsy series, the incidence has been reported as high as 28%. Breast and lung cancer are the most common cancers to metastasize to the pituitary gland, but many other cancers have been reported. Unlike adenomas, which affect the anterior pituitary gland, metastases tend to have a predilection for the posterior pituitary [38, 39].

Over 80% of pituitary metastases are asymptomatic. In patients who present with symptoms, visual impairment has been reported in almost 50% of cases. The most common visual field deficit seen with pituitary lesions is a bitemporal hemianopia due to compression of the optic chiasm, which overlies the pituitary gland. Endocrine dysfunction, specifically diabetes insipidus (DI) and panhypopituitarism, was reported in over one-third of cases each. Patients with diabetes insipidus often present with increased thirst and urine output. Panhypopituitarism can be more difficult to diagnose as symptoms may be nonspecific including fatigue, lethargy, and orthostasis. Headaches were also common, occurring in 35% of patients. Pituitary apoplexy is a life-threatening emergency characterized by hemorrhage into the pituitary gland. While this is of concern with pituitary adenomas, it is rarely seen with metastases [39].

Leptomeningeal Disease

The leptomeninges include the pia mater, subarachnoid space, and arachnoid membrane surrounding the brain and spinal cord [19]. Metastases to this space are typically a late-stage complication of cancer. While leptomeningeal disease (LMD) is most common in adenocarcinomas and hematologic malignancies, almost any cancer can metastasize to the leptomeninges [40, 41]. As the cerebral spinal fluid (CSF) flows throughout the entire leptomeningeal space, bathing the brain and spinal cord, the presentation of LMD is highly variable and can range from symptomatic hydrocephalus to isolated cranial neuropathies, multifocal deficits, and/or seizures.

When LMD involves the cerebral leptomeninges, patients often present with signs of elevated ICP. Leptomeningeal metastases can interfere with CSF reabsorption through the arachnoid granulations, causing hydrocephalus, or limit ventricular compliance such as in the setting of diffuse subarachnoid tumor, resulting in elevated ICP without radiographic hydrocephalus [42]. Patients often present with positional headaches, worse in the morning or when bending over. These can be associated with nausea or vomiting and sometimes with neck pain and stiffness [43]. Vision changes including blurry vision or horizontal diplopia from a partial cranial nerve VI palsy may also be seen. As ICP increases, patients may become increasingly lethargic [41]. Other alterations in consciousness include seizures or abrupt unresponsiveness precipitated by changing position, a phenomenon known as pressure or plateau waves [42].

Cranial nerve involvement from leptomeningeal disease can manifest as vision changes, numbness over the face, facial weakness, hearing loss, tinnitus, or hoarseness [42, 43]. Involvement of the spinal cord and cauda equina nerve roots can contribute to radicular pain, bowel or bladder dysfunction, or focal numbness or weakness

in the legs [41, 42]. A combination of symptoms affecting multiple levels of the neuro-axis should raise suspicion for LMD in a patient with metastatic cancer [1].

Spinal Metastases

Tumors involving the spine are divided into three categories based on location: extradural, intradural extramedullary, and intradural intramedullary. The vast majority of metastases are extradural [44]. Extradural tumors often arise from the vertebral bodies, most commonly in the thoracic spine, and extend into the extradural space [42, 44]. Initially, these lesions may present with severe back pain. Pain is often severe, worse at night, and may wake the patient from sleep. Both extradural and intradural extramedullary lesions can present with cord compression. As the spinal cord becomes compressed, patients can develop focal neurologic deficits including weakness, numbness, bowel or bladder dysfunction, or gait impairment [43]. Approximately 5% of patients with metastatic cancer initially present with cord compression [45].

Intramedullary metastases are rare, with an incidence of <2%. Although they may be the presenting symptom of disease, intramedullary metastases are typically seen in the setting of known brain metastases or leptomeningeal disease [46]. Patients may present with spinal cord syndromes, such as a Brown-Sequard syndrome, characterized by ipsilateral weakness and vibratory/proprioceptive loss and contralateral loss of pinprick and temperature below the level of the lesion. Pain, weakness, and sensory changes are the most commonly reported symptoms; however, bowel or bladder dysfunction and spasticity can also be seen. Typically patients have a relatively rapid decline as the lesion increases in size, but it is possible for diagnosis to be delayed [47].

Workup and Management

The imaging modality of choice for CNS metastases is gadolinium-enhanced magnetic resonance imaging (MRI) [12]. For patients presenting with focal neurologic complaints, imaging can be focused to the area of highest concern, such as the brain alone or a particular spinal level. In the case of patients with parenchymal brain metastases identified on imaging, full CNS staging is not always necessary if the patient is otherwise asymptomatic. For patients presenting with leptomeningeal disease, workup should include complete imaging of the neuro-axis including brain and total spine, with and without contrast. When there is clinical suspicion for LMD but negative imaging, the gold standard for diagnosis is a lumbar puncture for CSF analysis. Multiple lumbar punctures may be necessary as the sensitivity of CSF cytology does not exceed 90% until after three studies [48]. Extradural spinal metastases arising from the vertebrae rarely occur in isolation, so imaging the entire spine is recommended [49]. Once CNS metastases are identified, systemic restaging is recommended as this has implications for both prognosis and treatment options.

The initial management of a patient with symptomatic brain metastases includes high-dose dexamethasone to decrease edema and reduce symptom burden. Steroids may not be necessary in asymptomatic brain metastases without significant edema. Treatment options for patients with brain metastases have evolved and may include a combination of radiation, surgery, chemotherapy, immunotherapy, or targeted agents. These will be discussed extensively in the later chapters of this book; however, the appropriate approach to the management of each patient depends on the burden of CNS disease, the extent of systemic disease, and the options available for systemic treatment [2, 50, 51].

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9 Management of Seizures in Brain Metastases

Ankush Bhatia and Edward K. Avila

Epidemiology, Incidence, and Etiology of Seizures in Patients with Brain Metastases

Managing seizures is an integral aspect of neuro-oncological care in patients with brain metastases. Seizure has been reported as the presenting symptom in brain metastases in up to 20% of patients [1, 2]. A recent systematic review reported the incidence of seizures at 14.8%, although this has been cited as high as 40% in the literature [1–18]. Regardless of the exact percentage, seizures are a common problem in this population. The incidence varies depending on tumor type: In a retrospective series of 470 patients with brain metastases, the likelihood of seizure was highest in melanoma (67%) and lowest in breast cancer (16%). Other common tumor types were lung (29%), gastrointestinal (21%), and unknown primary (25%). The high incidence of seizure with melanoma brain metastases is thought to be due to the tendency toward hemorrhagic conversion, which can be epileptogenic.

Tumor location is another important factor that can impact the frequency of seizures in patients with brain metastases. Seizures are almost exclusively due to supratentorial disease, most commonly cortical lesions in the frontal lobe, parietal lobe, and temporal lobe. This is undoubtedly due to the inherent epileptogenicity of the cortical gray matter [2]. Occipital lobe seizures are seen less frequently. Masses near the fissure of Rolando are more prone to seizures, but lesions in the pituitary or posterior fossa are rarely associated with seizures unless they invade supratentorially [19]. There is increased risk of seizures with a higher number of metastatic lesions.

Clinicians should carefully consider the etiology of seizures in a patient with brain metastases. In addition to the metastasis itself acting as a focus for seizure, other possibilities include leptomeningeal or dural metastases, metabolic conditions, cerebral infarction or hemorrhage, infections, and treatment-related causes. Table 9.1 identifies some of the potential etiologies of seizures in patients with metastatic brain tumors. Cancer patients are at higher risk for metabolic encephalopathies such as hyponatremia or hypoglycemia, opportunistic infections, or side effects of therapy. Paraneoplastic encephalitis is another potential cause of seizures in patients with systemic cancer.

Much research has attempted to clarify the various factors that contribute to seizure development in patients with brain metastases. While the mechanism of tumor-associated epilepsy remains poorly understood, theories focus on peritumoral amino acid disturbances, local metabolic imbalances, cerebral edema, pH abnormalities, and

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Table 9.1 Possible etiologies of seizures in the patient with brain metastases

Metastatic central nervous system neoplasms	Treatment-related causes
Parenchymal metastases	Radiation therapy
Dural-based metastases	Acute
Leptomeningeal metastases	Early-delayed
	Late-delayed
Toxic/metabolic conditions	Chemotherapy
Hyponatremia	Antimetabolites
Hypoglycemia	Methotrexate
Hypoxia	Cytarabine
Hypocalcemia	l-asparaginase
Hypomagnesemia	Vincaakaloids
	Topoisomerase inhibitors
Cerebral infarction	Alkylators
	Ifosfamide
Cerebral hemorrhage	Nitrosoureas
	Cisplatin
Infections	Bevacizumab
Bacterial	
Listeria monocytogenes	Opioids
Viral	Meperidine
Cytomegalovirus	Antiemetics
Herpes simplex	Phenothiazines
Fungal	Butyrophenones
Cryptococcus neoformans	Antibiotics
Aspergillus fumigatus	Penicillins
Candida species	Fluoroquinolones
Parasites	Imipenem-cilastatin
Toxoplasma gondii	Paraneoplastic disease

**Edited and updated from (Table 4–9, pg. 108, from DeAngelis/Posner book "Neurological Complications of Cancer" 2nd edition. Edited and updated with permission from Oxford University Press

altered immunologic activity (Fig. 9.1) [20, 21]. Further understanding of these mechanisms may elucidate why some patients with seizures become refractory to antiepileptic drugs even after removal of the metastatic lesion.

Clinical Manifestations

Seizures in patients with brain metastases are usually focal but can appear generalized if the focal discharge is asymptomatic. The presence of an aura (warning sign), or specific ictal and peri-ictal phenomena, typically reflects the tumor's location within the brain. The ictus can be caused by cortical irritation from invasion of cortical brain parenchyma, adjacent leptomeningeal deposits, or local edema. Tumor-related seizures are often repetitive or stereotyped, preceded by an aura and followed by a postictal phase. The International League Against Epilepsy (ILAE) recently proposed a new classification of seizure types that classifies focal seizures based on whether consciousness is altered during the episode [22].

Focal seizures with retained awareness (previously known as simple partial seizures) are further separated based on the semiology and epileptic region on the cortex. For example, a seizure in the occipital cortex may manifest as flashing lights in the opposite field of vision, whereas a seizure that begins in the motor cortex may cause rhythmic jerking movements of the contralateral face, arm, and leg. A parietal cortex seizure can disrupt spatial perception, while a mass in the dominant frontal cortex can disrupt language and cause aphasic seizures. Temporal lobe seizures may begin with auras such as an abnormal taste, smell, or gastrointestinal symptoms. Patients may experience only auras, which are focal seizures that can cause symptoms, but not impair consciousness. Auras can be present for months and eventually progress to a generalized seizure [23]. Patients may either return to normal immediately after the event or have a prolonged postictal period of worsened neurological function, corresponding to where the seizure originated in the brain. Notably, a patient with a focal motor seizure of the arm may suffer from postictal weakness that can last for minutes to hours, also known as Todd's paralysis.

Focal seizures with impaired consciousness, formerly known as complex partial seizures, occur in patients who have alteration of awareness during the event. During these seizures, patients may be alert but not respond to environmental stimuli; they may engage in repetitive behaviors like facial grimacing, chewing, or lip smacking, otherwise known as automatisms. Hostile or aggressive behavior can also occur in patients who have a focus in the deep frontal lobe. Similarly, patients may have an aura, ictal period, followed by a postictal period.

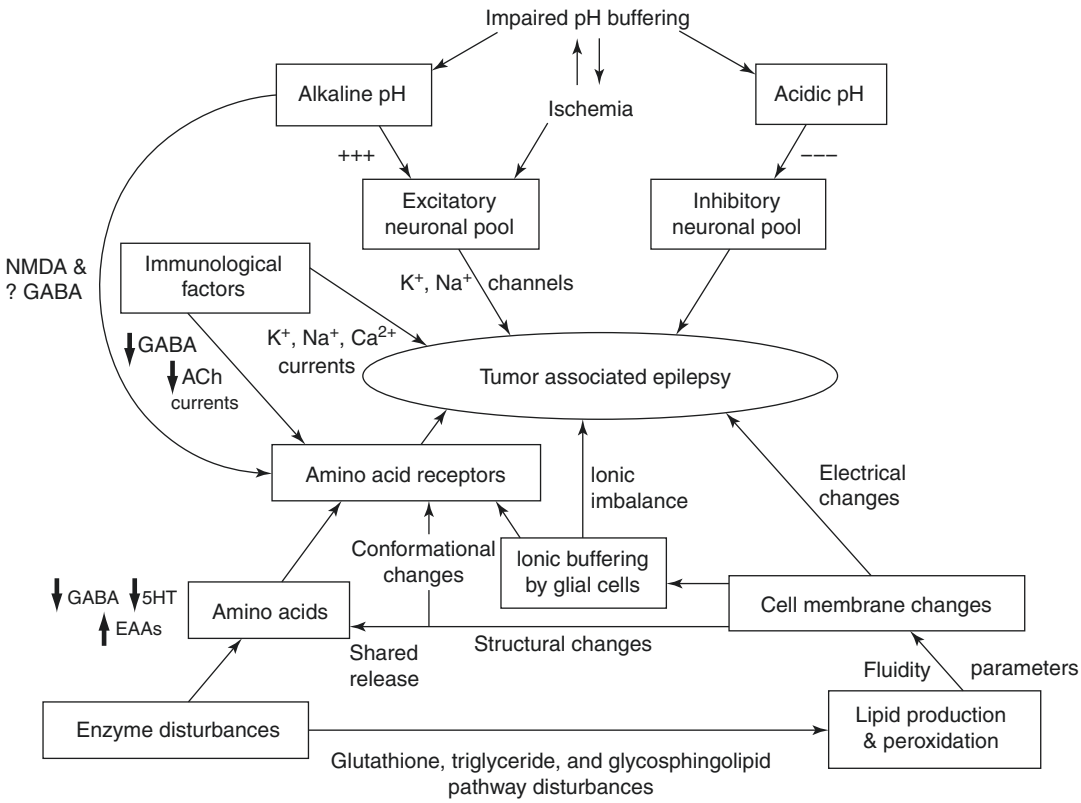

Fig. 9.1 Summary of possible causative and influencing mechanisms on tumor-associated epilepsy. The rich interplay of the varied factors and many plausible routes for seizure causation is highlighted. (From: Beaumont A, Whittle IR. The pathogenesis of tumour associated epilepsy. Acta Neurochir (Wien). 2000;142(1):1–15. Reprinted with permission from Springer)

Any type of focal seizure can progress to generalization, which often involve tonic-clonic movements. The tonic phase begins with a sudden loss of consciousness followed by stiffening of the arms, legs, chest, and back, which can then evolve into jerking of muscles for minutes. The clonic phase is characterized by tongue biting as well as frothy and bloody sputum. The postictal phase begins after movement has ceased; the patient usually enters a deep sleep that can last several minutes before the patient gradually wakens.

Of note, plateau waves (or pressure waves) in a patient with elevated ICP, often due to leptomeningeal disease, can frequently mimic seizure; however, the two diagnoses should not be confused as treatment differs significantly. Plateau waves are events that can involve dizziness, lightheadedness, presyncope, or even frank syncope and are typically associated with positional changes (e.g., sitting to standing). These episodes occur in the setting of increased intracranial pressure (ICP) or venous obstruction, even in the absence of headache. Key physical exam findings that would suggest increased ICP include papilledema on funduscopic exam and hydrocephalus on imaging. Seizures have been reported in up to 25% of patients with leptomeningeal disease. Patients with seizures should be treated with antiseizure drugs, while patients with increased ICP should be treated with steroids and/or neurosurgical intervention.

Brain tumor patients can also develop status epilepticus, which may be either focal or generalized, convulsive or nonconvulsive. Management of status epilepticus is discussed later in this chapter.

Diagnostic Evaluation

The diagnostic evaluation of a brain metastasis patient with a seizure requires careful history taking, detailed neurological exam, electroencephalography (EEG), and neuroimaging [19, 24]. The history of present illness should include a reliable description of the event not only from the patient but also from an eyewitness, understanding that one is not always present. Questions should focus on possible triggers or precipitants of seizure that can lower the seizure threshold, such as strong emotions, exercise, and alcohol use [25]. An accurate description of the seizure involves descriptions of the events leading up to the seizure, the ictal phenomena, and the postictal state. The history summarizes the various seizure semiologies, past antiepileptic use with associated side effects, birth history, and any history of CNS infections. The neurological exam of a seizure patient is usually normal unless a structural CNS lesion causing localizing signs such as Todd's paralysis is present. Comprehensive laboratory testing including AED levels, complete blood count, electrolytes, glucose, calcium, magnesium, renal function, liver function, and urinalysis should all be completed in case there are any reversible metabolic abnormalities lowering the seizure threshold [26].

EEG is an important diagnostic tool for the evaluation of a seizure patient. EEG can help support the diagnosis of epilepsy, localize the origin of epileptic activity, and at times assist in determining the underlying epileptic syndrome. However, there are limitations of EEG. For example, intermittent EEG changes and interictal epileptiform discharges (IEDs) can be infrequent and not always present during the recording of a patient who has had a prior seizure. Additionally, epileptic activity from brain metastases that are small or deep in the brain may not have a concordant EEG finding as these microvolt signals may not be visible on scalp recordings. Clinicians must thus understand the strengths and weaknesses of EEG to diagnose a patient with epilepsy. An EEG may not be required in a patient who has had a clinically obvious seizure with full recovery. EEG is also not routinely needed for those without clinical evidence of a seizure. However, EEG is essential for diagnosing nonconvulsive seizures and nonconvulsive status epilepticus (NCSE) and should be considered in all patients with brain metastases who have altered mental status.

Monitoring patients during the diagnostic workup can be done with a routine EEG (ambulatory or inpatient) or with prolonged video EEG monitoring while inpatient. During a routine EEG, electrical activity is recorded from electrodes placed on the scalp in standard positions for a short amount of time—generally 30 min. The sensitivity of detecting IEDs is low in a routine EEG and can be increased with prolonged monitoring overnight with video EEG monitoring [27]. Sensitivity can also be increased when seizure frequency increases and timing of EEG is closer to last seizure or if seizures are provoked by hyperventilation, photic stimulation, sleep deprivation, or medication withdrawal. However, treatment should never be delayed if the clinician believes that seizure is the most likely diagnosis. Interpretation of EEG findings is best done by an experienced clinician with specific training in EEG. Lateralized periodic discharges (LPDs, previously known as PLEDs) are commonly seen in patients with rapidly growing cerebral malignancies, which cause acute cortical injury. LPDs are defined by lateralized, persistent spikes, sharp waves, or sharply contoured slow waves that occur repetitively [28]. Focal slowing or generalized slowing of the EEG rhythm is nonspecific and can be seen in patients with multiple systemic issues, a postictal period, or an underlying structural lesion that is not necessarily epileptogenic.

Neuroimaging is vital to the evaluation of seizure in a patient with suspected or known brain metastases [29]. Computed tomography (CT) is usually the first imaging modality obtained in a patient with a new-onset seizure because it is available quickly and can exclude certain neurological emergencies such as hemorrhage [29, 30]. Contrast-enhanced magnetic resonance imaging (MRI) is a more sensitive imaging modality for the detection of brain metastases

than CT and is the neuroimaging modality of choice [31]. Better spatial resolution and soft-tissue contrast allows for visualization of smaller brain metastases and leptomeningeal disease. Positron-emission tomography (PET) and functional MRI are additional neuroimaging modalities that can be used for presurgical evaluation of patients with brain metastases [32].

Lumbar puncture should be performed if there is suspicion for a CNS infection or leptomeningeal metastasis. Appropriate neuroimaging with CT or MRI should be performed before lumbar puncture to rule out any space-occupying lesion that may render the procedure unsafe.

Treatment

Seizures in patients with brain metastases contribute to morbidity and mortality and should be aggressively treated when they occur [33]. The two mainstays of treatment include antiepileptic drug therapy and tumor-directed therapy. Anti-seizure drug therapy is usually first to be administered while plans are made for tumor-directed therapy.

Anti-seizure Drug Therapy

Every patient who has a seizure due to a brain metastasis should be treated with anti-seizure medications due to the high risk of recurrent seizure. There are no randomized trials that have established superiority of one agent over another agent in this population. AEDs should be chosen with the goal of controlling seizure at the lowest effective dose while minimizing toxicity. Certain AEDs require monitoring serum levels at recommended intervals. AED interactions with chemotherapy regimens should also be considered before prescribing.

AEDs with no or minimal hepatic enzyme-inducing or enzyme-inhibiting properties, such as levetiracetam, brivaracetam, pregabalin, lamotrigine, lacosamide, and topiramate, are generally preferred in initial treatment due to a favorable side effect profile and minimal drug-drug interactions (Table 9.2) [34–37]. Levetiracetam is often prescribed in the general population because it is well-tolerated; however some patients can have neuropsychiatric side effects such as irritability, agitation, anxiety, and depression [37]. Clinicians should remain vigilant as patients with frontal lobe brain metastases are at higher risk for these neuropsychiatric side effects.

Multidrug regimens should be avoided if possible since monotherapy will increase the likelihood of compliance, provide a wider therapeutic window, and be more cost-effective over time. Single-drug therapy also minimizes potential interactions with chemotherapy and other drug-drug interactions. Data from patients with primary brain tumors suggest approximately 50% of patients with tumor-related epilepsy will respond adequately to a single AED [38]. If a patient experiences recurrent seizures, the initial AED dose should be maximized, and appropriate serum levels should be checked before switching or adding a second anti-seizure drug. Lacosamide has been shown to be efficacious as an adjunctive agent in patients with medically refractory epilepsy and primary brain tumors [39, 40].

Levetiracetam

One retrospective study examined the role of levetiracetam in patients with metastatic brain tumors—of the 13 patients treated with levetiracetam as monotherapy (6 patients) or adjunctive therapy (7 patients) with a median dose of 1000 mg/day, the median seizure frequency decreased to 0 per week, suggesting complete seizure control. Only 3 of 13 patients reported somnolence or headache as the most common adverse event [41]. There does not appear to be any significant interaction with other drugs or chemotherapy, which is why levetiracetam is often the first drug used for neuro-oncologic patients. It is also conveniently available in both oral and intravenous forms. Brivaracetam is a newer formulation that is advertised to have similar efficacy without the psychiatric side effects of levetiracetam; however, there have been no studies of this drug in brain metastases.

Table 9.2 Antiepileptic drugs

	Average dose (serum therapeutic range)	Metabolism	Mechanism of action	Common adverse effects
Enzyme-inducing AEDs				
Phenytoin	20 mg/kg load, then 3–5 mg/kg daily or twice daily (10–20 ug/mL)	Hepatic	Sodium channel	Rash, osteomalacia, Stevens-Johnson syndrome, gum hyperplasia, hirsutism
Carbamazepine	800–2400 mg, two to four times a day (8–12 ug/mL)	Hepatic	Sodium channel	Drowsiness, diplopia, rash, Stevens-Johnson syndrome, leukopenia, hyponatremia
Phenobarbital	10 mg/kg load, then 1–3 mg/kg/d (15–40 ug/mL)	75% hepatic; 25% renal	GABA	Drowsiness, Stevens-Johnson syndrome, frozen shoulder, rash, ataxia, mood change
Oxcarbazepine	900–2400 mg two to four times a day	80% hepatic	Sodium channel	Hyponatremia, diplopia, headache, drowsiness
Nonenzyme-inducing AEDs				
Valproic acid	10–60 mg/kg three to four times a day (60–100 ug/mL); intravenous infusion rate is 20 mg/min, same dose as oral	Hepatic	GABA, sodium channel	Hair loss, weight gain, pancreatitis, thrombocytopenia, platelet dysfunction, tremor, parkinsonism, extrapyramidal syndrome
Gabapentin	900–4800 mg daily in three to four doses	Renal	GABA	Drowsiness, rapid titration, ataxia, weight gain
Pregabalin	150–600 mg/day	Unknown	Calcium channel	Drowsiness, dizziness, ataxia
Topiramate	100–400 mg twice a day	30–50% hepatic; 50–70% renal	Sodium channel, GABA, AMPA/kainate	Cognitive impairment, paresthesias, slow titration, weight loss, renal calculi
Levetiracetam	500–2000 mg twice a day	Enzymatic hydrolysis	Synaptic vesicle protein binding	Agitation, psychosis, drowsiness, glaucoma
Brevitaracetam	50–100 mg twice a day	Hepatic and extrahepatic amidase mediated hydrolysis	Synaptic vesicle protein binding	Drowsiness, ataxia, nystagmus, hypersomnia
Lamotrigine	300–500 mg twice a day	85% hepatic	Sodium channel	Drowsiness, rash, particularly with concurrent valproate, slow titration
Zonisamide	200–600 mg once or twice a day (10–30 ug/mL)	>90% hepatic	Calcium, sodium channel	Drowsiness, headache, weight loss, renal calculi, slow titration
Lacosamide	200–400 mg/day	Hepatic demethylation	Sodium channel	Dizziness, headache, diplopia, blurred vision
Clobazam	5–40 mg/day	Hepatic N-demethylation	GABA agonist	Sedation, cognitive effects, drowsiness

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Phenytoin

Phenytoin is very effective in controlling seizures in brain metastases and is often preferred in the setting of status epilepticus as it can be conveniently loaded intravenously or given orally. It is often not preferred in routine management of seizures in patients with cancer, however, due to its activity as a CYP3A4 inducer and potential interaction with chemotherapy. It also has several side effects including elevated liver function tests, osteomalacia, ataxia, nystagmus, myopathy, and myelotoxicity.

Zonisamide

Zonisamide has not been specifically studied in brain metastases, but it has been investigated in other brain tumors. A study of six patients with glial brain tumors showed an 83% response rate and 69% reduction in seizure frequency [42]. Limiting side effects include renal calculi, sexual dysfunction, and drowsiness. The drug does not appear to interfere with the metabolism of other drugs that utilize the cytochrome P-450 enzyme system.

Oxcarbazepine and Carbamazepine

A retrospective study analyzed oxcarbazepine (mean dosage, 1162.5 mg/day) to assess efficacy and tolerability compared to phenobarbital and carbamazepine in patients with brain metastases. The results showed significantly fewer side effects with oxcarbazepine compared to these other drugs with equivalent efficacy [43]. Patients on therapeutic doses of carbamazepine may complain of intermittent diplopia as well as drowsiness. Carbamazepine can also cause leukopenia, which can be especially concerning in patients who are receiving myelosuppressive chemotherapy. The drug has also been reported to be associated with SIADH, aseptic meningitis, and rash. While oxcarbazepine can rarely cause rash and sedation, it is thought to have a more favorable side effect profile than carbamazepine.

Gabapentin and Pregabalin

Gabapentin was studied as an adjunctive antiepileptic in four patients with metastatic brain tumors, and there was reported seizure resolution in half of patients [44]. Similarly, another study showed that pregabalin (median dose, 300 mg) had a greater than 50% reduction in seizure frequency in patients with primary brain tumors [45]. Gabapentin and pregabalin appear to be quite safe, and these drugs are widely used in cancer patients to treat chemotherapy-induced peripheral neuropathy. There is little to no interaction with other agents; however, side effects include somnolence, dizziness, ataxia, fatigue, and weight gain.

Topiramate

Topiramate has been studied in primary brain tumors (n = 47) as an adjunctive therapy or monotherapy (mean dose, 240 mg/day). It has been reported to result in a 76% seizure reduction of greater than 50% with only 8% of patients experiencing side effects that led to discontinuation in 6% [46]. Notable side effects include somnolence, fatigue, psychomotor slowing, confusion, weight loss, glaucoma, and kidney stones. Little is known regarding its interaction with anticancer agents.

Tumor-Directed Therapy

Treatment of brain metastases with surgery, radiation therapy, and/or chemotherapy may also improve seizure activity. Lesionectomy of the suspected epileptogenic zone has been shown to be efficacious in non-brain tumor patients, which has been extrapolated to brain tumor patients. But while several studies have examined the role of surgery in control of epilepsy, few of these studies were specifically focused on brain metastases; there are no standardized surgical approaches for seizure control in brain tumor patients. Additionally, it is difficult to compare studies focused on seizure surgery and brain tumors due to variable histology, pathology, and tumor locations. It is hypothesized that seizures in tumor-associated epilepsy do not necessarily originate from the mass lesion but rather from the adjacent brain tissue, and therefore tumor-associated epilepsy may differ from idiopathic epilepsy [47].

Three operative strategies exist for brain tumor resection for patients with seizures: (1) focal tumor resection, (2) radical tumor resection without electrocorticography, and (3) radical tumor removal with electrocorticography. Despite these options, resection without electrocorticography may not eliminate the epileptogenic focus. Likewise, many patients require antiepileptic drugs before, during, and after tumor resection. Several studies have demonstrated seizure frequency reduction after treatment

of primary brain tumors with chemotherapy, although none of these studies specifically included brain metastases [48–53].

Prophylaxis

The data for prophylactic anticonvulsants in patients with brain metastases are limited. A recent meta-analysis found only one study which met their inclusion criteria, the most strenuous of which was baseline information on study participants, including subgroups of those with brain metastasis [54]. The recommendation was level 3 for adults with brain metastasis who do not experience a seizure due to their metastatic brain disease; routine AED prophylaxis was not recommended. The recommendation was based on a study included in the meta-analysis, which used phenytoin or phenobarbital as a prophylactic AED [55]. Since seizure incidence was not significantly different in the treatment versus nontreatment group, the authors cited adverse effects of AEDs as a reason against their use.

However, newer AEDs such as levetiracetam and lacosamide have gained popularity in the brain tumor population and are thought to be useful and safe. In a retrospective study of patients with frequent, weekly seizures, levetiracetam use in metastatic lesions was tolerated well [41]. Seizure frequency was reduced in all patients with metastatic lesions to less than 50% of pre-levetiracetam baseline. There may be some subgroups of brain metastasis patients who benefit from prophylactic AED use. A group of patients with metastatic melanoma brain metastasis were evaluated for prophylactic AED use over a 2-year period [9]. Seizure risk was studied relative to brain metastasis characteristics—hemorrhage and multiple supratentorial metastases were associated with increased seizure risk. Univariate analysis revealed AED prophylaxis was significantly associated with a decreased seizure risk. Limitations of the study included its retrospective nature and small patient cohort. However, it suggests that AED prophylaxis may be beneficial in some subgroups of patients with brain metastasis.

Untoward Effects of Anticonvulsants

Drug Interactions

Interactions between antiepileptic drugs and chemotherapy are complex and mainly revolve around the cytochrome P-450 (CYP) system (Table 9.3). Phenobarbital, phenytoin, and carbamazepine, for example, are three antiepileptic drugs known to be strong CYP3A4 inducers and can significantly decrease the levels of vincristine, paclitaxel, irinotecan, teniposide, methotrexate, and busulfan. Valproic acid has several complex interactions with certain chemotherapies, as it is one of the few cytochrome enzyme-inhibiting AEDs with highly protein-bound properties, in addition to potential CYP2A6 induction. Highly protein-bound AEDs or chemotherapy agents—including phenytoin, phenobarbital, valproic acid, cisplatin, etoposide, and teniposide—can interact with each other, affecting free and bound levels of both drugs. It should be noted that some patients who take oral AEDs may have difficulty tolerating them while on highly emetogenic chemotherapy regimens. Clinicians should be cautious of heightened toxicity from the increased amount of unbound drug, especially in patients who are cachectic or malnourished. Chemotherapeutic agents such as methotrexate, doxorubicin, and cisplatin can decrease AED levels of valproic acid, carbamazepine, and phenytoin.

In the last decade, we have seen a substantial increase in the effectiveness of tyrosine kinase inhibitors (TKI) for the treatment of brain metastases from various systemic malignancies. It is necessary to pay close attention to drug interactions between antiepileptic drugs and TKIs moving forward. CYP3A4-inducing AEDs can significantly increase the clearance and reduce the AUC of TKIs, specifically crizotinib, dasatinib, imatinib, and lapatinib [56]. There are other TKIs that are 3A4 inhibitors; however, there is very little data reported on the metabolism of AEDs in this context.

Side Effects

All antiepileptic drugs have potential side effects, summarized in Table 9.2. The most common side effects across all AEDs are lethargy and cognitive

Table 9.3 Pharmacological aspects of antiepileptic drugs and interactions with chemotherapy agents

AED	IV?	CYP inducer	PB (%)	AED effect on chemo	Chemo effect on AED
PHB	Yes	**1A2, 2A6, 2B6, 2C9, 3A4,** 2C19	50	Thi↓ Nit↓ Vbl↓ Vnc↓ Mtx↓ Pac↓ 9AC↓ Ten↓ Pro↑ Prd↓ Dox↓ Tam↓ Ifo↓	Tmz
PHT	Yes	**2B6, 2C9, 2C19, 3A4,** 1A2	**90**	Pro↑ Pac↓ Bus↓ Top↓Vbl↓ Vnc↓ Mtx↓ Iri↓ 9AC↓ Ten↓ Dex↓ SrI↓	Mtx↓ Pro↑ Cis↓ Nit↓ Eto↓ Dox ↓ Dac↓ Vbl↓ Ble↓ Dex ↓↑ Car↓ 5FU↑ Cpc↑ Tam↑ Tmz
CBZ	No	**1A2, 2B6, 2C9, 2C19, 3A4**	**75**	MTX↓ Pac↓ Vbl↓ Vnc↓ Ten↓ 9AC↓ Srl↓ Pro↑	Cis↓ Dox↓ Tmz
OXC	No	3A4	40	–	Tmz
VPA	Yes	2A6 (inhib. 2C9, 2C19, 3A4)	**90**	–	Mtx↓ Dox↓ Cis↓
TPX	No	3A4	30	–	Tmz
ZNS	No	(Inhib. 2E1)	50	–	–
LTG	No	No	50	Mtx	–
GBP	No	No	< 5	–	–
PGB	No	No	< 5	–	–
LVT	Yes	No	<5	–	–
LCS	Yes	No	<5	–	–

5FU 5-fluorouracil, *9AC* 9-aminocampothecin, *AED* antiepileptic drug, *Ble* bleomycin, *Bus* busulfan, *Ca* calcium channel, *Car* carboplatin, *CBZ* carbamazepine, *chemo* chemotherapy, *Cis* cisplatin, *cog* cognitive/behavioral, *Cpc* capecitabine, *CYP* cytochrome P-450, *Dac* dacarbazine, *Dex* dexamethasone, *Dox* doxorubicin, *Eto* etoposide, *GABA* ϒ-aminobutyric acid, *GBP* gabapentin, *Ifo* ifosfamide, *inhib.* enzyme inhibition, *Iri* irinotecan, *IV* intravenous, *K* kidney, *L* liver, *LCS* lacosamide, *LTG* lamotrigine, *LVT* Levetiracetam, *MAOI* monoamine oxidase inhibitor, *Mech* mechanism, *Met* metabolism, *Mtx* methotrexate, *Na* sodium channel, *Nit* nitrosourea, *NMDA* N-methyl-D-aspartate, *n/v* nausea and vomiting, *OXC* oxcarbazepine, *Pac* paclitaxel, *PB* protein binding, *PGB* pregabalin, *PHB* phenobarbital (and primidone), *PHT* phenytoin, *Prd* prednisone, *Pro* procarbazine, *Srl* sirolimus (and temsirolimus), *SV* synaptic vesicle, *Tam* tamoxifen, *Ten* teniposide, *Thi* thiotepa, *Tmz* temozolomide, *Top* topotecan, *TPX* topiramate, *Vbl* vinblastine, *Vnc* vincristine, *VPA* valproic acid, *ZNS* zonisamide

Boldface in table body denotes strong enzyme activity

**Edited and updated from Table 2 of Avila and Graber, Curr Neurol Neurosci Rep (2010) 10:60–67 with permission from Springer Nature

dysfunction, even if levels are within therapeutic range. These side effects are often enhanced when patients have several brain metastases. Side effects of specific antiepileptic drugs among individual patients can vary, and their use often requires an individualized approach. See Table 9.2 for a more detailed list of side effects of various antiepileptics.

Convulsive and Nonconvulsive Status Epilepticus

Status epilepticus is defined as either continuous or intermittent seizures without recovery of consciousness between seizures [57]. Status epilepticus can be either convulsive or nonconvulsive [58, 59]. Convulsive status epilepticus is a medical emergency and often requires aggressive intensive care with intubation and general anesthesia [57]; one approach is illustrated in Table 9.4.

Nonconvulsive status epilepticus (NCSE) in patients with brain metastases may be underdiagnosed as patients are often altered or comatose with no overt signs of seizure activity. One study suggests an increased risk of mortality within 2 months in patients with metastatic disease and progressing brain lesions [60]. In another series, 8% of comatose patients were found to be in electrographic status epilepticus [59]. In any comatose patient with risk factors for seizures and subtle motor or oculomotor movements, electroencephalogram is recommended to definitively rule out electrographic seizures.

Table 9.4 Protocol for the treatment of convulsive status epilepticus at Memorial Sloan Kettering Cancer Center

First 5 min
ABCs
Diagnose status epilepticus
Obtain IV access
Begin ECG monitoring
Fingerstick for glucose—correct if necessary
Draw blood for BMP, Mg, Ca, Ph, CBC, LFT, AED levels (PHB, PHT, VPA, CBZ), toxicology screen
Call Neurology consult
6–10 min
Thiamine 100 mg IV; 50 ml of D50 IV in appropriate clinical setting
Lorazepam 4 mg IV over 2 min; if necessary, repeat once every 5 min. If no IV access, give diazepam 20 mg rectally or midazolam 10 mg intranasally or intramuscularly
10–20 min
Add fosphenytoin 20 mg/kg IV at 50 mg/min with BP and ECG monitoring. Can re-bolus fosphenytoin 10 mg/kg if seizures persist. Maintain level 15–20 μg/mL
20–60 min
If seizures persist, *intubate* and start phenobarbital IV 20 mg/kg at 50–100 mg/min
If still seizing, can add or switch (PHB) to midazolam: load 0.0.2 mg/kg; repeat 0.2–0.4 mg/kg boluses every 5 min until seizures stop, up to a maximum total loading dose of 2 mg/kg. Initial rate 0.1 mg/kg/h. Continuous IV range 0.05–2 mg/kg/h
Or
Propofol: Load 1 mg/kg; repeat 1–2 mg/kg boluses every 3–5 min until seizures stop, up to a maximum total loading dose of 10 mg/kg. Initial rate 2 mg/kg/hour. Dose range 1–15 mg/kg/hour
After 60 min
If seizures persist, use anesthetics
Continuous IV propofol: Load 1 mg/kg; initial 2 mg/kg/hr. Titrate until burst suppression
Will need to arrange continuous EEG monitoring (preferably as soon as the patient does not awaken rapidly)
Another possible consideration for fourth line treatment is valproate 40 mg/kg over 10 min. Can re-bolus 20 mg/kg over 5 min
If bacterial meningitis is suspected, start ceftriaxone, vancomycin, and ampicillin (can start along with treatment for SE). Start acyclovir if HSV encephalitis is suspected. Perform LP when stable

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Driving

Placing driving restrictions on patients with seizures from brain metastases is a highly controversial topic. The development of efficacious seizure medications over the last several decades has reversed historical conviction that no patient with seizures—controlled or uncontrolled—should be allowed to drive. There is consensus, however, that patients with uncontrolled seizures should not drive given their increased risk of motor vehicle accidents and subsequent property damage, as well as potential for injury to self or others. For those patients with controlled seizures, clinicians must balance the risk of public safety with patient autonomy and preservation of quality of life. Driving restrictions can significantly impact a patient's ability to maintain employment, attend social activities, and/or participate in school. Data are limited in determining which patients with seizures can safely drive, and therefore regulations vary considerably in the USA from state to state. Clinicians should consult the regulations of their respective state or country in which they practice before advising patients. It should be emphasized, however, that clinician judgment supersedes any state regulation.

While no studies have specifically looked at patients with brain metastases, data extrapolated from other epilepsy studies suggest that the most reliable predictor of risk of seizure while driving

is the seizure-free interval. Limited data have advocated for a seizure-free interval ranging anywhere from 3 to 12 months [61–65].

Seizures at the End of Life

Seizures are common at the end of life in patients with brain metastases. For those who are able to swallow medications and have a previous history of seizures, patients should continue their antiepileptic drugs. However, clinicians should be aware of the often inevitable depressed mental status and the need to convert oral antiepileptics to non-oral routes. In patients who cannot safely swallow, seizure management will depend on the location of care support. If the patient requires inpatient care, intravenous access can be maintained and parenteral antiepileptics can be continued. For those at home, subcutaneous/sublingual lorazepam or buccal clonazepam can be used to control seizures. Rectal diazepam and rectal/subcutaneous phenobarbital are another option in the home setting. Initiation of dexamethasone should be considered for patients with seizures caused by increased intracranial pressure from mass effect.

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Cerebrovascular Complications in Patients with Cancer

10

Jaclyn E. Burch and Alan Z. Segal

Introduction

The hypercoagulable state associated with cancer, known since the descriptions of Trousseau in the nineteenth century, has become a well-recognized cause of venous thromboembolism. It has only more recently become apparent that cancer increases the risk of arterial thromboembolism as well. In patients with cancer, cerebrovascular disease is the second leading cause of lesions of the central nervous system (CNS), only behind metastases [1]. The most frequent cause of cerebrovascular disease in this population is stroke, both ischemic and hemorrhagic; this chapter will focus primarily on these entities. While patients with cancer remain at risk for conventional mechanisms of cerebrovascular disease, cancer patients have unique risk factors including complications of coagulation disorders, direct tumor effects, toxicity of cancer treatment, and increased risk of infection in the setting of immunosuppression. These features make this population distinct from the general population and should be considered carefully during their evaluation and care.

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Ischemic Stroke

Epidemiology

Over 15 million Americans have or have had cancer, making up approximately 3.5% of the population. In 2018, an estimated 1.7 million patients will be diagnosed with new cases of cancer in the USA [2]. In general, the risk of developing ischemic stroke is increased after a new diagnosis of most cancer types, with the risk highest in the first several months after diagnosis. In a Swedish study, the overall risk of ischemic stroke in the first 6 months after diagnosis was increased 1.6-fold [3]. Incidence of stroke seems to correlate with the aggressiveness of the underlying cancer type, with the highest rates occurring in patients with newly diagnosed lung, pancreas, colorectal, and nervous system cancers and leukemia. The increased risk also correlates with stage of cancer—patients with metastatic disease at baseline demonstrate an elevated risk of ischemic stroke when compared to more localized disease [3–5]. Additionally, a correlation also exists between patients who present with acute stroke and a concurrent or subsequent diagnosis of cancer. Notably, a study using the Nationwide Inpatient Sample found that approximately one in ten patients who presented with an acute ischemic stroke also had a diagnosis of cancer [6]. Stroke can also be the presenting symptom of cancer, with occult malignancy being diagnosed in as many as 0.4–3% at the time of presentation

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[7, 8]. Finally, in a Norwegian study, 4.3% of patients were diagnosed with cancer after initial stroke, with a median time from stroke to cancer diagnosis of 14 months [9].

Historically, there has been a lack of consensus regarding whether cancer itself is a separate risk factor for stroke as both share common risk factors such as age, smoking, and obesity. However, recent studies have demonstrated that this increased risk persists despite controlling for age and other cardiovascular risk factors [5]. In addition, a higher risk of experiencing cerebral ischemic events was found even in patients whose cancers are not traditionally related to a history of tobacco use, such as non-Hodgkin lymphoma [3, 5]. Otherwise, the prevalence of traditional vascular risk factors appears to be similar in patients with stroke when comparing those with and without cancer [10–13].

Clinical Presentation

Typically, the clinical presentation of acute stroke is the acute onset of focal neurologic symptoms, similar to patients in the general population. In a retrospective study evaluating ischemic stroke patients at Memorial Sloan Kettering Cancer Center, the most common presenting symptoms were hemiparesis (78%), speech disturbance (51%), and visual field deficits (26%) [10]. Another common symptom is encephalopathy, particularly because cancer patients have higher likelihood of embolic infarcts in multiple arterial territories [14]. They may also have other areas of systemic thrombosis at the time of presentation, including deep vein thrombosis (DVT) and pulmonary embolism (PE) [11, 15]. Finally, stroke may also be incidentally found as a result of surveillance and screening brain imaging.

Pathophysiology

Stroke Mechanisms

As mentioned previously, patients with cancer have unique mechanisms of stroke. However, cancer and its treatment also play an important role in the increased risk of stroke from conventional mechanisms. This is due in part to shared risk factors between cancer and stroke, (e.g., smoking) as well as cancer-specific mechanisms. Patients with cancer have increased levels of systemic inflammation, which is thought to result in higher rates of atherosclerotic plaque formation [16]. Prior radiation exposure in patients with head and neck cancer predisposes to the development of radiation-induced vasculopathy, also increasing risk of stroke from large vessel disease [10]. Patients with cancer may also have higher rates of atrial fibrillation. For example, women diagnosed with atrial fibrillation were more likely to go on to be diagnosed with malignant cancer [17]. Another study found that patients were more likely to have atrial fibrillation at the time of their initial cancer diagnosis [18].

The rate of cryptogenic stroke is higher in patients with cancer [13, 15] and can be associated with a higher D-dimer, infarcts in multiple vascular territories, as well as metastatic disease at the time of the stroke [19]. The mechanism postulated to unify these facts is stroke secondary to nonbacterial thrombotic endocarditis (NBTE), which is characterized by noninfectious fibrin deposition on the heart valves and is thought to be increased in the setting of cancer-related hypercoagulability. NBTE was found to be the most common cause of symptomatic stroke in an autopsy study [1]. However, its presence can be difficult to establish antemortem, and the clinical tools available to do so, including echocardiography, have relatively low sensitivity [20, 21]. Cerebral intravascular coagulation, characterized by multiple thrombotic cerebral infarcts without an embolic source, has also been reported as a rare cause of multifocal infarcts, usually occurring in patients with advanced disseminated disease [1].

Tumor emboli have also been described and are another potential cause of embolic strokes [22–24]. A patent foramen ovale (PFO), present in approximately 25% of the population, can allow paradoxical embolism which is an important source of stroke to consider in the cancer population where increased rates of DVT are seen. Immunosuppression and invasive procedures, such as indwelling catheters, may also pre-

dispose patients to the development of infective endocarditis with resultant septic emboli [1].

Cancer-Related Hypercoagulability

The hypercoagulable state induced in patients with cancer plays a role in several of the mechanisms of stroke. This state is complex and not entirely understood but is most certainly multifactorial. These effects include the host response to the cancer, which includes the production of acute-phase reactants, paraproteins, as well as inflammation and necrosis [25]. When white blood cells, like monocytes or macrophages, interact with cancer cells, certain factors such as tumor necrosis factor, interleukin-1, and interleukin-6 are released. This leads to endothelial vessel wall damage, causing increased thrombogenicity [26]. Cancer cells also produce factors promoting thrombosis themselves, including tissue factor and cancer procoagulant, a protein that can directly activate factor X [25].

Patients with malignancy are commonly noted to have abnormalities in laboratory tests of coagulation. Schwarzbach et al. found that patients with cancer had significantly higher D-dimer levels at the time of stroke [15]. These tests are often limited in their ability to assist with diagnosis because the values for the common coagulation factors, such as D-dimer, can overlap with those of cancer patients without stroke, lacking the sensitivity and specificity to direct therapy [27]. Cancer-mediated hypercoagulability likely plays its most prominent role during the first few months after cancer diagnosis (when it is most severe) as well as in aggressive metastatic disease. Compounding this, some antitumor therapy may lead to hypercoagulability, including platinum compounds, high-dose fluorouracil, tamoxifen, mitomycin, and growth factors; the mechanism of this toxicity is not well understood [26, 28].

Diagnosis

Magnetic resonance imaging (MRI) is crucial in the diagnosis of ischemic stroke, particularly in distinguishing between neoplastic and vascular etiologies. Contrast enhancement is most often a sign of a neoplastic etiology; however, ischemic strokes can cause contrast enhancement at the subacute stage in the absence of any neoplasm. As it may be impossible to differentiate between the two based on baseline imaging, follow-up imaging to assess interval change may be necessary. Rarely, biopsy is necessary to fully diagnose the etiology. As in the general stroke population, the pattern of infarct on imaging can clarify the underlying mechanism. For example, the distribution of infarcts in multiple vascular territories suggests an embolic source such as atrial fibrillation, NBTE, as well as septic, paradoxical, or tumor emboli. Vascular imaging can be important to evaluate for sources of large vessel disease, especially if there is history of head and neck radiation, and to evaluate for evidence of mycotic aneurysm in the setting of potential bacterial endocarditis. Echocardiography can evaluate the structure of the heart, evaluating for stigmata of atrial fibrillation, the presence of a PFO, and any marantic or septic endocarditis. Notably, transthoracic echocardiography (TTE) is limited in its ability to detect marantic endocarditis given the typically small size of these vegetations. Transesophageal echocardiography (TEE) is superior to TTE for detecting a cardiac source of stroke. A retrospective study by Merkler et al. evaluated the diagnostic yield of TTE and TEE in cancer patients with ischemic stroke. Of those who were suspected to have a cardiac source, TTE demonstrated a definite or possible cardiac source in only 24% of patients, compared to 76% of patients who were evaluated with TEE [20]. However, this increase in the diagnostic yield needs to be weighed carefully against the more invasive nature of the procedure, as well as the patient's clinical stability and other comorbidities. Rhythm monitoring, with ECGs and telemetry, remains important, especially if the stroke appears embolic in nature. There are often abnormalities in coagulation factors such as D-dimer, although they are also often nonspecific in the cancer patient and may not significantly alter management [27]. Physical examination should include evaluation for evidence of septic emboli and DVT. Limb venous Dopplers can be considered, particularly if there is evidence of PFO on echocardiography.

Management

Acute Treatment

The mainstay of acute treatment for ischemic stroke is administration of IV tissue plasminogen activator (tPA) and consideration for endovascular therapy. Patients with cancer often have contraindications for IV tPA such as coagulation abnormalities, recent surgery, or systemic bleeding. Per the 2018 American Stroke Association guidelines for management of acute ischemic stroke, patients with systemic malignancy may benefit from IV tPA in the absence of other contraindications [29]. Providers should also consider whether other laboratory testing such as complete blood count for platelets or a coagulation panel should be obtained prior to administration of thrombolytics. It should be noted that a structural gastrointestinal malignancy contributes to a higher risk of bleeding and is a contraindication to administration of IV tPA in the guidelines [29]. No prospective trials have specifically evaluated IV tPA in cancer patients; however, several studies have demonstrated that rates of intracerebral hemorrhage are similar to those found in non-cancer patients from the original IV tPA trials [30–32]. Similarly, unstudied are patients with primary or metastatic brain tumors. A few case series have surprisingly demonstrated relatively low hemorrhage rates in this group [33, 34]. However, intratumoral hemorrhage remains a concern, and the presence of known intracranial intra-axial tumors is considered a contraindication for IV tPA in the 2018 guidelines. However, it may be reasonable to consider tPA in patients with small extra-axial tumors, such as meningioma [29]. Endovascular therapy is another treatment option to be considered in the acute setting, although again, there are limited data in cancer patients. A recent case series demonstrated a beneficial outcome for patients with cancer treated with endovascular therapy [35]. Several retrospective studies have shown similar rates of mortality and ICH after endovascular therapy in patients with cancer when compared to the general population, although prospective data are lacking [30, 31]. As patients with a large vessel occlusion can have severe deficits, it may still be worthwhile considering endovascular therapy even if expected survival is limited.

Secondary Prevention

Prevention of recurrent stroke hinges on identifying treatable mechanisms such as atrial fibrillation or carotid stenosis. However, a large proportion of strokes remain cryptogenic, especially in the cancer population. While mechanisms secondary to cancer-related hypercoagulability like NBTE may be suspected, these can be difficult to diagnose clinically. Furthermore, cancer-related hypercoagulability may theoretically play a role in exacerbating more conventional stroke mechanisms, such as large artery atherosclerosis, which is typically treated with antiplatelet agents [36].

The standard treatment for venous thromboembolism in patients with cancer is anticoagulation, with prior studies demonstrating a benefit with low-molecular-weight heparin (LMWH) [37]. Recently, a study comparing the treatment of venous thromboembolism with an oral factor Xa inhibitor (edoxaban) versus LMWH demonstrated non-inferiority [38]. A non-inferiority trial of another factor Xa inhibitor, apixaban, versus LMWH is ongoing and will be completed soon [39]. The treatment of ischemic stroke in patients with cancer is less clear, and overall there is a lack of data to guide treatment. A few studies have provided a rationale for the use of anticoagulation in the ischemic stroke associated with cancer-mediated hypercoagulability, demonstrating a reduction in levels of D-dimer with improved survival [40, 41]. Regarding the specific choice in anticoagulant, a retrospective study comparing enoxaparin with oral warfarin found no statistical difference for either recurrent stroke or major bleeding [14].

However, anticoagulation carries its own risks and is often contraindicated in patients with coagulopathies and thrombocytopenia. Furthermore, patients with cancer already face an increased bleeding risk (10% risk of clinically relevant bleeding in the absence of anticoagulation), and many already carry a history of prior major bleeding [42]. LMWH, which has been the preferred choice of anticoagulant for oncologists for the management of venous thromboembolism [42],

has additional drawbacks. In a recent feasibility study by Navi et al., cancer patients with ischemic stroke were randomized to secondary prevention with enoxaparin versus aspirin. Sixty percent of patients in the LMWH group crossed over to the aspirin group primarily because of injection-related discomfort or cost [43].

The alternative to anticoagulation for secondary prevention is treatment with antiplatelet agents, primarily aspirin. Aspirin incurs a lower bleeding risk than anticoagulation and is often easier to administer and less expensive. There may also be a cancer-specific rationale for aspirin—platelets are postulated to promote cancer growth and metastasis [44]. There are limited data comparing the use of antiplatelets to anticoagulation for the secondary prevention of ischemic stroke in cancer patients. In a retrospective study by Cestari et al., there did not appear to be a survival benefit for either treatment modality; a more recent retrospective study at Memorial Sloan Kettering Cancer Center found no difference in treatment effect with regard to recurrent thromboembolic events [10, 45]. In the feasibility study by Navi et al., 20 out of 49 eligible patients were enrolled, with a 60% crossover rate from the enoxaparin group to the aspirin group. This pilot did demonstrate feasibility, but with the recommendation that future trials use an oral anticoagulant given the low rates of recruitment and high crossover from LMWH. Data are still lacking to definitively identify which agent would be best for secondary prevention of stroke in the cancer population.

Prognosis

Risk of Recurrence

Patients with cancer are at a higher risk of recurrent thromboembolic events, including recurrent stroke. In a retrospective study at Memorial Sloan Kettering Cancer Center, 31% of patients with cancer had a recurrent thromboembolic event at 3 months after their index stroke. This includes 13% with a recurrent acute ischemic stroke, which is threefold higher than what is seen in the general population. Adenocarcinoma histology was associated with increased recurrent stroke rate [45]. High rates of recurrent stroke were also seen in a Korean case-control study, where 28% of cancer patients had recurrent stroke within 1 year of the index stroke [46].

Survival

Overall, strokes tend to be more severe in patients with cancer, with a worse functional status and a higher likelihood of developing early deterioration [47]. In a study by Cestari et al., the median survival after ischemic stroke was 4.5 months. Survival was worse if the stroke was embolic—median survival was 2.6 months in patients with embolic appearing stroke, while it extended to 9.8 months in those with strokes of other etiologies. In a more recent study by Navi et al., the median survival for those with active cancer and an identified stroke mechanism was 147 days, while only 55 days for those whose stroke was cryptogenic [13]. Predictors of worse outcome or mortality include stroke severity, metastatic disease, diabetes, cryptogenic etiology of stroke, and elevated levels of C-reactive protein or D-dimer [13, 47, 48].

Intracranial Hemorrhage

Epidemiology

In an autopsy study, cerebrovascular disease was the second most common cause of complications involving the CNS, behind only intracranial metastasis. About half of these cases were intracranial hemorrhage (ICH) [1]. Several studies have sought to establish the incidence of ICH in patients with both systemic and intracranial tumors, ranging between 2 and 14% of patients [1, 49–51]. ICH in cancer patients is most frequently intraparenchymal/intracerebral (including intratumoral hemorrhage). However, ICH in cancer can be associated with hemorrhage into any intracranial compartment, with order of frequency from most common to least being intraparenchymal hemorrhage (IPH), subarachnoid hemorrhage (SAH), subdural hemorrhage (SDH), and epidural hemorrhage (EDH). In a

recent study, it was found that close to half (44%) of cancer patients with ICH experience hemorrhage at multiple foci [52]. The most frequent causes of symptomatic ICH in patients with cancer are intratumoral hemorrhage (ITH) and coagulopathy, which occur most commonly in patients with solid tumors and hematologic malignancy, respectively. The hemorrhage location largely depends on the location of the tumor. Dural or skull-based tumors, such as prostate metastases, can be associated with SDH or EDH [1, 53].

Certain tumor types are more likely to be associated with ITH. Of solid tumors, melanoma, lung, breast, and renal cell cancer are most commonly associated with ICH [52]. This is partly explained by a higher incidence of intracranial metastasis among these cancer types [54, 55]. In addition, other solid tumors such as thyroid cancer, hepatocellular carcinoma, and choriocarcinoma are less common causes of intracranial metastases, but seem to have a higher propensity to be associated with ITH [1, 50]. The individual histology of these tumors is likely important; increased intratumoral vascularization (resulting in dilated, thin-walled vessels that are more likely to rupture) and necrosis predispose intracranial metastases to bleed [50]. Primary brain tumors, in particular glioblastoma, are associated with ITH. This is likely multifactorial due to angiogenesis, distal vessel necrosis, and dilation, distention, and erosion of vessels by tumor growth [50, 56]. Oligodendrogliomas, although less common, seem to have an increased likelihood for ITH, potentially related to infiltration of retiform capillaries [57].

Mechanisms and Pathophysiology

The most commonly seen mechanisms of ICH in cancer patients are ITH, seen in solid tumor types, and coagulopathy, seen in hematological malignancy. However, it is not uncommon for the etiology of ICH to be multifactorial, including when ITH is complicated by concomitant coagulopathy. Other less common causes include head trauma, hypertensive hemorrhage, hemorrhagic conversion of ischemic stroke, venous thrombosis, aneurysmal rupture (including mycotic and neoplastic aneurysms), and posterior reversible encephalopathy syndrome (PRES). Acute leukemia can be associated with hyperleukocytosis (considered peripheral blast count >100,000/mm^3), which can cause leukostasis with associated local vessel destruction and rare parenchymal hemorrhage. Other causes, such as cerebral amyloid angiopathy, are possible but uncommon [1, 27, 52].

Coagulopathy can be seen in cancer patients for many reasons. These include thrombocytopenia in the setting of hematologic malignancy, treatment-related myelotoxicity, or tumor marrow infiltration. Coagulopathy can also be seen secondary to platelet abnormalities and/or coagulation factor abnormalities secondary to liver failure and poor nutrition with associated vitamin K deficiency. Disseminated intravascular coagulation (DIC) may also cause coagulopathy. The mechanism in cancer is not entirely understood, but is thought to be caused by inappropriate consumption of platelets and coagulation factors secondary to excess production of thrombin. DIC is also seen in the setting of sepsis, which bone marrow transplant patients are particularly vulnerable to [1, 27, 58, 59].

The anti-angiogenic agent bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor (VEGF), can also increase risk of hemorrhage. For a period of time, patients with intracranial metastases were excluded from trials of bevacizumab after an early case report of a young man with hepatocellular carcinoma developed fatal ICH while being treated with bevacizumab [60]. However, a study evaluating bevacizumab at Memorial Sloan Kettering Cancer Center found similar rates of ICH in bevacizumab-treated patients with and without intracranial tumors, when compared to patients not receiving bevacizumab [61]. Brain radiation can cause delayed vascular abnormalities, including cavernous malformations, with subsequent ICH [58].

Clinical Presentation

In a study performed at MSKCC, only about half (56.5%) of patients found to have ICH at autopsy were previously symptomatic [1]. However, in a more recent study assessing patients with radiographic ICH, most patients (94%) were symptomatic at the time the imaging was performed [52]. This difference likely stems from the fact that the diagnosis of ICH in the cancer patient occurs along a spectrum and can range from incidentally found hemosiderin deposition to more significant hemorrhage resulting in mass effect and elevated intracranial pressure [62]. Patients with primary brain tumors were more likely to demonstrate foci of asymptomatic hemorrhage when compared to patients with solid or hematopoietic tumors [52]; this may be because primary brain tumor patients often have pre-existing neurologic deficits and also undergo more frequent surveillance imaging. Notably, only 5% of cancer patients were found to have acute hypertension (defined as SBP >180 or DBP >120) at the time of ICH presentation. The most common presenting symptoms were hemiparesis, headache, impairment of consciousness, and seizure. Relatively fewer patients (6%) presented with coma [63].

Diagnosis

In cases where there is suspicion for ICH, patients should be evaluated with a non-contrast CT head (CTH). If there are no contraindications to contrast, a CT angiogram can later be obtained to evaluate for any vascular malformations. When clinically stable, a contrast-enhanced MRI should be performed in order to evaluate for underlying tumor. Features suggestive of underlying tumor include multiple hemorrhage sites, areas of hemorrhage at the gray-white junction, more heterogeneous signal patterns, multiple stages of a hematoma development in a single lesion, as well as delayed evolution of the hematoma, excessive and persistent edema at the site of the hematoma, and lack or absence of a well-defined hemosiderin rim [64, 65]. Enhancement in areas outside the hemorrhage is also suggestive of an intracranial metastasis underlying the hemorrhage. Diffusion restriction in setting of hemorrhagic conversion of ischemic stroke as well as multifocal lobar microhemorrhages (seen in patients with cerebral amyloid angiopathy) can also be evaluated with MRI. Cerebral venous sinus thrombosis may also be considered on the differential, which is discussed later in this chapter.

Management

An exhaustive discussion of the management of acute ICH is outside the scope of this chapter, and the standard guidelines for management of ICH still apply [66, 67]. In the cancer population, steroids are used much more frequently in the management of ICH, as was seen in a retrospective study where 75% of patients were treated with steroids after a diagnosis of ICH [52]. Steroids should be considered for the treatment of mass effect associated with vasogenic edema in the setting of ITH. For hemorrhage in the setting of a coagulopathy, treatment should include addressing the underlying hematologic abnormality. In the case of DIC, the appropriate treatment is unclear but generally includes treating any underlying factors, such as sepsis, and may include replacement of clotting factors with fresh frozen plasma, cryoprecipitate, and platelets [27]. Craniotomy can be considered for resection in the case of ITH, as surgical treatment has been shown to be beneficial in the setting of a symptomatic intracranial metastasis; this may be followed by radiation [52, 68, 69]. If the lesion is not resectable or if there are multiple lesions, then treatment with whole brain radiation or stereotactic radiosurgery for palliation may be considered [52]. In the setting of SDH or EDH, surgical decompression would fall under the same indications as it would in the general population, albeit with careful consideration of safety in the setting of any coagulopathies [66]. SAH should also be managed as per standard guidelines with added consideration for increased likelihood of mycotic aneurysms given the increased

risk of infection in this population [67]. These aneurysms are often not amenable to surgery and are generally treated with antibiotics [52]. Neoplastic aneurysms are rare, and although treatment has not been clearly established, chemotherapy and radiation may be considered [70]. Finally, intermittent pneumatic compression devices for the legs should be initiated on the day of hospital admission, while early treatment with chemoprophylaxis for deep venous thrombosis with enoxaparin or heparin should be considered 1 to 4 days from onset of ICH if there is no further bleeding [66].

Prognosis

The outcomes for cancer patients with ICH are largely dictated by the prognosis of the underlying malignancy. The 1-year mortality was 78% in a retrospective study by Navi et al. Median survival was 3 months but was better for those with primary brain tumors (5.9 months), as compared to a 2.1-month median survival for those with solid tumors and 1.5 months for those with hematologic malignancies. Survival was also affected by the underlying mechanism of the hemorrhage, with longer survival seen in those suffering ICH secondary to ITH (3.7 months) or a combination of ITH and coagulopathy (1.8 months), as compared to those with ICH secondary to coagulopathy alone, where median survival was only 0.3 months. Only 15% of patients were completely independent at discharge, with 22% dying during admission. Patients with solid tumors had the best functional outcome at time of discharge, with 53% completely or partially independent. Patients with hematologic malignancies were most likely to die during the hospitalization, while patients with primary brain tumors had the lowest rate of in-hospital mortality [52].

Safety of Anticoagulation in Patients with Intracranial Tumors

Venous thromboembolism is commonly seen in the cancer population, which is primarily managed by treatment with anticoagulation. Therapeutic anticoagulation in patients with intracranial tumors, including both primary brain tumors and intracranial metastases, generally appears to be safe. Several studies have shown similar rates of ICH and mortality compared to patients not treated with anticoagulation [39, 52, 62, 71–74].

CVST

Cerebral venous sinus thrombosis (CVST) results from an occlusion within the venous system of the brain. The risk of CVST, like systemic deep venous thrombosis, is increased in patients with cancer. In a recent case-control study, the risk of CVST in cancer patients appeared to be about fivefold higher. The risk was highest in the first year after diagnosis and was also elevated in patients with hematologic malignancies, as compared to those with a solid malignancy. In fact, the risk of developing CVST was about 90 times higher in the first year after diagnosis of a hematologic malignancy, when compared to the general population [75]. The mechanism for this heightened risk is likely similar to the elevated incidence of ischemic stroke shortly after diagnosis, reflecting increased prothrombotic changes in the setting of increased cancer activity, as well as adverse effects of surgery and certain chemotherapies. In particular, L-asparaginase is thought to be associated with the development of CVST and may account in part for some of the increased risk of CVST seen in hematologic malignancies [27]. Mechanisms specific to the cancer patient include cancer-induced hypercoagulability, tumor compression or invasion, local infection, and chemotherapy-related toxicities [76]. The superior sagittal sinus is most frequently affected [75, 76], but thrombosis can also occur in the other sinuses such as the inner cerebral or superficial veins [77].

The most common presentation of CVST is headache. Other common symptoms include seizures, nausea/vomiting, altered level of consciousness, and focal neurologic findings such as weakness or aphasia [75, 76]. Increased density of the transverse or sagittal sinuses can indicate

thrombosis on non-contrast CTH, but the sensitivity of this sign is not high, and if there is clinical concern for CVST, additional imaging should be pursued [78]. On MRI, the clot may be acutely isointense on T1 and hypointense on T2 [78]. MRI may also demonstrate sequelae of the clot, such as intraparenchymal hemorrhage or infarction. An infarction with associated hemorrhage that crosses vascular distributions or is near a venous sinus is suggestive of CVST [77, 78]. CT venography will show a filling defect, which in the sagittal sinus is referred to as the "empty delta sign." MR venography (MRV) will similarly demonstrate a loss of flow in the area of the clot, with contrast-enhanced MRV better demonstrating the venous structures than time-of-flight MRV [78]. Treatment should be aimed at the underlying cause of CVST. If due to tumor compression or invasion, then cancer treatment, either by chemotherapy, radiation, or surgery, may be possible [39]. There are a limited number of randomized trials of treatment of CVST in the general population, but treatment guidelines generally recommend anticoagulation, even in the setting of ICH, barring any other contraindications [78].

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Mood Disorders in Patients with CNS Metastases

11

Kaleena Chilcote

Abbreviations

AEDs	Antiepileptic drugs
CBT	Cognitive behavioral therapy
CNS	Central nervous system
DBT	Dialectical behavior therapy
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
HADS	Hospital Anxiety and Depression Scale
HPA axis	Hypothalamic-pituitary-adrenal axis
IL-2	Interleukin-2
IL-6	Interleukin-6
MBSR	Mindfulness-based stress reduction
MDD	Major depressive disorder
NCCN	National Comprehensive Cancer Network
NSAIDs	Nonsteroidal anti-inflammatory drugs
PHQ-9	Patient Health Questionnaire-9

Introduction

Patient distress is becoming more widely assessed as national agencies and credentialing bodies highlight the importance of monitoring patients' well-being. The National Comprehensive Cancer Network (NCCN) has developed guidelines to assist clinicians in assessing and managing patient distress. This guideline defines distress as "a multifactorial unpleasant experience of a psychological (i.e., cognitive, behavioral, emotional), social, spiritual, and/or physical nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment." By this definition, multiple factors contribute to one's sense of well-being as well as to the development of mood and anxiety disorders, and all of these factors warrant monitoring and intervention when appropriate [1]. As data is collected from studies using this definition and guidelines, the importance of addressing mood disorders in patients with cancer is becoming more apparent. In patients with intracranial involvement, quality of life is more closely tied to a patient's sense of emotional well-being than physical well-being [2]. Comorbid mood disorders are associated with increased patient distress, lower quality of life, higher healthcare costs, caregiver burden, other maladaptive health behaviors, and poorer cancer-related outcomes.

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Depressive Disorders

Etiology

Multiple factors have been studied as potential causes of depression with evidence suggesting that development and perpetuation of depression are multifactorial. There is increasing evidence linking depression and inflammation in the body. Similarly, there is evidence linking cancer and inflammation, perhaps providing a link between higher rates of depression observed in patients with cancer, particularly those cancer types associated with more systemic inflammation. Cancer cells can produce multiple pro-inflammatory mediators, including cytokines, chemokines, growth factors, and transcription factors. Cell death resulting from cancer treatments, like radiation therapy and chemotherapy, leads to production of cytokines that can trigger a cascade of immune responses [3, 4]. There is also a correlation between depression and elevated levels of interleukin-6 (IL-6) [5, 6]. In a study of women with breast cancer, there was a clear association between major depressive disorder and elevated IL-6 levels as well as consistent abnormalities on dexamethasone suppression testing, which suggests a link between IL-6 and the hypothalamic-pituitary-adrenal (HPA) axis [7]. The HPA access has been studied extensively in its relation to mood disorders. Growing evidence exists about how cancer might relate to HPA dysfunction. For example, women with ovarian cancer have been found to have higher evening cortisol levels than controls [8]. The degree of causation in this relationship remains unknown. Patients receiving immunotherapy with IL-2 and/or interferon-alfa were found to have lower levels of tryptophan, a precursor for serotonin, which suggests that cytokines might have a direct impact on the production of neurotransmitters implicated in mood regulation [9]. These shared mechanisms between depression and cancer raise questions about the potential interplay of these disorders and how depression can impact cancer occurrence and progression [10, 11].

Lesions involving the brain can disrupt important structures and pathways that also lead to the development of mood symptoms [12]. Depressive disorders are most frequently associated with lesions of the frontal and temporal lobes, though there is no clear connection between depression and lesion location [13, 14]. Several syndromes caused by pathway disruption can present with symptoms that overlap with mood disorders. A dysexecutive syndrome with frontal lobe lesions impacting the dorsolateral prefrontal circuit presents with impairments in executive functioning (perseveration, difficulty managing multiple and new tasks). Patients may also experience psychomotor slowing, flattened affect, and impairments in self-care that resemble depression. Disinhibition syndrome occurs with frontal lobe lesions impacting the orbitofrontal circuit and presents with emotional lability, impulsivity, and impaired judgment that can mimic mood disorders, including depression or a bipolar illness. Lesions of the anterior cingulate circuit can lead to apathy, which also commonly mimics depression [15]. Multiple primary psychiatric diagnoses have ties to dysfunction in these circuits as well. This includes attention-deficit hyperactivity disorder, obsessive compulsive disorder, Tourette syndrome, Huntington's disease, and schizophrenia [15–17].

Epidemiology

The prevalence rates for depressive disorders in patients with cancer vary and are often related to factors such as cancer type, disease stage, treatment modalities, time from diagnosis, physical symptom burden, and patient demographics [18–21]. For example, in patients with breast cancer, predictors of depression include being in the year following diagnosis, younger age, receiving adjuvant chemotherapy, experiencing an impact on fertility, and physical side effects from treatment [22]. These variables, along with inconsistent ways of defining and measuring depression, have made it difficult to fully appreciate the impact of depression on this patient population as a whole. Depressive symptoms as well as mixed anxiety/depressive symptom states have been found to be more common in certain cancer types, including stomach, pancreatic, oropharyngeal, lung, and

gynecologic, and those with intracranial involvement [20, 23]. To date, studies of prevalence generally focus on the impact of primary cancer type, and there is limited information specifically assessing the impact of central nervous system (CNS) metastases. Overall, approximately 25% of patients with cancer have a depressive disorder that warrants treatment, representing at least a threefold increase compared to the general population [20, 24–26].

Differential Diagnosis

The term "depression" now has a wide range of meanings, varying from more social uses to severely impairing symptoms that warrant intensive treatment. The Diagnostic and Statistical Manual of Mental Disorders, currently in its fifth edition (DSM-V), provides a framework for conceptualizing mental health diagnoses and details widely accepted diagnostic criteria for clinical syndromes. Major depressive disorder (MDD) is the most commonly referenced depressive disorder. To meet criteria for MDD, patients must have at least five symptoms present for at least 2 weeks with subsequent impairments in daily functioning. Symptoms of depression include depressed mood or predominant irritability, decreased interest in activities, significant change in appetite and/or weight, significant change in sleep, psychomotor agitation or retardation, low energy/fatigue, feelings of worthlessness or guilt, impaired attention and concentration, and suicidal ideation. The depression also cannot be due to the effects of a substance, illicit or prescribed, or other medical condition [27].

When working with patients with medical illness, particularly cancer, it can be a challenge to differentiate a physical complaint related to the illness from a somatic manifestation of a mood disorder. Consider a patient with cancer who suffers from nausea leading to weight loss, impaired sleep and irritability while on steroids, fatigue, and difficulty with concentration and short-term memory loss since starting chemotherapy. When providing a diagnosis for patients with cancer, greater stress might be placed on symptoms that are less closely tied to physical symptom burden. This includes a deeper assessment of sadness, tearfulness, social withdrawal, worthlessness, guilt, and suicidal ideation [28]. One must also keep an open mind regarding other possible causes or contributors to the patient's symptoms.

Persistent depressive disorder is another depressive disorder that has been studied less formally in the cancer population but should remain on the differential diagnosis. With persistent depressive disorder, formerly called dysthymia, patients experience a depressed mood more days than not for a period of at least 2 years. They also experience other symptoms of depression but have fewer requirements in order to meet criteria when compared to MDD. Patients can experience major depressive episodes superimposed on persistent depressive disorder. This should be considered in patients with periods of symptom exacerbation that improve but never fully resolve between episodes [27]. There are no studies specifically examining persistent depressive disorder in patients with CNS metastases and limited data on the general cancer population.

When depressive symptoms occur exclusively in the context of a stressor and cause impairment in daily life or functioning, an adjustment disorder would be the most appropriate diagnosis [27]. This is common in patients who have cancer and often warrants treatment approaches similar to that of MDD.

For patients whose symptoms of depression are directly due to a substance or other medical problem, the appropriate diagnosis may be substance-/medication-induced depressive disorder or depressive disorder due to a general medical condition [27]. Substances can be illicit, prescribed, over-the-counter, and/or supplements and include intentional and accidental ingestions. Depression in a patient with at least one CNS metastatic lesion would be appropriately diagnosed in this category if the lesion itself is believed to be causing the symptoms.

The differential diagnosis for depression in patients with cancer is broad, and the etiology is often multifactorial. Factors that might contribute to a depression-type picture and should be considered are as follows.

Potential contributors to depressed mood in patients with cancer

- Depressive disorder
- Bipolar disorder
- Substance/Medication use
  - Alcohol
  - AEDs
  - Interferon-alfa, IL-2
  - Corticosteroids
- Vitamin D deficiency
- Malnutrition
- Hypothyroidism
- Low testosterone
- Pain
- Cancer-related fatigue
- Sleep disorders
- Apathy
- Demoralization
- Delirium
- Dementia

Hypoactive delirium often masquerades as a depressive disorder. Symptoms can include blunted affect, emotional lability including tearfulness, apathy, decreased involvement in daily activities, apparent lack of motivation, low energy, decreased PO intake, decreased physical activity, and impairments in attention/concentration. A waxing and waning course, alterations in level of consciousness, and perceptual disturbances can be helpful in distinguishing delirium from depression. Risk factors for delirium in cancer include a number of factors commonly associated with patients with CNS metastases: history of delirium, advanced age, premorbid cognitive impairment, intracranial disease involvement, leptomeningeal disease, low albumin, dehydration, infection, hypoxia, recent surgery, cytokine release syndrome, comorbid bone or liver metastases, and use of steroids, benzodiazepines, and opioids [29–34]. There is limited evidence to guide the management of agitated delirium associated with new immunotherapy approaches [35, 36]. Delirium can be distressing for patients, family members, and members of the care team and continue to impact patients into the future. In a study of 154 patients with cancer who experienced delirium while hospitalized, 53.5% recalled their delirium, and the majority of these patients recalled this experience as being highly distressing after resolution [37]. Up to 90% of patients with cancer have delirium at the end of life [32]. When depression and delirium occur together, priority should be given to addressing the causes of delirium, which are typically multifactorial in patients with cancer [25, 34].

In patients presenting with predominant cognitive complaints and possible mood disorder, it is important to consider an underlying cognitive disorder in addition to other causes. A gradual onset of impairments can often allow patients to compensate in day-to-day functioning. With the increasing demands that come with a cancer diagnosis and treatment, such as managing new medications and frequent appointments, underlying symptoms can be unmasked and become more impairing.

Bipolar Disorders

Bipolar disorders are differentiated from depressive disorders by the presence of at least one episode of hypomania or mania in a person's lifetime. Although depressive episodes typically occur at higher rates than manic episodes, history of a depressive episode is not a requirement for a diagnosis of a bipolar disorder. As with depressive disorders, the DSM-V identifies multiple diagnoses that help further classify the symptom profile and guide treatment decisions. These include bipolar I disorder, bipolar II disorder, cyclothymic disorder, substance-/medication-induced bipolar disorder, and bipolar disorder due to another medical condition. Hypomanic and manic episodes differ in their severity with hypomania lasting fewer days and having a noticeable, but less impairing, impact on daily functioning. Symptoms may include grandiosity, decreased need for sleep, increased and pressured speech, racing thoughts, distractibility, an increase in goal-directed activi-

ties, and involvement in activities that are likely to have negative outcomes (i.e., risky financial decisions, spending sprees, driving very fast, sexual indiscretion, etc.) [27].

Much as in depressive disorders, patients with a bipolar illness are at an elevated risk of negative health outcomes when compared to the general population. This includes some factors that are associated with cancer, such as tobacco and alcohol use. However, there is no evidence that a patient with a bipolar illness is at a higher risk of developing cancer than others. There is also limited data specifically looking at cancer-related outcomes in patients with an underlying bipolar disorder.

There are examples of hypomania/mania being caused by a medical condition. Some of the most well-studied include stroke, traumatic brain injury, multiple sclerosis, and disorders of adrenal functioning [27, 38].

Some medications and other substances can lead to hypomania/mania and might be part of a patient's treatment while targeting cancer. Perhaps the most well-known example is that of corticosteroids. As previously mentioned, interferon-alfa also has rarely caused mania and should be monitored. Treatment-related mood symptoms are discussed later in this chapter.

Anxiety Disorders

Although the focus of this chapter is on mood disorders, we cannot discuss mood disorders without some mention of anxiety. Like depression, anxiety presents in patients with cancer at significantly higher rates than in the general population. When depression and anxiety symptoms occur together, they are associated with more severe depression, less robust response to treatment, lower quality of life, poorer adherence to mental health treatments, slower recovery, higher suicide rates, and higher overall healthcare costs [23]. Studies also suggest that patients with brain metastases have higher rates of anxiety than depression, particularly at specific points in treatment, such as prior to initiating radiation therapy [39].

Suicidality

Suicidal thoughts, attempts, and completions are more common in patients with cancer compared to those without. Rates have also been found to be higher in the cancer population when compared to those with other medical illness, even when controlling for expected prognosis [40]. Rates vary widely across studies and highlight the challenges of studying this heterogeneous patient population [41]. In general, the risk factors for suicidality that apply to the general population also apply to patients with cancer. Risk factors specific to patients with cancer include hopelessness independent of depression, impaired physical functioning, poor health overall, increasing stage of disease, and specific primary cancer types such as CNS malignancy [42–45]. There are mixed results on the impact of gender in this population as a whole [41].

There are no studies looking specifically at suicidality in patients with CNS metastases, but advanced stage of disease and involvement of a primary CNS lesion both suggest that this population is at increased risk. The highest rates occur close to the time of diagnosis [46]. Although there is consensus that suicidality generally decreases over time following cancer diagnosis, providers should always keep in mind that suicidality can occur at any time. In a study of more than 720,000 breast cancer survivors, participants continued to demonstrate elevated risk of suicide compared to the general population, even 25 years after cancer diagnosis [42]. Similarly, multiple studies show continued elevated risks in adult survivors of childhood cancers [43].

Mood Symptoms Related to Cancer Treatments

The side effects of specific chemotherapy agents will not be discussed in this chapter, but it should be noted that numerous neuropsychiatric side effects are possible with cancer treatments. In fact, receiving chemotherapy independently correlates with rates of depression in the breast cancer population, regardless of the agent being used

[47]. This reinforces the importance of monitoring for mood disorders in all patients receiving treatment.

Hormonal Agents

The use of hormonal agents also increases the risk for depression. There are clear links between hormones and depressive symptoms in healthy individuals. For example, mood disorders in women can have cyclical patterns related to menses, and women are at higher risk for depression in the postpartum period and surrounding menopause. There is mixed evidence about tamoxifen's effect on depression risk [47–50]. Perhaps unsurprisingly, patients with other risks factors for depression have higher rates of developing depression while on tamoxifen [50]. Increased depressive symptoms also correlate with other physical symptoms, such as hot flashes and sexual dysfunction, both of which are more common in women on tamoxifen compared to those who were not [51, 52].

Immunotherapy

As immunotherapies become more commonly used, there is increasing data about the neuropsychiatric side effects, particularly in the acute phase. Interferon-alfa is one of the most well-known examples of a medication causing depression and has warnings for the risk of suicidality. Depression occurs in up to 58% of patients receiving this medication. It should also be noted that there is a lower, but still significant, risk of mania associated with interferon-alfa use [53–55]. IL-2 has also been associated with higher depression rates [56].

Antiepileptic Drugs

The antiepileptic drug class (AEDs) as a whole has warnings about increased risk of depression, with rates varying between medications [56]. Clinical studies for oral levetiracetam show 13% of adults and 38% of those less than 18 years of age experience "behavioral symptoms" that might include depression, anxiety, mood lability, and agitation. One percent of adults developed psychotic symptoms [57]. On the other hand, many AEDs function as mood stabilizers and can be beneficial in treating mood disorders.

Steroids

Glucocorticoids have a clear association with the onset of multiple psychiatric side effects including depression, hypomania/mania, suicidal ideation, psychosis, delirium, and sleep changes [38, 56]. Onset is often within the first couple of weeks and dose-dependent but can occur after long-term use. A diagnosis of primary bipolar disorder does not increase the risk of steroid-related mania. However, patients who have a history of this response to steroids are at an increased risk, and prophylaxis with a mood stabilizer for future treatments should be considered. One should not underestimate the impact steroid-related sleep impairments can have on a patient's functioning and sense of well-being. This should be monitored closely and treated aggressively.

Radiation Therapy

Chapter 29 of this book discusses the potential neuropsychiatric impacts of radiation therapy in depth. These potential adverse outcomes cannot be overlooked. In a study of 170 patients with brain metastases undergoing whole brain radiation, self-reported measures of postradiation symptoms showed a high prevalence of symptom burden, most commonly fatigue, poor sense of well-being, anxiety, drowsiness, and poor appetite. They also found that symptoms tend to cluster together—anxiety and depression are frequent covariables [58]. Distress measures show similar patterns in patients undergoing whole brain or hypofractionated stereotactic radiotherapy compared to those without brain mets undergoing radiation to the breast [39]. Fatigue, a common side effect of radiation, can mimic depression in this phase of treatment.

When a medication suspected of contributing to a mood disorder is an integral part of a patient's cancer treatment, it is often not feasible to discontinue the medication. Providers should consider lowering the dose of the offending agent or transitioning to another agent in the same class, if possible. It is important to consider the benefit of psychiatric medications as adjuvant therapy, behavioral strategies, and lifestyle changes.

Impact of Mood Disorders on Cancer-Related Outcomes

Engagement in Treatment

Psychosocial stress has been linked to multiple factors that potentially play a role in cancer development or progression including inflammation, oxidative stress, decreased immune surveillance, and dysfunction of the HPA axis [10, 11]. Unsurprisingly, clinicians and researchers are interested in how these relationships can impact cancer-related outcomes in patients who struggle with mood disorders. Studies show that there are differences in how patients make decisions related to their cancer treatment. For example, in a study of women with breast cancer conducted by Colleoni et al., only 51.3% of women with comorbid depression accepted the recommendation of adjuvant chemotherapy compared to 92.2% of women without depression [59]. Treatment adherence rates also differ. Studies have found that patients with depression are up to three times more likely to be nonadherent with medication recommendations from their medical team [60]. Guilt is a common feeling in patients with cancer who may fear they are a burden on others or somehow deserve illness because of a perception of previous wrongdoings—this has been found to be an independent risk factor for treatment nonadherence [61]. As the treatment paradigm in cancer continues to shift toward managing a chronic disease, long-term follow-up and chronic medication use become more important. Kaul et al. noted that young adult cancer survivors are approximately twice as likely to report medication nonadherence as their peers and that mental distress is a significant risk factor for this behavior [62].

Morbidity

Cancer-related morbidity can similarly be impacted by the presence of a mood disorder. Depression rates correlate with levels of anxiety, fatigue, and pain [63, 64]. Distress is also associated with other maladaptive behaviors, some of which have their own associated cancer risks, such as tobacco use [65]. Current depression is a risk factor for future psychiatric comorbidities, which can negatively impact a patient's progress. Patients with depression during hospitalization following hematopoietic cell transplant were found to have higher rates of post-traumatic stress disorder and lower quality of life ratings at their 6-month follow-up visits [66]. In a study of 154 patients admitted to the hospital for surgery for thoracic and head and neck cancers, depression and fear of cancer recurrence were strongly associated with higher nicotine relapse rates [67]. El-Jawahri et al. compared 1116 patients with depression prior to allogeneic hematopoietic cell transplantation to 6317 patients without pretransplant depression and found higher rates of grade 2–4 acute graft-versus-host disease, lower overall survival rates, and fewer days alive and out of the hospital in the first 100 days posttransplant in patients with premorbid depression [68].

Mortality

It is challenging to study the impact of mood disorders on cancer-related mortality given the high number of confounding factors. However, studies have found that patients with higher depressive symptom burden have shorter survival times [69–73]. Also, having depression prior to cancer diagnosis correlates with lower survival compared to those without precancer depression. This difference is especially prominent for patients with depression and precancer physical limitations [74]. The etiology of this relationship is likely multifactorial with potential impact from cancer treatment nonadherence or maladaptive behaviors like comorbid substance use as discussed previously [10, 69].

Healthcare Utilization and Costs

The impact of comorbid mood disorders and cancer can also be felt on a systems level. With a shifting focus toward patient satisfaction, we see that depressive symptom severity inversely correlates with satisfaction in medical care [75]. Patient distress levels also correlate with the number of reported concerns during an outpatient oncology visit [76]. This translates to increased time spent with members of the treatment team, either through longer visits, more frequent visits, or increased utilization of urgent and emergency services [77]. Studies have clearly shown that mental health issues lead to higher healthcare costs as a whole. Implementation of appropriate treatment strategies that target mood disorders and anxiety lowers those costs [77, 78]. Also, studies show that proactive involvement of psychotherapy, particularly cognitive behavioral therapy (CBT) skills, can lead to higher quality of life reports, fewer psychiatric symptoms, and lower healthcare costs, even in patients who did not report elevated levels of distress at the time of diagnosis [78, 79]. This underscores the importance of addressing mental health needs in all patients.

Interactions with Caregivers

Caregivers can serve a wide range of functions, providing emotional, cognitive, spiritual, physical, and social support. The presence of brain metastases often corresponds with increasing care demands as patients develop new or worsening symptoms that impact daily life. The concept of caregiver burden has become a focus of research as patients with cancer live longer and the caregiver role has correspondingly become more fluid, transitioning in focus from end-of-life care to that of long-term survivorship. Being a caregiver correlates with higher levels of anxiety, depression, social isolation, and concerns about financial stress and stigma related to the cancer [80]. Studies have shown that caregivers of those with advanced cancer have higher rates of depression and anxiety compared to those caring for patients with earlier-stage disease. Studies specifically looking at caregivers of patients with CNS metastases are limited, but do show increased rates of depression and anxiety symptoms [81]. In addition to the vital role that caregivers play as part of the treatment team, evidence also reveals an association between high levels of caregiver distress and high levels of patient distress.

Role of Screening

Studies reveal that healthcare providers often fail to recognize patients who are experiencing emotional distress, highlighting the importance of routine screening for all patients [82]. As mentioned, confounding factors related to cancer, cancer treatment, and medical comorbidities can make screening for mood disorders more challenging. Many instruments are available, including some that have been validated for use specifically in patients with cancer, though no screening tools have been validated specifically in patients with CNS metastases. This validation occurs by comparing outcomes on the screening instrument with those of a gold standard tool, such as a standardized structured clinical interview [83]. Identifying the most appropriate screening tool requires assessing several factors including the symptoms of primary interest, patient population, clinic work flow, procedures for who will administer and follow-up when a patient screens positive, available technology for administration and/or interpretation, available time, etc. Systematic reviews of English instruments completed by Luckett et al. and Vodermaier et al. provide additional information on individual screening tools [84–86].

The Patient Health Questionnaire-9 (PHQ-9) is a self-report instrument with nine items that reflect the diagnostic criteria for MDD outlined in the DSM-V. Patients rate the severity of their symptoms in the past 2 weeks on a scale from 0 for "not at all" to 3 for "nearly every day" [87]. This was developed for use in primary care and since validated for use in patients with cancer [88].

The Hospital Anxiety and Depression Scale (HADS) is a 14-item self-report tool commonly

used in research and clinical settings to screen for anxiety and depression symptoms in patients with medical illness. This has been validated in a wide range of patient populations, including those with cancer, and has proven to be particularly reliable in screening for depression in this population [89].

The NCCN Distress Thermometer has been validated for use in patients with intracranial tumors [82, 90]. It serves as a screening tool by asking patients to rate their distress on a scale from 0 to 10 with 10 representing the highest level of distress. Patients also have the opportunity to select areas in which they would like additional support and/or resources by checking off topics on a Problem List. Areas include practical problems, family issues, emotional stress, spiritual concerns, and physical ailments [1]. Although this instrument can gather information about a wider range of issues compared to the others discussed, results are less easily correlated with specific diagnoses, and studies show that the distress detected correlates with anxiety more than depression [91, 92].

Treatment Strategies

Comorbid mood disorders are best treated with a multidisciplinary approach that addresses patient needs while taking into account their inherent strengths and weakness and the environment in which they spend their time. Although therapy and medication have independently been shown to be effective for both unipolar and bipolar mood disorders, a comprehensive approach utilizing both tools should be encouraged.

Psychotherapy

Gathering comprehensive data on the effectiveness of different therapy modalities for patients with cancer has its challenges. Studies vary considerably in regard to the targeted symptoms, utilized treatment modality, training of those delivering the treatment, and the means of assessing effectiveness [41]. While numerous studies demonstrate benefit for patients in specific populations, data is limited in regard to patients with CNS metastases in particular.

Cognitive behavioral therapy (CBT), originally developed to target depression, is a widely used form of psychotherapy. It focuses on identifying dysfunctional patterns of cognition, which often occur automatically and without awareness, in order to change one's emotional response and behavior [93]. Evidence exists for using CBT in patients with cancer to target many symptoms, including depression, fear of cancer recurrence, pain intensity, and fatigue [94–96].

Mindfulness-based stress reduction (MBSR), developed by Jon Kabat-Zinn, has helped contribute to the rise in popularity of "mindfulness" practices in popular culture. Mindfulness is a form of meditation that refers to a purposeful and sustained focus on one's self and the immediate situation and/or surroundings to help bring focus and clarity [97]. When incorporated into formal treatment, this can involve multiple strategies, such as individual meditation, guided meditations in person or through the use of pre-recorded audio, body scans, and yoga [98]. This has been studied in patients with cancer and found to be helpful for many symptoms including overall anxiety, fear of cancer recurrence, quality of life, depression, cognitive symptoms, and physical tension [94, 98–100]. There is mixed evidence about the longevity of these benefits [99, 100]. Providers who teach these skills suggest they be incorporated as a lifestyle change rather than a time-limited therapy.

Motivational interviewing relies on a collaborative relationship between patient and provider to help illicit and build upon one's motivations for change while honoring patient autonomy [101]. Although this style has been most studied in patients with substance use disorders, it is being applied more widely over time. In patients with cancer, potential targets include optimizing diet, exercise, and lifestyle factors that impact sleep and fatigue, pain, mood, and substance misuse, among other aspects of daily life [102–104].

Similarly, dialectical behavior therapy (DBT) has seen a significant broadening of applications since the original skills training manual was pub-

lished in 1993 [105]. Originally developed to treat patients with borderline personality disorder, this therapy modality focuses on four sets of skills: mindfulness, interpersonal effectiveness, emotion regulation, and distress tolerance [106]. This modality typically requires a greater time commitment each week, but should be strongly encouraged.

Additional therapy modalities have been developed specifically to assist patients with chronic medical illness and those facing the end of life. Dignity therapy was developed to help patients find meaning and hope as they approach death [107]. Meaning-centered psychotherapy, both as individual and group modalities, is similarly focused on assisting patients in finding and sustaining meaning [108–110].

Medications

Before considering medication management to target mood disorders, it is important to evaluate and address other contributing factors. The impact of comorbid substance use disorders should not be overlooked, and incorporating screening for substance use is an integral part of mental health care. Impairments in sleep correlate with depression risk, and treating sleep disorders can result in lower depression symptoms [111, 112]. Rates of sleep apnea are higher in patients with cancer compared to the general public, and sleep-disordered breathing correlates with increased mortality in cancer patients, specifically [113]. It has also been found to correlate to increased rates of cancer development, though there are many confounding factors [114]. All patients should be screened for malnutrition, nutritional deficiencies, and hypothyroidism.

Antidepressants

There is a robust body of evidence for using antidepressants to treat depression, including specifically for patients with cancer. There is less evidence available to help guide treatment in patients who have symptoms of depression but do not fully meet diagnostic criteria for one of the depressive disorders. There is also less evidence specifically related to patients with CNS metastases. Despite this paucity in formal evidence, antidepressants are routinely used to manage both depression and anxiety symptoms in this patient population. In fact, rates of medication use for depression and anxiety in patients with cancer in the USA are typically about two times that of the general population, and these medications are used more frequently as disease progresses [115].

Choosing an appropriate medication to target depression in patients with metastatic cancer requires attention to a number of factors:

1. *Primary symptom of interest:* See Table 11.1 for information on the most commonly used antidepressants and considerations for their use. Of note, there is limited evidence for the use of stimulants as monotherapy to treat depression. If this is considered, it would be wise to involve a psychiatric provider to assist with proper use.
2. *Other potential targets:* While effective in treating depression, antidepressants have other effects that might be beneficial and should be considered. Sleep, appetite, nausea, hot flashes, sexual dysfunction, and neuropathic pain are the most common targets. See Table 11.1 for examples. In addition to those listed, trazodone is an antidepressant that is used off-label for insomnia. With less risk of tolerance or withdrawal and limited risk for a paradoxical reaction more common in patients with CNS pathology, trazodone is often viewed as superior to benzodiazepines for this purpose. Primary caution is with orthostasis.
3. *Potential problematic side effects*: Patients with intracranial pathology are often more sensitive to medication side effects. In general, starting at low doses and titrating slowly is the best approach. It should be noted that all serotonergic antidepressants have some risk for osteoporosis with long-term use, gastrointestinal bleeding through antiplatelet activity, and hyponatremia. Bupropion, which acts by increasing norepinephrine and dopamine, can be quite beneficial for some patients by increasing daytime motivation/energy,

Table 11.1 Most commonly used antidepressants and considerations for use in patients with cancer

	Primary mechanism of action	Reasons to consider	Cautions with use
Selective serotonin reuptake inhibitors (SSRIs)	Inhibition of 5-HT reuptake	Considered first-line Generally well-tolerated	Risk of headaches, GI upset, sexual dysfunction
Citalopram			
Escitalopram			
Fluoxetine			
Fluvoxamine			
Paroxetine			
Sertraline			
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	Inhibition of 5-HT and norepinephrine reuptake	Helpful for neuropathic pain	Risk of HTN
		Activating impact of NE can increase motivation and daytime energy	Discontinuation syndrome is more prominent and requires slower taper
Desvenlafaxine		Venlafaxine for hot flashes	
Duloxetine			
Venlafaxine			
Bupropion	Inhibition of norepinephrine and dopamine reuptake	Helpful for smoking cessation	Risk of HTN, seizures
		Activating impact can increase motivation and daytime energy	Can exacerbate anxiety
		Off-label use for attentional issues	Can cause appetite suppression and weight loss
		Low risk of sexual side effects	Caution in psychotic disorders
		Less weight gain	
Mirtazapine	Inhibition of 5-HT_2 and 5-HT_3	Antiemetic properties	Risk of dry mouth, weight gain
	Increased serotonin and norepinephrine through alpha-2 adrenergic antagonism	Increases appetite	Rare risk of neutropenia through bone marrow suppression
		Sedating impact helpful for sleep	
Tricyclic antidepressants (TCAs)	Inhibition of 5-HT and norepinephrine reuptake	Helpful for neuropathic pain	Anticholinergic, anti-muscarinic, and anti-alpha adrenergic side effects
Amitriptyline		Sedating impact helpful for sleep	
Desipramine			
Doxepin			
Imipramine			
Nortriptyline			

improving attention, and aiding in smoking cessation. However, it should be used with caution in patients with CNS metastases or primary brain tumors due to a dose-dependent risk of seizures [116]. When combining medications, one should keep in mind the additive effects of side effect profiles. Use of anticholinergic medications is a common example in patients with cancer. As part of chemotherapy, pain, nausea, and psychiatric medication regimens, these medications can lead to the development of bothersome dry mouth and constipation as well as potentially more problematic effects like urinary retention, bowel ileus or obstruction, dental caries impacting oral intake, and cognitive impairment. There are also additional risks when combining multiple serotonergic medications, such as tramadol, fentanyl, triptans, and antiemetic agents, in addition to antidepressants. Serotonin syndrome can present with autonomic instability, altered mental status,

tremor, hyperreflexia, and myoclonus and can progress to seizures, coma, or death if not recognized and treated.

4. *Drug-drug interactions:* Providers should always assess for possible drug-drug interactions before prescribing a new medication. When working with patients who have cancer, it is important to consider what agents are typically used in the cancer treatment standard of care and make decisions accordingly. There are numerous potential interactions between psychiatric medications and other medications commonly used in cancer treatment. The most frequently discussed drug-drug interaction in this category is that of tamoxifen and paroxetine, a selective serotonin reuptake inhibitor (SSRI). Tamoxifen is an inactive prodrug metabolized through the liver by cyp2D6 into its active metabolites. Multiple antidepressants are inhibitors of this enzyme and pose a theoretical risk of decreasing the effectiveness of tamoxifen. Interestingly, studies have not shown this to be true in clinical practice. In the largest study to date, Haque et al. found that there was no correlation between antidepressant use and cancer recurrence or contralateral breast cancer diagnosis in patients taking both an antidepressant and tamoxifen [117]. The risks and benefits of using this combination should be considered for each individual case.
5. *Mechanism of delivery:* Patients with cancer often have temporary difficulty taking medications by mouth. In the USA, parenteral formulations are not as readily available [118, 119]. Patients may also have surgical interventions or other medical issues that impact bioavailability of medication. Psychiatric providers can be of assistance in these challenging cases.

Mood Stabilizers

There are multiple mood stabilizers that can be used in the treatment of bipolar illness. If a patient is currently stable on a psychiatric medication, it is advisable to avoid changes in this regimen as much as possible. This class of medication typically has more significant drug-drug interactions than other psychotropics and should be watched closely. Medication nonadherence can also be more detrimental. For example, lamotrigine is classically known for its risk of the life-threatening Stevens-Johnson syndrome during dose titration. If a patient misses approximately 5 consecutive days' dosing, regardless of the reason for this nonadherence, the dose must be re-titrated from the beginning of the titration schedule, which can have adverse effects on a patient's mood and behavior. Lithium can be a powerful mood stabilizer but it is very reliant on consistent body water status. Lithium toxicity, which can be fatal, occurs more frequently with dehydration, infection, and multiple medication interactions, including the use of low-dose nonsteroidal anti-inflammatory drugs (NSAIDs). Management with lithium in the context of cancer requires close monitoring and should involve a psychiatric provider.

Antipsychotic medications also have mood stabilizing properties. Although most are used for psychotic disorders and bipolar mania, there is evidence to support off-label use for many indications benefitting patients with cancer. This can include use as an antiemetic, benzodiazepine-sparing sleep aid, appetite stimulant in failure to thrive, treatment for agitation or severe irritability related to intracranial disease, and to treat steroid-related mood disorders, anxiety, and insomnia [120].

Conclusion/Summary

Patients with CNS metastases are at an increased risk for mood disorders. This correlation is multifactorial, with contributions from shared mechanisms on a cellular level, involvement of specific brain regions linked to the processing and generation of emotions, and side effects of cancer treatment to name a few. Comorbid mood disorders are linked to a number of poor cancer-related outcomes and problematic behaviors, including medication nonadherence, comorbid substance misuse, higher healthcare utilization and costs, and even mortality. Screening and early interventions are important and often involve collabora-

tion with mental health professionals to provide medications, psychotherapy, and other behavioral strategies. Although a wide range of treatment strategies are used in clinical practice, the body of literature for this specific patient population is small. Additional research is needed to provide evidence-based management recommendations for patients with CNS metastases.

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12 Leptomeningeal Disease and the Role of Intrathecal Therapy

Fadi Saadeh and Adrienne Boire

Introduction

The meninges (*meninx*, Greek for membrane) are complex connective tissue structures that surround the brain and spinal cord. Embryologically derived from meningeal mesenchyme, the meninges are divided into the *leptomeninx* (thin membrane) that houses the pia, arachnoid mater and CSF, and the *pachymeninx* (tough membrane) or dura mater. The dura mater is a well-innervated, highly vascularized collagenous membrane that contains lymphatics [1, 2]. Beneath the dura lies the multilayered arachnoid mater. This membrane encases the CSF-filled subarachnoid space creating a cellular barrier through tight junctions [3, 4]. Adjacent to the brain parenchyma, a one to two cell-layer membrane, the pia mater, covers the brain and spinal cord. Intimately associated with the nervous tissue, the pia extends into sulci and fissures, delves deep into the parenchyma, and reflects on subarachnoid vessels. Fibroblast-like cells produce collagen bundles that along with trabeculae connect the two layers of the leptomeninges [5]. Between the pia and the outermost surface of the brain parenchyma lies the glia limitans: a layer of astrocytic end feet that projects on the pia mater cells to create an additional protective barrier [6]. The glia limitans permissively allows size-dependent passage of select molecules from the CSF to the brain parenchyma [6–9].

Unlike the dura mater, supplied by the systemic circulation, the leptomeningeal blood supply arises from the anterior, middle, and posterior cerebral arteries before penetrating the brain parenchyma. The leptomeningeal space enjoys a somewhat complex relationship with the systemic circulation. The leptomeninges reside behind the blood-CSF barrier, consisting of the choroid plexus epithelium (Fig. 12.1). CSF circulating through the leptomeninges is absorbed via the arachnoid granulations where it returns to the venous system. Small molecules may enter and exit the parenchyma via perivascular (Virchow-Robin) spaces [10]; the functional relevance of these pathways remains an area of active study.

Spread of cancer cells into the leptomeningeal space is described as leptomeningeal metastasis (LM). Historically, this pathophysiologic entity has been described as "carcinomatous meningitis," "meningeal carcinomatosis," and/or "leptomeningeal carcinomatosis." We prefer the more inclusive term leptomeningeal metastasis as it encompasses all malignancies and remains agnostic to the role that inflammation may play in this pathophysiology. LM

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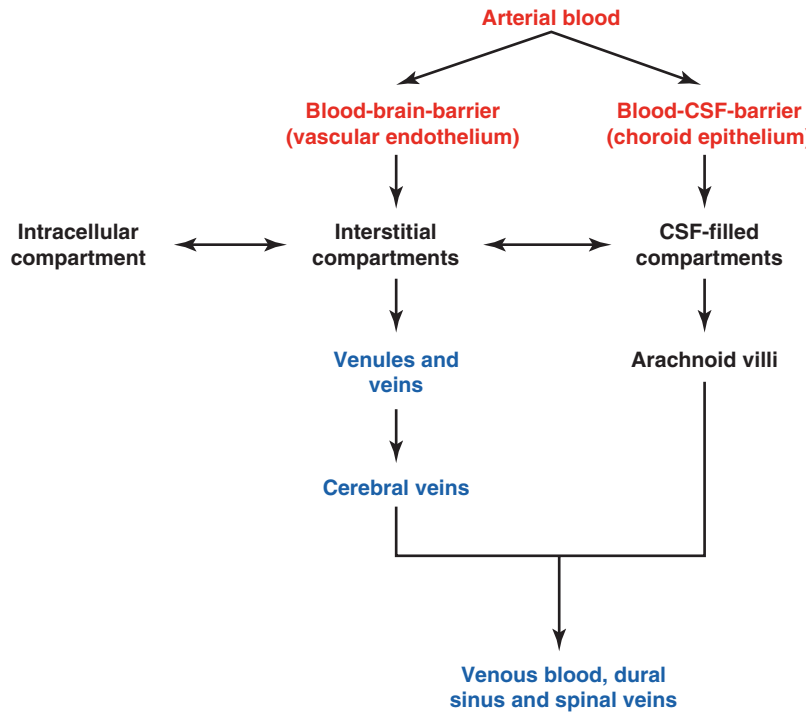

Fig. 12.1 Arterial and venous circulations communicate through compartments across the blood-brain and blood-CSF barriers. (Adapted from Malcolm B Carpenter. Human Neuroanatomy. 7th ed. United States: Baltimore: Williams & Wilkins, ©1976; Carpenter's Human Neuroanatomy)

occurs in approximately 5–8% of patients with solid tumors and 5–15% of those with hematologic malignancies [11]. Cancer cells may gain access to CSF compartments through four potential routes: spread through Bateson's plexus via the venous circulation [12], pass through choroid plexus via arterial circulation [13], direct invasion of spinal and cranial nerves [13] or brain parenchyma through direct penetration of the glia limitans [14] (Fig. 12.2). Once within the leptomeninges, cancer cells face an additional challenge—survival within the nutrient-poor CSF. Employing animal models, we have recently found that cancer cells upregulate complement C3. Focal generation of the split product C3a leads to the loss of blood-CSF barrier integrity, enriching CSF composition [15].

The Incidence of LM in Different Cancers

The improvement in overall survival of patients with metastasis at other sites and advances in diagnostic techniques have contributed to the rising incidence of LM, which varies by primary tumor type. The most common cancers that develop LM are breast cancer (12–34%) particularly lobular carcinoma [16–18], lung cancer especially NSCLC (3–5%) [19], acute non-lymphocytic leukemia (5–15%) [20, 21], non-Hodgkin lymphoma (6%) [22, 23], melanoma (5–25%), GI malignancies (4–14%), and unknown primaries (1–7%) [24–27]. Tumors with lower LM predilection are mycosis fungoides [28–30], multiple myeloma [31, 32], squamous cell carcinoma [33], thyroid cancer [34], rectal cancer [35], carcinoid [36], rhabdomyosarcoma [37], CLL [38], and neuroblastoma [39]. However, it cannot be overstated that any malignancy may seed the leptomeningeal space.

Prognosis of Leptomeningeal Metastasis in Different Cancers

Median overall survival in LM patients is poor and ranges between 6–8 weeks untreated and up to 4 months with treatment [40–43]. There is a wide range of outcomes for treated patients. For

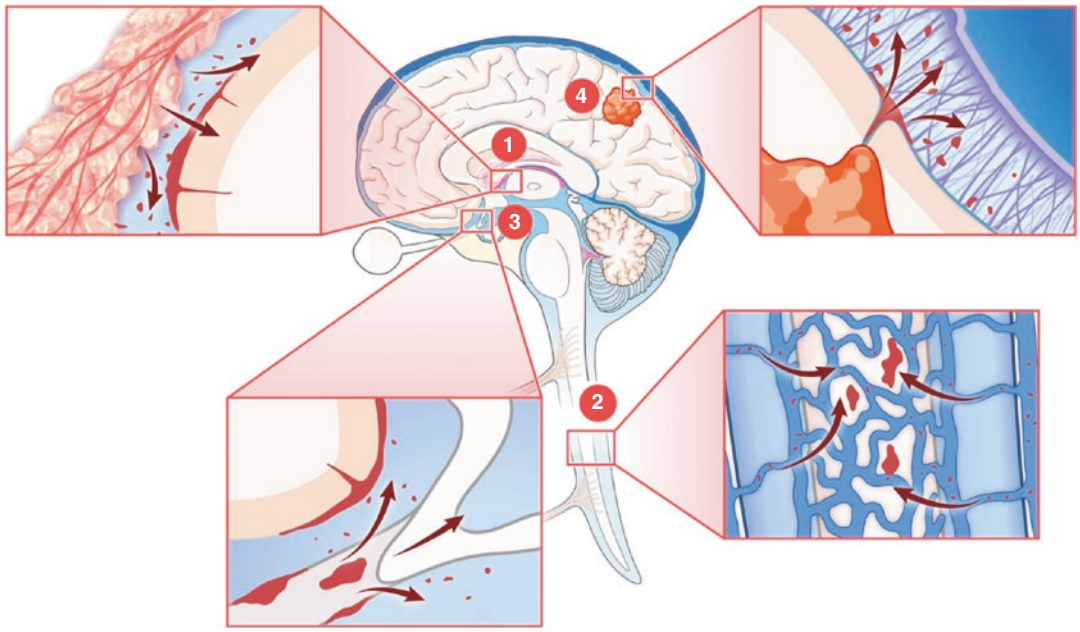

Fig. 12.2 Metastatic cancer cells may employ four portals of entry to access the leptomeningeal space: *1*. hematogenous arterial route, *2*. hematogenous venous route, *3*. invasion along the nerve roots, and *4*. invasion from the parenchyma

instance, reported overall survival for breast cancer patients ranges from 1.75 to 4.5 months with a 1-year survival rate of 16–24%. Outcomes are less favorable in lung cancer (average 3–6 months and 1-year survival of 19%) and melanoma (1.7–2.5 months and 1-year survival rate of 7%) [44–62]. Prognosis can be stratified according to risk (refer to treatment section) with performance status and systemic disease burden as robust prognostic factors. In the era of targeted therapies, molecular subtypes play a major role in determining a patient's prognosis; e.g., patients with LM from HER-2-positive breast cancer demonstrate longer median overall survival as compared to their triple negative counterparts (5.2 vs. 2.5 months) [63].

Diagnostic Scheme

The diagnosis of LM rests on three pillars: (1) neurologic signs and/or symptoms consistent with leptomeningeal localization, (2) demonstration of characteristic findings on MR imaging of the brain and spinal cord, and (3) CSF examination. We therefore recommend that all patients suspected of LM undergo formal neurologic examination, MR imaging of the brain and spine, as well as CSF sampling.

Signs and Symptoms

Clinical signs and symptoms in patients with LM range from subacute to acute and present within days to weeks. Leptomeningeal metastasis presents with protean manifestations; while unsurprising given the ubiquity of the leptomeningeal space over the central nervous system, certain signs and symptoms are characteristic and should raise clinical suspicion. Multifocal neurologic signs and symptoms in a patient with or without a primary malignancy should raise the suspicion of LM. For instance, 64% of patients with LM usually present with multifocal signs and symptoms [27, 64].

Cerebral

Patients harboring LM most commonly present with headache [24, 27]. This can be due to elevated ICP or meningeal irritation. With the former, patients present with nausea, vomiting, and dizziness precipitated by a change in head position (plateau waves) [65, 66]. Although no specific headache location or pattern is specific to a LM diagnosis, severe episodic headaches consistent with elevated and labile ICP should raise concern. Funduscopic examination can reveal papilledema depending on the degree and duration of ICP elevation. Brain MRI may demonstrate hydrocephalus due to obstruction of CSF egress or infiltration of arachnoid villi. In severe cases, tentorial herniation may occur, notably in leptomeningeal leukemia [67]. Even without hydrocephalus, CSF flow dynamics in LM may remain abnormal [68]. Headaches can also be caused by direct meningeal irritation, which can elicit afebrile neck stiffness and meningeal signs such as Kernig's and Brudzinski's signs. Lateral and midline cerebellar signs and symptoms can be present in up to 20% of LM patients including vertigo, nausea, and gait disequilibrium [24, 27].

LM tumors may invade Virchow-Robin spaces into the parenchyma or remain perivascular causing disruption of the brain's vasculature and electrical activity [69]. A common symptom of LM is a change in mental status including memory loss, personality changes, and disorientation. While these symptoms are not specific to LM, they could indicate underlying cerebral dysfunction, undiagnosed/subclinical seizures, or hydrocephalus. In some patients with LM, angiography shows partial occlusion or complete obliteration that leads to transient ischemic attacks or strokes [70–72]. Up to 25% of LM patients develop seizures, most commonly partial with secondary generalization. Seizures can be due to cortical irritation, local edema, or parenchymal invasion [24, 48].

Cranial Nerves

The cranial nerves pass through the subarachnoid space; symptoms involving greater than one cranial nerve suggest LM. The most common cranial nerve sign in LM patients is diplopia, which can be due to oculomotor, trochlear, or abducens nerve involvement [48, 64, 71]. LM deposits on the trigeminal nerve may elicit facial pain or numbness. Involvement of the mandibular division causes the "numb chin syndrome" reported by up to 22% of LM patients [73, 74]. Facial nerve involvement typically causes a lower motor neuron palsy affecting the upper and lower face; patients with metastatic cancer presenting with Bell's palsy merit additional workup to address possible LM. Less common symptoms include sensorineural hearing loss (vestibulocochlear nerve) in less than 5% of patients and brainstem involvement (vagus and glossopharyngeal nerve) manifesting in dysarthria, dysphagia, and/or hoarseness.

Spinal

Leptomeningeal involvement at the level of the spine may result in radiculopathies presenting as lower extremity weakness, numbness, and absent reflexes. A cauda equina syndrome (diminished rectal tone, urinary retention, constipation, saddle anesthesia) may be present. Asymptomatic bladder enlargement is frequently found and is the most characteristic bladder pathology in LM patients [25].

Diagnosis

The above neurologic signs and symptoms are often difficult to differentiate from treatment effects or primary disease. In the setting of such presentations, a high degree of suspicion for LM is appropriate and formal diagnosis is recommended.

Neuroimaging

MRI is considered the most sensitive method for detecting LM [75]. With a specificity of 77% and sensitivity of 75% [76], in the appropriate clinical context, an MRI finding of leptomeningeal enhancement confirms LM diagnosis [77–79]. Neuroimaging findings in LM can be divided into two groups [80]: (1) diagnostic features, including leptomeningeal enhancement, subependymal enhancement, and multiple nodules in the vertebral canal and ventricles, and (2) suggestive features, including nodular enhancement over the

cerebral cortex, metastatic lesion(s) approaching sulci and gyri, dural enhancement in the intracalvarium or vertebral canal, bulky metastasis inside or in proximity to ventricles, direct invasion to the intracalvarium by head and neck malignancy, cranial nerve enhancement, or communicating hydrocephalus [81]. Diagnostic features are nonspecific and must be interpreted with caution.

Contrast-enhanced T1 images have the highest specificity (93%) and sensitivity (59%) for detecting LM compared to other MRI sequences [82]. MRI should not be limited to T1 post-contrast sequences. Consensus guidelines (EANO, ESMO) recommend that cerebral MRI should include axial T1-weighted, axial FLAIR, axial diffusion, axial T2-weighted, post-gadolinium 3D T1-weighted, and post-gadolinium 3D FLAIR sequences; spinal MRI should include sagittal T1-weighted sequences without contrast and sagittal fat suppression T2-weighted sequences combined with axial T1-weighted images with contrast of regions of interest [83].

CSF Analysis

Although MRI is typically the first diagnostic test performed, CSF examination is definitive. At a minimum, CSF examination should include measurement of opening pressure, cell count, cytological examination, and protein and glucose concentrations.

Pressure

Elevated intracranial pressure is present in almost 50% of LM patients and may be attributed to impairment of CSF drainage by obstructing malignant cells [84]. Before attributing elevated ICP to LM, care must be taken to exclude other causes, including elevated systemic venous pressure or respiratory disease [85]. Normal ICP levels in the correct lateral recumbent position can range from 90 to 250 mm H_2O [86]; measurements obtained while prone or seated may be falsely elevated. In patients with LM, ICP levels can range from 90 to 550 mm H_2O [87] with most values less than 150 mm H_2O on first LP. Measurement should be done directly after needle insertion to avoid CSF leakage and falsely low ICP readings [29]. Importantly, low or zero pressures can also be seen in patients with complete spinal blocks which occur late in the course of the disease.

Cell Count

CSF leukocyte count is typically increased in patients harboring LM. Leukocytic infiltrate is typically dominated by lymphocytes. However, other profiles may occur—eosinophils have been found in CSF samples of leptomeningeal metastasis from lymphoma [88], Hodgkin's disease [89], and an unidentified epithelial tumor [90], while CSF basophils have been found with leptomeningeal leukemia [91].

Cytology

With a sensitivity ranging from 45% to 100%, and a specificity of 95% [92], CSF cytology remains the gold standard diagnostic test for LM. Errors may be due to insufficient sample volume, delayed sample processing time, collection of less than two samples, and collection from a location far from the symptomatic site [93]. To maximize cytology sensitivity, we recommend a sample volume of 10 mL or more, brisk processing, and collection from a site close to the symptomatic area. CSF cytology remains challenging due to the irregular shedding of cancer cells and their limited presence in CSF [92–94].

Protein Concentration

CSF protein levels are elevated (>38 mg/dL) in 60–80% of patients. This is usually attributed to the breakdown of tumor and infiltrating cells along with a disruption of the blood-CSF barrier allowing serum protein to flow in [24, 25, 27]. However, the composition of this CSF protein remains under study. Interpretation of CSF protein levels must account for the sample site—ventricular taps through an Ommaya reservoir have lower normal protein concentration thresholds than cisternal or lumbar taps [25].

Glucose Concentration

CSF glucose concentration is diminished (CSF:serum ratio < 0.6 or glucose <40 mg/dL) in about one-fourth to one-third of cases [70, 95].

Abnormally low CSF glucose may be the sole indicator of LM in the absence of any other CSF abnormality [96, 97] and usually reflects diffuse meningeal involvement [97]. However, low CSF glucose (hypoglycorrhachia) may be found in several other neurologic diseases [98] and is therefore sensitive but not specific. Several causes of low glucose are postulated: (1) increased utilization of glucose by malignant cells in the leptomeninges due to their high metabolism and correlation with high lactate levels [99], (2) increased utilization by cerebral cells surrounding CSF, and (3) ineffective glucose entry into CSF by impaired transport systems [25].

Other CSF Markers

With a sensitivity ranging from 95 to 100% and a specificity of about 100% in the absence of neuroimaging findings, immunocytochemical analysis has proven useful in diagnosing LM from hematological malignancies [100]. Similarly, flow cytometry of CSF is more useful in hematological malignancies than LM from solid tumors [101]. Detection of aneuploid or hyperdiploid cells in the CSF due to abnormal chromosomal migration and erratic cell division is a robust indicator of LM. These techniques have not been proven useful in LM from solid tumors.

Tumor Markers

In the absence of cytological evidence of disease, select tumor markers have diagnostic utility. Detection of tumor markers is not universally available in clinical laboratories, but it may be useful in certain cases. Generally, LM should be high on the differential if the CSF tumor marker concentration exceeds 2% of the serum value (Table 12.1).

Other markers have been investigated as possible diagnostic tools in the absence of positive cytology results. CSF vascular endothelial growth factor (VEGF) was reported to be a useful biomarker in high-risk breast cancer, lung cancer, and melanoma patients (sensitivity, 75%; specificity, 97%) [102]. CSF microRNA analysis has also been studied as an early indicator of LM in breast and lung cancer patients (true-positive rate, 98.9%) [103]. PCR of specific mRNA from CSF has high sensitivity and may be considered [104]. Neither of these approaches has transitioned to clinical use. However, a rare cell capture technology to detect E-CAM-expressing circulating tumor cells (CTCs) [105, 106] is currently employed at select cancer centers to detect LM [105, 107–109]. With a sensitivity of 93% and a specificity of 95%, detection of ≥1 CSF-CTC/mL represents a robust marker for diagnosing LM and should be considered during routine LM workup, if available [106].

Table 12.1 Cerebrospinal fluid markers in leptomeningeal metastasis from different primary cancers

Marker	Primary disease
Beta 2 microglobulin	Lymphoma
AFP	Germ cell
Beta glucuronidase	Nonspecific
CEA	Colon, ovarian, breast, bladder, lung
CA-125	Ovarian
CA-15-3	Breast
CA19-9	Adenocarcinoma
CK-BB	Small cell lung cancer
GFAP	Glioma
HCG subunit	Choriocarcinoma, embryonal, and germ cell tumors
5-HIAA	Carcinoid
LDH isoenzyme D	Carcinoma
PSA	Prostate
Protein S-100	Melanoma
HMB45	Melanoma

Modified from Demopoulos, A; Posner, J. Cerebrospinal fluid biochemical markers. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2018. Rogers LR. Neurologic Complications of Cancer, 2nd ed. Contemporary Neurology Series. Neuro-Oncol. 2009;11:96–7

Mutational Analysis

Importance of Mutational Analysis

Once LM is confirmed, molecular characterization of the tumor cells becomes the next diagnostic priority. Several studies have shown that different regions of the same tumor can harbor a genetically heterogeneous group of cells

[110–119]. In one study of parenchymal brain metastases, whole exome sequencing revealed additional oncogenic alterations distinct from those found in the primary tumor. Fifty-three percent of cases showed clinically targetable alterations that were not detected in matched primary tumors. In the case of LM, several studies demonstrate mutations within the LM that were not detected in the original tumor [120]. In the era of targeted molecular therapy, such information is indispensable. While whole exome or even targeted exome sequencing of CSF remains an area of active translational investigation, in many cases immunohistochemistry of CSF cytology samples may be useful to detect sensitizing or resistance mutations, e.g., T790Min EGFR-driven NSCLC. It is recommended that clinicians avail themselves of such resources.

Treatment

General Considerations

LM remains an incurable site of metastasis. As such symptomatic management and palliative care are crucial for treatment of all LM patients. Due to the brisk nature of LM progression and disproportionate impact of neurologic symptoms for patient quality of life, management of symptomatic lesions takes first priority in clinical management. Once symptomatic lesions are treated, further management is dictated by risk group.

Patients with LM are stratified into two risk groups. Patients in the poor-risk group have low KPS, multiple serious or fixed neurologic deficits, and extensive systemic cancer with few remaining therapeutic options. Patients in the good-risk group have a KPS of >60%, few or no neurologic deficits, minimal systemic disease, and/or available therapeutic options for treatment. In both groups, symptomatic lesions are generally treated with radiation therapy (RT) and/or surgical management, while chemotherapy is used for the rest of the neuraxis [70, 121, 122]. Patients in the good-risk group may receive both local and systemic treatments, as discussed below.

Response Measurement

In clinical practice, response to therapy is assessed over 6–8 weeks with a combination of clinical exam, MRI of the brain and spine, and CSF examination. Standardized criteria have been proposed by the Response Assessment in Neuro-Oncology (RANO) group. The proposal includes standardized neurologic exam, CSF cytology, and neuroimaging [123, 124]. These criteria have not yet been validated in a prospective manner. Therefore, at present, response to treatment remains a clinical assessment. Commonly, stable MRI scans with stable to improving CSF picture in a neurologically stable patient is interpreted as a good clinical response. Improvement in several (>1) modalities (MRI, exam, CSF) is unusual but welcomed. Progressive disease is evident by worsening in one or more of these modalities.

Radiation Therapy

Radiotherapy in LM aims to alleviate symptoms by reducing the size of bulky masses blocking CSF flow or compressing cranial nerves [84, 125, 126]. This may also improve medical therapy penetration to residual disease [123, 127]. Sites of CSF flow obstruction as visualized by a radionuclide CSF flow study could also be targeted by focal radiotherapy as an initial treatment. However, in practice, a ventriculoperitoneal shunt (VPS) is typically required prior to such treatments. WBRT is used in cases of extensive nodular, symptomatic linear LM, or coexisting parenchymal lesions. While WBRT has not been associated with improved survival in LM patients, it can improve patients' quality of life [54–56, 59, 62]. Focal RT is typically given at a dose of 30 Gy in three fractions or 20 Gy in five fractions to sites of symptomatic or bulky disease [128]. However, the dose may be reduced to 20 Gy in two fractions in patients with better predicted survival (>12 months) to limit local side effects [128, 129]. Extensive RT leads to substantial toxicities including mucositis, esophagitis, myelosuppression, and leukoencephalopathy. For a

typical heavily pre-treated solid tumor patient, such toxicities effectively preclude full craniospinal radiation. The risk of leukoencephalopathy is high when systemic or intrathecal chemotherapy is combined with extensive RT, particularly with the use of methotrexate.

Chemotherapy

Intrathecal Therapy

Although delivering treatment to the site of disease is intuitively appealing, practical considerations limit the use of intrathecal chemotherapy in many patients. To receive intrathecal chemotherapy, patients must demonstrate normal ICP and CSF flow dynamics. Bulky disease will not be adequately treated with intrathecal approaches—intrathecal therapies only penetrate a few cell layers. If intrathecal chemotherapy is indicated, it may be delivered through an Ommaya reservoir (intraventricularly) or into the thecal sac via lumbar puncture.

Methotrexate (MTX) is the most commonly used intrathecal chemotherapy and can transiently clear malignant cells from CSF in up to 61% of LM patients [40, 130]. With a CSF half-life of 4.5 h, MTX is administered at 10–12 mg twice weekly for 4 weeks as induction regimen. In the event of clinical response, dosage is decreased to once weekly for 4–8 weeks followed by biweekly maintenance therapy for several months. The ideal duration of therapy with MTX is unknown, but treatment beyond 6 months may be unwarranted [130]. MTX is renally excreted after being absorbed by the choroid plexus into the systemic circulation where it is bound to albumin [131]. Therefore, coadministration of drugs that displace MTX from albumin should be done cautiously. Oral leukovorin, which dose not enter the CSF, is administered to counter systemic MTX toxicity. Other neurologic toxicities due to MTX include delayed leukoencephalopathy, aseptic meningitis, acute encephalopathy, and transverse myelopathy.

Cytarabine may also be administered intrathecally in two forms: standard and liposomal (DepoCyt). In patients with solid tumors, liposomal cytarabine is preferred, while standard cytarabine is restricted to LM patients with liquid malignancies. Liposomal cytarabine was discontinued in the USA in 2017 but may be available in other countries. While standard cytarabine has a half-life of less than 4 h and can be eliminated within 1–2 days, liposomal cytarabine may remain therapeutic within the CSF for up to 28 days [132, 133]. When comparing DepoCyt to IT MTX, one trial demonstrated no significant difference in PFS [134]; another demonstrated delay to neurologic progression in DepoCyt-treated patients [41, 135]. In a nonrandomized trial, the combination of cytarabine and MTX demonstrated higher cytologic response and longer median survival when compared to MTX alone, but no patient risk stratification was performed [136].

Thiotepa can also be used for the intrathecal treatment of LM. It is highly lipid soluble and hence has the shortest half-life of all IT agents. Like MTX, it is administered twice weekly and can cause myelosuppression [40, 137]. It is typically employed as a second-line therapy in the case of MTX-refractory disease or MTX-induced leukoencephalopathy. Since concurrent chemotherapy (MTX) and RT can exacerbate side effects, MTX may be replaced by thiotepa for patients requiring concurrent RT. Clinical response to thiotepa is largely equivalent to IT MTX [40, 138, 139].

Systemic Therapy

Untargeted

Many systemic chemotherapeutic agents can achieve therapeutic concentrations in CSF. Systemic therapy avoids the risk of Ommaya placement surgery and catheter-related complications. For patients with CSF flow abnormalities, systemic chemotherapeutic agents may allow uniform distribution, even with bulky tumors [140].

High-dose MTX is the most commonly used systemic agent in LM patients. However, clinical response after systemic high-dose MTX is mixed [140, 141]. An important consideration is the need for close inpatient monitoring, including aggressive hydration and urinary alkalinization

followed by leucovorin rescue. Comparison of IT therapy (MTX) to combined IT and systemic therapy in breast cancer patients with LM demonstrated no survival benefit [142]. Additional neurologic complications were reported in the intrathecal group. High-dose cytarabine can also be used systemically with a CSF concentration reaching up to 22% of serum levels [143, 144]. As with other systemic therapies for LM, high doses carry significant toxicity. Efficacy of such an approach in patients with solid tumor LM has not been demonstrated.

Capecitabine is a fluoropyrimidine carbamate that is used as an oral substitute for 5-fluorouracil, a capecitabine precursor that is active in tumor sites. Despite limited information regarding capecitabine's pharmacokinetics in the CSF, several observational studies have documented the effect of capecitabine on patients with LM [145, 146]. A case series reported response to capecitabine and trastuzumab combination therapy in patients with breast cancer LM [147]. Compared to other regimens, capecitabine is not associated with central neurotoxicity and is generally well tolerated [148]. However, in practice, a substantial proportion of breast cancer LM patients may have already received capecitabine, limiting the utility of the regimen.

Temozolomide is an oral alkylating agent that has been employed in case studies of LM from solid tumors. These involved administration of 100 mg/m^2 temozolomide daily every other week for 4 weeks, with temporary disease stabilization in two patients (median overall survival of 43 days) [149].

Targeted

As with systemic malignancies, targeted therapies are poised to revolutionize the management of LM. Studies have shown high levels of VEGF in the CSF of LM patients, which correlated with poor prognosis [102, 150, 151]. Angiogenesis inhibition has been shown to prolong median overall survival in a preclinical model of breast cancer LM [152]. Combined therapy of bevacizumab, etoposide, and cisplatin (BEEP) was reported in two breast cancer patients with progressive LM after radiation. BEEP therapy led to decreased leptomeningeal enhancement, negative CSF cytology, and overall survival of 8 and 7.5 months, respectively [153]. A pilot study with a similar patient population reported median overall survival of 4.7 months and CNS response rate of 70% [154]. When used alone in a mixed population of solid tumor LM, bevacizumab resulted in median overall survival of 14 weeks and CNS response rate of 13% [155].

Case studies report good response to BRAF inhibitors such as vemurafenib and dabrafenib in patients with melanoma LM harboring the BRAF V600E mutation [156, 157]. This alteration constitutively activates the MAP kinase pathway, while resistance to targeting this mutation is mediated through MEK. While several trials have successfully demonstrated the superiority of BRAF and MEK inhibitors together as compared to BRAF alone in melanoma [157–159], patients with LM were excluded from these trials.

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors have been useful therapies in patients with EGFR-driven non-small cell lung cancer (NSCLC). Erlotinib was shown to improve performance status in patients with LM from NSCLC [160–162]. Nevertheless, erlotinib failure was still seen in some studies of these patients [163, 164]. Clinical and radiological improvement was seen in patients with LM from lung adenocarcinoma following treatment with gefitinib, especially at high doses [160, 165–169]. Since second- and third-generation TKIs have better CNS penetration [170, 171], several trials have assessed these drugs in EGFR-mutant NSCLC patients with LM. Afatinib, an inhibitor of Her2 and EGFR kinases, showed 35% response rate in EGFR-mutant NSCLC patients with LM [172] and had efficacy in patients progressing on first-generation TKIs [173, 174]. Promising results have been reported for osimertinib, a third-generation TKI, in EGFR-mutant NSCLC patients with LM [175]; a phase 2 trial is currently recruiting patients harboring T790M-mutated NSCLC with LM who failed initial EGFR TKI therapy (NCT03257124). Another new-generation TKI currently in trials is AZD3759 which has superior CNS penetration and good tolerability in advanced NSCLC patients [176] (NCT02228369).

Similarly, ALK inhibitors have been employed for patients with ALK fusion gene-positive NSCLC and CNS metastasis. Prior trials combined all CNS metastasis, parenchymal or leptomeningeal; no studies have specifically targeted LM patients. Alectinib has demonstrated favorable activity in LM from ALK fusion-positive NSLCLC [177–180].

Supportive Therapy

Supportive therapy in LM aims at relieving neurologic symptoms to improve quality of life [181]. Steroids can be used to reduce vasogenic edema caused by the tumor and lessen neurologic symptoms. In addition, dexamethasone is essential in the management of chemical-induced meningitis that may develop after IT therapy, irrespective of the agent used [41, 42]. LM can cause seizures in 10%–15% of patients—transient symptoms should prompt evaluation for ictal activity by EEG, and antiepileptic drugs (AEDs) should be started. Modern AEDs that do not induce CYP-450 enzyme activation such as levetiracetam, lacosamide, and zonisamide are preferred for treating patients with cancer [182].

New Treatment Agents

Immune therapy agents have been used for the treatment of many systemic malignancies and are currently under investigation for the treatment of LM. A phase 2 trial using nivolumab (PD-1 inhibitor) and ipilimumab (CTLA-4 inhibitor) is currently recruiting patients with leptomeningeal metastasis from any solid tumor primary (NCT02939300) [183]. Close monitoring is necessary in these studies since immunotherapy can often result in life-threatening toxicities. For instance, IT interferon alpha and interleukin-2 trials did not move forward due to significant toxicities despite clinical response [150, 184].

ANG1005 is a conjugated paclitaxel molecule with enhanced BBB penetration. It has been shown to be effective in breast cancer patients with LM, and a phase 3 study is currently in preparation for this population (NCT03613181).

Monoclonal antibodies against tumor-specific epitopes conjugated to radioisotopes like iodine-131 (131I) and yttrium-90 (90Y) have been employed to deliver brachytherapy to tumors intrathecally. An early study by Moseley et al. in patients with LM showed some clinical efficacy of radioisotope-labeled HMFG1, an antigen present on normal and neoplastic derivatives of glandular epithelium [185, 186]. More recent studies have reported the utility of intra-Ommaya injection of radiolabeled ^{131}I-3F8 and ^{131}I-8H9, targeting tumor-associated antigens GD2 and B7H3, respectively, in neuroblastoma with CNS involvement, including LM [187, 188]. Phase 2 and 3 trials are currently being planned to evaluate the use of 131I-omburtamab, an 8H9 target, for neuroblastoma patients with CNS metastasis (NCT03275402).

Future Directions

Efforts to expand administration of systemic chemotherapeutic agents intrathecally have proven somewhat disappointing. Such approaches have included IT etoposide [189–191], topotecan [192], busulfan [193], melphalan [194], nitrosoureas [195], and dacarbazine [196]. For tumors with molecularly established therapeutic targets, repurposing currently available targeted agents intrathecally (like IT trastuzumab) has proven more useful.

In the case of systemically administered targeted therapies with good CNS penetration such as osimertinib, leptomeningeal responses have been promising. This molecularly driven approach to treatment of LM suggests that we are on the verge of a new paradigm in the management of LM—molecular characterization of LM tumor cells prior to design of therapy. Numerous studies are currently underway to capture the molecular phenotype of cancer cells within the leptomeninges. Approaches include sequencing of cell-free tumor DNA (ctDNA) [120] as well as flow cytometry-based investigations [197–200].

Once identified, molecular vulnerabilities of leptomeningeal tumors must be targeted, and these treatments must be formally assessed in prospective clinical trials. A major impediment to this has been the lack of response criteria as well as inability to reliably quantify the burden of disease. Much work is being done regarding to investigate the use of circulating tumor cells and/or flow cytometry to quantify LM disease burden [120, 197–200]. Together, these complimentary approaches will empower clinical and translational researchers to make true progress in the treatment of leptomeningeal metastasis.

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13 Paraneoplastic Neurological Disorders

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Introduction

Neurological complications are common in patients with cancer and can arise from toxic, infectious, or metabolic abnormalities. Additionally, neurological complications can be due to the direct effect of the cancer from brain metastasis, spinal cord and nerve root compression, leptomeningeal disease, and side effects of medications. Patients with cancer can also develop paraneoplastic neurological disorders (PNDs). PNDs are syndromes that involve nervous system organs physically remote from a malignant neoplasm or metastasis, and PNDs can lead to significant disability and even death [1]. Most PNDs are subacute and progressive, with onset of symptoms over the course of weeks to months. PNDs can precede the detection of a cancer or its recurrence by years [2]. A patient presenting with subacute symptoms with neurological findings and risk factors including personal history of smoking, cancer, or autoimmune disease or a family history which includes cancer or autoimmune disease raises the suspicion for a PND [1]. PNDs are thought to be the product of immune cross-reactivity between tumor cells and normal components of the nervous system (Fig. 13.1) [3]. This immune response can also be effective against a systemic cancer, with the inciting cancer often asymptomatic or occult. The presentations of PNDs are diverse and variable, reflecting the potential involvement of multiple areas of the nervous system in isolation or simultaneously. The presenting symptoms are dependent on the areas of the nervous system affected. PNDs can affect the central nervous system (e.g., limbic encephalitis, paraneoplastic cerebellar degeneration), spinal cord (e.g., necrotizing myelopathy, tractopathies), peripheral nervous system (e.g., subacute sensory neuropathy), neuromuscular junction (e.g., myasthenia gravis and Lambert-Eaton myasthenia syndrome), and muscle (e.g., necrotizing myopathies) [4]. It is important to note that these syndromes can also occur in the absence of cancer. For example, 70% of limbic encephalitis and 85–90% of myasthenia gravis are not associated with malignancy [5]. Therefore, presence of these clinical syndromes does not necessarily indicate the presence of a malignancy.

Epidemiology

Symptomatic PNDs are rare and have variable prevalence, affecting approximately 0.01–0.2% of all patients with cancer; however, this may be an underestimation [4]. The age of onset of PNDs is variable, typically occurring in the sixth to seventh decades. However, pediatric PNDs have been reported, often in association with neuroblastoma [6, 7]. The prevalence of a PND

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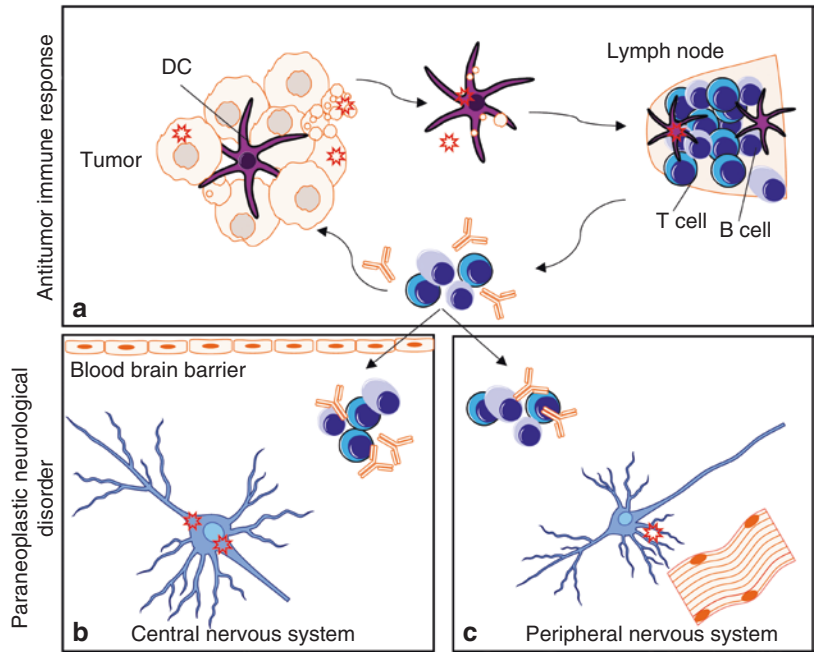

Fig. 13.1 Pathogenesis of paraneoplastic neurological disorders (PNDs)

(**a**) Onconeural antigens are expressed by tumor cells. Apoptosis and necrosis of tumor cells cause release of onconeural antigens that are phagocytosed by antigen-presenting cells (APCs). In the lymph node (LN), dendritic cells (DCs) present onconeural peptides to T and B cells and activate the adaptive immune response, thus promoting antitumor immunity. (**b**) T and B cells specific for onconeural antigens and onconeural autoantibodies cross the blood-brain barrier to react with neuronal cells expressing onconeural antigens and trigger PNDs in the central nervous system. (**c**) T and B cells specific for onconeural antigens and onconeural autoantibodies react with peripheral nerves, neuromuscular junction, or muscles and trigger PNDs

is dependent on the type of cancer, as certain malignancies have substantially higher incidence of PNDs. For example, 50% of patients with the rare osteosclerotic form of plasmacytoma present with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS syndrome) and have demyelinating peripheral neuropathy, while only 10–15% of patients with a thymoma present with myasthenia gravis [5]. Close neurological exams and electrophysiological studies in asymptomatic patients with small-cell lung cancer have demonstrated subtle proximal weakness or delayed conduction along peripheral nerves further suggesting that the true incidence of PNDs may be higher. Furthermore, in one prospective, 5-year study of patients with small-cell lung cancer, 9% developed a PND [8].

Among patients with PNDs, overrepresented cancers include cancers that express neuroendocrine proteins (small-cell lung cancer, neuroblastoma), contain mature or immature neuronal tissues (teratomas), involve immunoregulatory organs (thymoma), or produce immunoglobulins (plasma-cell dyscrasias, B-cell lymphomas) [4, 9]. Furthermore, many of these cancers frequently metastasize to regional lymph nodes, which promotes early recognition and priming of the immune response. Unlike paraneoplastic endocrine syndromes which generally present after the diagnosis of cancer, PNDs are detected prior to the diagnosis of cancer in approximately 80% of cases [5]. Therefore, it is crucial to closely screen all patients presenting with PNDs for malignancy given the possibility of detection and diagnosis of an occult cancer at an early and potentially highly treatable stage [2]. Furthermore, prior research has suggested that patients who present with PNDs may have improved survival and a more benign cancer

course as the immune response that drives the PND may also target the tumor [10].

Diagnosis of Paraneoplastic Neurological Disorders

As neurological symptoms are common in patients with cancer and are most commonly due to multiple etiologies including infection, electrolyte abnormalities, medication side effects, or metastasis, it is important to distinguish between neurological syndromes that coincide with the presence of cancer and true PNDs. Additionally, autoimmune neurological disorders can occur in the absence of malignancy and are frequently associated with the same autoantibodies against neuronal antigens [11]. PNDs can also present without identifiable antibodies against neuronal antigens, either due to lack of a humoral immune response or technical limitations in identifying the autoantibody. Furthermore, patients can present with detectable autoantibodies but no associated PND [12, 13]. The diagnosis of PNDs incorporates clinical presentation and neurological findings, detected cancer or cancer recurrence, imaging findings, electroencephalography (EEG), cerebral spinal fluid (CSF) analysis for signs of inflammation, and electromyography and nerve conduction studies (EMG/NCS) [14].

PNDs are subdivided in "classical" and "nonclassical" syndromes according to guidelines proposed in 2004 by an international panel of neurologists with expertise in PNDs [14]. Classical paraneoplastic neurological disorders are syndromes that are strongly associated with certain types of cancer and specific autoantibodies. Classical PNDs include syndromes of the CNS (limbic encephalitis, subacute cerebellar degeneration, encephalomyelitis, and opsoclonus-myoclonus), syndromes of the peripheral nervous system (subacute sensory neuronopathy and chronic gastrointestinal pseudo-occlusion syndrome), and syndromes of the neuromuscular junction and muscle (Lambert-Eaton myasthenic syndrome and dermatomyositis) [14]. These PNDs are generally associated with typical autoantibodies and malignancies. In addition to classical PNDs, there are also well-characterized onconeural autoantibodies that are frequently associated with malignancy and PNDs, including anti-Hu, anti-Yo, anti-CRMP5/CV2, anti-Ri, anti-Ma1/Ma2, and anti-amphiphysin [6, 14]. Interestingly, certain autoantibodies found in PNDs are more closely associated with specific cancers types as compared to specific neurological syndromes (Table 13.1) [15]. The association with cancer for certain classical PNDs and well-characterized autoantibodies is so specific that if occult cancer is not identified at time of diagnosis of PND, it is recommended that the patient follow up with surveillance imaging every 3–6 months for 2–3 years [2]. For example, the presence of anti-Yo antibodies and cerebellar degeneration is highly suggestive for adenocarcinoma of the ovary, uterus, fallopian tube, peritoneum, or breast, and these cancers are found in 90% of patients presenting with this classical PND and autoantibody [16, 17]. If another malignancy is identified, it is recommended that workup is pursued to diagnose a second more commonly associated tumor [14].

PNDs have variable presentations reflecting involvement of multiple areas of the nervous system [15]. Nonclassical PNDs are neurological syndromes that are not as closely associated with malignancy or specific onconeural antibodies. Nonclassical PNDs include syndromes of the CNS (optic neuritis, brainstem encephalitis, and stiff person syndrome), syndromes of the peripheral nervous system (neuropathy, vasculitis, and brachial neuritis), and syndromes of the neuromuscular junction and muscle (myasthenia gravis and acute necrotizing myopathy) [14].

Specific criteria are used to diagnose PNDs as it is important to distinguish between PNDs and neurological symptoms that coexist with cancer. The 2004 consensus panel developed criteria to distinguish "definite" from "possible" and "unlikely" PNDs. Definite criteria include (1) classical syndrome associated with cancer diagnosis within 5 years, (2) nonclassical syndrome associated with cancer that improves with treatment of the cancer but no immunotherapy, (3) nonclassical syndrome with onconeural autoantibodies and cancer diagnosis, and (4) classi-

Table 13.1 Onconeural antibodies associated with cancer (well characterized or partially characterized antibodies)

Antigen location	Antibody	Antigen	Classical PND associated	Nonclassical PND associated	Associated cancer
Nuclear	**Anti-Hu (ANNA-1)**	Hu family of RNA binding proteins	Limbic encephalitis	Myelitis	Small-cell lung
					Extrapulmonary small cell
			Subacute cerebellar degeneration	Autonomic neuropathy	Neuroblastoma
			Sensory neuronopathy	Peripheral neuropathy	Thymoma
				Encephalitis	
	Anti-Ri (ANNA-2)	NOVA family of RNA binding proteins	Subacute cerebellar degeneration	Myelopathy	Small-cell lung
			Opsoclonus-myoclonus	Peripheral neuropathy	Breast
				Encephalitis	Neuroblastoma
	Anti-Ma1/Ma2	Homologous 40 and 42 kDa neuronal nuclear proteins of uncertain function	Limbic encephalitis	Encephalitis	Testicular germ cell
			Subacute cerebellar degeneration	Hypothalamic encephalitis	Non-small cell lung
			Encephalomyelitis		Colon
					Breast
	Anti-Sox-1 (AGNA)	Transcription factor sex determining region Y (SRY)-box-1 (SOX-1) protein	Lambert-Eaton myasthenia	Encephalitis	Small-cell lung
	ANNA-3	170 kDa protein of unclear significance	Limbic encephalitis	Encephalitis	Small-cell lung
			Subacute cerebellar degeneration	Brainstem encephalitis	Gastrointestinal
				Neuropathy	

Cytoplasmic	**Anti-Yo (PCA-1)**	Cerebellar degeneration-related protein 2 (cdr2)	Subacute cerebellar degeneration	Brainstem encephalitis	Ovarian
				Myelopathy	Fallopian tubes
				Peripheral neuropathy	Endometrium
					Cervix
					Breast
	PCA-2	280 kDa of unknown identity or function	Subacute cerebellar degeneration	Autonomic neuropathy	Small-cell lung
				Peripheral neuropathy	
				Encephalitis	
	Anti-Tr (PCA-Tr)	Delta/Notch-like epidermal growth factor	Limbic encephalitis	Autonomic neuropathy	Hodgkin's lymphoma
			Subacute cerebellar degeneration		Non-Hodgkin's lymphoma
	Anti-CV2 (CRMP5)	Collapsin response-mediator protein 5 (CRMP5)	Limbic encephalitis	Encephalitis	Small-cell lung
			Subacute cerebellar degeneration	Cranial neuropathies	Thymoma
			Sensory neuronopathy	Uveitis	Uterine sarcoma
				Optic neuritis	
				Myelopathy	
				Retinopathy	
				Peripheral neuropathy	
				Autonomic neuropathy	
	Anti-Zic 4	Zic proteins	Subacute cerebellar degeneration		Small-cell lung
	Anti-recoverin	Recoverin		Retinopathy	Small-cell lung
Intracellular synaptic	**Anti-Amphiphysin**	Amphiphysin	Limbic encephalitis	Stiff person syndrome	Breast
			Subacute cerebellar degeneration	Encephalitis	Small-cell lung
			Sensory neuronopathy	Myelopathy	Thymoma
				Peripheral neuropathy	
	Anti-GAD 65	65 kDa glutamic acid decarboxylase enzyme	Limbic encephalitis	Stiff person syndrome	Thymoma
				Epilepsy	Renal cell
				Brainstem encephalitis	Breast
				Cerebellar ataxia	Colon
				Myelopathy	
Extracellular synaptic	Anti-mGluR1	Metabotropic glutamate receptor 1	Subacute cerebellar degeneration		Hodgkin's lymphoma
	Anti-mGluR5	Metabotropic glutamate receptor 5	Limbic encephalitis		Hodgkin's lymphoma

(continued)

Table 13.1 (continued)

Antigen location	Antibody	Antigen	Classical PND associated	Nonclassical PND associated	Associated cancer
Cell surface membrane antigens	**Anti-AChR**	Muscle acetylcholine receptor		Myasthenia gravis	Thymoma
	Anti-ganglionic N-acetylcholine receptor	Neuronal acetylcholine receptor α3 subunits		Encephalopathy	Small-cell lung
				Subacute pandysautonomia	Thymoma
				Peripheral neuropathy	
	Anti-NMDAR	NR1 subunits of N-methyl-D-aspartate receptor		Encephalitis	Ovarian teratoma
				Anxiety	Neuroblastoma
				Psychosis	Small-cell lung
				Epilepsy	Testicular germ cell
				Extrapyramidal disorder	
				Central dysautonomia	
	Anti-GlyR	Glycine receptor α1	Limbic encephalitis	Stiff person syndrome	Infrequent association
				Ataxia	
				Hyperekplexia	
				Progressive encephalomyelitis with rigidity and myoclonus	
	Anti-VGCC	N-type and P/Q-type voltage-gated calcium channels	Subacute cerebellar degeneration	Lambert-Eaton myasthenia	Small-cell lung
				Encephalitis	Breast
					Ovarian
	Anti-VGKC	Voltage-gated potassium channel (VGKC) complex subunits	Limbic encephalitis	Encephalitis	Small-cell lung
				Epilepsy	Thymoma
				Psychiatric symptoms	Breast
				Hypothalamic disorders	Prostate
	Anti-LGI1	Leucine-rich, glioma-inactivated protein interacts with Kv1 channels and AMPAR	Limbic encephalitis	Faciobrachial dystonic seizures	Thymoma
				Abnormal sleep	
	Anti-CASPR2	Contactin-associated protein-like 2 of the neurexin IV superfamily interacts with axonal Kv1 channels		Encephalitis	Thymoma
				Morvan syndrome	
				Neuromyotonia	

	Anti-DPPX	Dipeptidyl-peptidase-like protein-6 subunit of Kv4.2 potassium channel		Encephalitis	Lymphoma
				Psychiatric symptoms	
				Tremor	
				Nystagmus, hyperekplexia	
				Ataxia	
				Progressive encephalomyelitis with rigidity and myoclonus	
	Anti-$GABA_BR$	γ-Amino butyric acid-B receptor	Limbic encephalitis	Orolingual dyskinesia	Small-cell lung
					Breast
	Anti-AMPAR	Glutamate receptors 1 and 2	Limbic encephalitis	Epilepsy	Thymoma
				Nystagmus	Breast
					Lung
	Anti-aquaporin 4	Aquaporin-4 channel		Neuromyelitis optica	Infrequent association
				Encephalitis	

Data from Probasco JC. Paraneoplastic Neurological Disorders. In: Johnsonton MV, Adams HP, Fatemi A. Neurobiology of Disease. 2nd ed. New York: Oxford University Press; 2016. p. 657–66

cal or nonclassical syndrome without cancer but with well-characterized onconeural antibodies [14]. Probable PNDs are defined as (1) classical syndromes with high risk of cancer but no cancer diagnosis or onconeural autoantibodies, (2) neurological syndrome without cancer and with partially characterized onconeural antibodies, and (3) nonclassical syndromes with cancer diagnosis within 2 years of neurological disorder development but no onconeural autoantibodies [14]. As previously mentioned, in patients with definite PND with no associated cancer or probable PNDs, it is important to complete a diligent screening for associated malignancies and closely monitor with repeat screening as malignancies may be identified years after the presenting PND [2, 9, 18].

Etiology and Pathogenesis

The study of PNDs allows for exploration of the hypothesis of immune surveillance and tolerance as immunological mechanisms form the link between malignancy and development of these syndromes. Nearly all PNDs result from generation of immune response to onconeural antigens of tumors that cross-react with the nervous system. This section will discuss the immunological mechanisms driving the development of PNDs.

Onconeural Antigens and Onconeural Antibodies

One of the main findings supporting an antitumor immune response driving PNDs is the presence of high titers of onconeural-specific autoantibodies in the serum and/or CSF of patients with PNDs [9, 19]. Onconeural proteins are proteins expressed by a tumor that are similar to proteins that are otherwise only expressed by neuronal cells. These proteins are either expressed intracellularly within the nucleus, nucleolus, or cytoplasm or are expressed on the plasma membrane [3]. Onconeural proteins are present in tumors of all patients with antibody-positive PND and detected cancer, and when a PND is associated with an atypical cancer, an attempt should be completed to identify the onconeural protein on the atypical tumor (or to identify the co-occurrence of a second more typical cancer) [14, 20]. Interestingly, a high mutational burden in cancers is not associated with PNDs, and there is no evidence to suggest that there are frequently mutations in the genes for onconeural proteins in tumor cells [21]. Therefore, the observed immune responses are not due to infrequency of the expression of relevant tumor antigens or mutations in genes encoding onconeural proteins. Instead, autoimmunization occurs in an inflammatory environment in response to the production of proteins by tumor cells that are usually restricted to neural cells [9]. In fact, the presence of onconeural protein expression on tumor cells does not necessarily indicate that an immune response will be generated against the onconeural protein; patients may instead develop T-cell tolerance to onconeural proteins expressed in tumors, and tumors may be able to evade immune surveillance [22].

The onconeural antibodies produced can either be a driving mechanism of pathogenesis or a marker of immunological activity. It has been suggested that cellular immunity is the main driver of PNDs. Onconeural antibodies are classified into three categories based on their association with malignancy: (1) molecularly well characterized with strong association with malignancy, (2) partially characterized with less well-described association with malignancy, and (3) associated with both cancer- and non-cancer-associated syndromes [5]. As previously discussed, the specific onconeural antibody is taken into consideration when diagnosing a patient with a definite or probable PND [14].

Activation of Immune Response Against Onconeural Proteins

Studies of patients with PNDs and immunohistopathological studies of biopsied and autopsied neural tissues have shed light into the pathogenesis of PNDs (Fig. 13.1). The immunological mechanism priming the immune response involves the

tumor microenvironment and extracellular space surrounding tumors, tumor draining lymph nodes (LNs), and immune cells such as antigen-presenting cells (APCs), including dendritic cells (DCs), and CD4+specific T cells (Fig. 13.1) [3, 20, 23]. As tumor cells undergo apoptosis and necrosis, intracellular onconeural peptides are released into a pro-inflammatory extracellular environment. These tumor-derived onconeural peptides are taken up and processed by DCs in this pro-inflammatory environment and taken to the draining LN [20]. Following onconeural peptide capture, DCs mature and enter T-cell-rich zones of the tumor-draining lymph nodes. There, DCs present onconeural peptides to both CD4+and CD8+T cells. Onconeural peptide-specific helper CD4+T cells are required for the activation of similarly specific CD8+T cells. Prior studies suggest that CD8+T-cell stimulation in the absence of CD4+help leads to the death of the onconeural antigen-specific CD8+T cells and promotes tolerance to these antigens [21, 23]. Activated helper CD4+ T cells also provide signals to onconeural peptide-specific B cells to proliferate and differentiate into onconeural antibody-producing plasma cells [20] (Fig. 13.1). These onconeural antibodies can be directly pathogenic or be markers of immunological activity. The cellular location of the target (intracellular or extracellular) tends to dictate whether the humoral or cellular immune response is the driving pathogenic response [20].

The priming of the antitumor immune response can be effective at killing cancer cells and limiting the development and growth of tumors. This is highlighted by the fact that patients with PNDs typically will have more successful cancer treatment and more benign cancer course as compared to patients without PNDs. Additionally, patients with detectable autoantibodies but no PND have more limited cancer burden and improved prognosis [12, 13]. In patients with anti-Yo paraneoplastic subacute cerebellar degeneration, circulating onconeural peptide-specific CD8+T cells have been demonstrated to lyse target cells presenting the onconeural peptide on major histocompatibility complex class I (MHC-I) molecules [24, 25]. Autopsied CNS tissues have also demonstrated multifocal inflammatory changes with perivascular and parenchymal CD8+T cells throughout the cerebellum, brainstem, and spinal cord in patients with cerebellar degeneration and seropositive for anti-Yo [26]. Cytotoxic CD8+T cells recognize MHC-I presented peptides on the surface of tumor cells and induce apoptosis or enzymatic lysis of tumor cells. Intracellular debris becomes available in the draining lymph node for binding by onconeural antibodies that may further amplify the immune response. Antibodies specific for onconeural antigens also have tumoricidal potential through activation of the complement cascade as well as Fc-receptor activation leading to cell death and antigen internalization [26].

Intracellular Onconeural Proteins

Onconeural peptide-specific autoantibodies are a fundamental finding in patients with PNDs. However, in studies involving the transfer of autoantibodies from patients with PNDs into animals, the animals frequently did not develop any neurological abnormalities suggestive of the PNDs [3, 27]. These were the first studies suggesting that in certain PNDs, detected autoantibodies are makers of respective immune response rather than directly pathogenic. Instead, the driving immune response is thought to be a robust T-cell-mediated response against the neuronal antigens.

In addition to the immune responses occurring in the tumor and the tumor draining lymph node, the systemic inflammatory state also causes changes within the nervous system that contribute to the development of PNDs. In the setting of inflammation, there are changes in the processing of self-peptides by neuronal cells; pro-inflammatory cytokines such as interferon-γ switch the proteasome in neuronal cells that generates peptides targeted for degradation into an immunoproteasome [3]. The immunoproteasome generates unique peptide fragments that are not recognized as "self-peptides." These "non-self" autoantigenic peptides are similar to the onconeural antigens presented on distant tumor cells,

and these peptides are presented by MHC-I on neuronal cells [3]. $CD8^+$T cells primed in the draining LN of the tumor migrate into the systemic circulation and exit the systemic circulation to attack peripheral neurons or cross the blood-brain barrier into the CNS parenchyma [3, 23] (Fig. 13.1). The $CD8^+$T cells recognize the "non-self" autoantigenic peptides presented on neuronal cells and cause neuronal damage and cell loss.

Cell Plasma Onconeural Proteins

Onconeural autoantibodies can play a crucial role in neurotoxicity in the setting of PNDs, particularly those associated with neural cell plasma membrane receptors and channels. Autoantibodies targeting cell surface membrane proteins can lead to neuronal dysfunction and injury through several mechanisms [20]. Autoantibodies targeting cell surface proteins can act as agonists or antagonists and lead to cellular dysfunction by altering signaling through receptors and channels [28–30]. Autoantibodies can also cause direct cellular damage through activation of the complement cascade or Fc receptors leading to antibody-dependent cell-mediated cytotoxicity. Finally, antibodies may lead to their internalization and thus decrease the density of a target receptor or channel on the cell surface causing neuronal dysfunction [31]. Examples of PNDs with a direct pathogenic role of autoantibodies targeting extracellular onconeural proteins include antibodies against voltage-gated calcium channels (anti-VGCC, Lambert-Eaton myasthenia syndrome), acetylcholine receptor antibody (anti-AchR, myasthenia gravis), and N-methyl-D-aspartate receptor (anti-NMDAR, anti-NMDAR encephalitis) [3].

PNDs involving the neuromuscular junction and peripheral nerves have strong evidence for the pathogenic role of autoantibodies targeting onconeural proteins. Lambert-Eaton myasthenic syndrome is associated with anti-VGCC antibodies (typically P/Q type). Antibody binding leads to impairment in postsynaptic signal transduction with decreased calcium ion entry and reduced release of acetylcholine into the neuromuscular junction causing the symptoms of muscle weakness [30]. Autoantibodies have been shown to be directly pathogenic as injection of polyclonal IgG isolated from serum of patients with LEMS is sufficient to transfer the clinical syndrome to laboratory mice [32]. In myasthenia gravis associated with anti-AChR antibodies, binding of anti-AchR antibody leads to functional blockade of the receptor from acetylcholine binding, accelerated endocytosis and degradation of the receptors, and overall decreased numbers of acetylcholine receptors at the neuromuscular junction [3].

Anti-NMDAR encephalitis is another PND with an autoantibody that is directly pathogenic. In anti-NMDAR encephalitis, autoantibodies are directed against the NR1 subunit of the NMDA glutamate receptor. Clinically, assay of the CSF for the presence of anti-NMDAR antibodies is more sensitive than serological testing as intrathecal synthesis of this autoantibody has been demonstrated [28, 33]. Autopsy studies have also demonstrated the crucial role of autoantibodies in the pathogenesis of anti-NMDAR encephalitis as significant deposits of IgG have been identified throughout the CNS with predominance in the hippocampus. Furthermore, B cells and antibody-secreting plasma cells are more frequently identified than T-cell infiltrates [3]. Studies in vitro and in vivo using anti-NMDAR autoantibodies isolated from the sera or CSF of patients with anti-NMDAR encephalitis have demonstrated that the mechanism of action is antibody-mediated capping and internalization leading to decrease in the density and localization of NMDAR clusters [28]. Passive transfer of anti-NMDAR autoantibodies causes transfer of disease symptoms to mice [34]. Additionally, decrease in the CSF anti-NMDAR autoantibody concentration is correlated with clinical improvement and response to treatment.

Distinct HLA Associations with PNDs

Studies have been completed to investigate how genetic susceptibility affects the development

of autoimmune encephalitis, both paraneoplastic and non-paraneoplastic. Specific HLA genes have been associated with various neurological autoimmune diseases such as muscle-specific kinase antibody-positive myasthenia gravis. Distinct HLA subtypes were also found in patients with anti-leucine-rich glioma-inactivated 1 (anti-LGI1) and anti-contactin-associated protein 2 (anti-CASPR2) autoimmune encephalitis [35–37]. This finding further supports the crucial role that $CD4^+$ T lymphocytes play in the pathogenesis of anti-LGI1 and anti-CASPR2 antibody encephalitis. Interestingly, these same studies indicated that anti-NMDAR encephalitis was not associated with any specific HLA alleles.

There is evidence to support both cell-mediated and humoral autoantibody-mediated processes in the pathogenesis of PNDs. The pathogenic role of each appears to be partially dependent on the cellular location of the onconeural protein target. PNDs involving intracellular targets are driven by a robust cytotoxic T-cell response, and the presence of detectable autoantibodies is a marker of immune system activity. However, in PNDs involving extracellular cell membrane proteins, antibodies may play a central role and have been shown to be directly pathogenic in some syndromes. However, as highlighted by the striking HLA allelic association with anti-LGI1 and anti-CASPR2 encephalitis, T cells still play a crucial role in these syndromes.

Common Classical Paraneoplastic Neurological Disorders

Malignancy can trigger both classical and non-classical PNDs. This section will discuss some of the common classical paraneoplastic neurological syndromes that have been associated with overt or occult malignancy including clinical features, diagnostic findings, onconeural autoantibodies, and closely mimicking neurological disorders. Of note, specific onconeural autoantibodies can be associated with multiple clinical disorders, and approximately 31% of patients with PNDs have multiple identified autoantibodies [38]. Prior studies have shown that a specific onconeural autoantibody is more predictive of the type of malignancy than the clinical syndrome [15]. This section will not discuss dermatomyositis, which is a classical PND and is characterized by an inflammatory myopathy.

Subacute Cerebellar Degeneration

Subacute cerebellar degeneration is one of the most common PNDs. It is characterized initially by nonspecific symptoms including dizziness, nausea, and vomiting with rapid progression to ataxia, diplopia, dysarthria, and dysphagia [26]. Initial magnetic resonance imaging (MRI) may be normal or show only subtle changes (see Fig. 13.2i, j). As the disease progresses, MRI demonstrates cerebellar atrophy [26]. The onconeural autoantibodies that are most associated with paraneoplastic cerebellar degeneration include anti-Yo, which is typically seen with gynecological or breast cancers, and anti-Tr, which is found with Hodgkin's lymphoma [16, 18, 39]. Patients with small-cell lung cancer can also develop paraneoplastic subacute cerebellar degeneration. It is often coincident with other paraneoplastic syndromes, and patients will frequently have onconeural autoantibodies positive for anti-Hu or autoantibodies directed at the voltage-gated potassium channel complex (VGKC) without further specifications [40]. The pathological findings associated with paraneoplastic subacute cerebellar degeneration include a relatively specific and extensive loss of Purkinje cells with associated inflammatory infiltrates during the early stages of the disease [4, 41]. Treatment includes management of the underlying cancer and immunotherapy; however, it is generally poorly responsive to immunotherapy, especially in those patients seropositive for anti-Yo antibodies [42]. When evaluating a patient with subacute paraneoplastic cerebellar degeneration, it is important to recall that approximately 50% of cases are not paraneoplastic in origin [42]. Other diagnostic considerations include vitamin deficiency (thiamine, vitamin E), non-paraneoplastic autoimmune cerebellar ataxia, alcohol toxicity, infectious or postinfectious cerebellitis, and Creutzfeldt-Jakob disease [4].

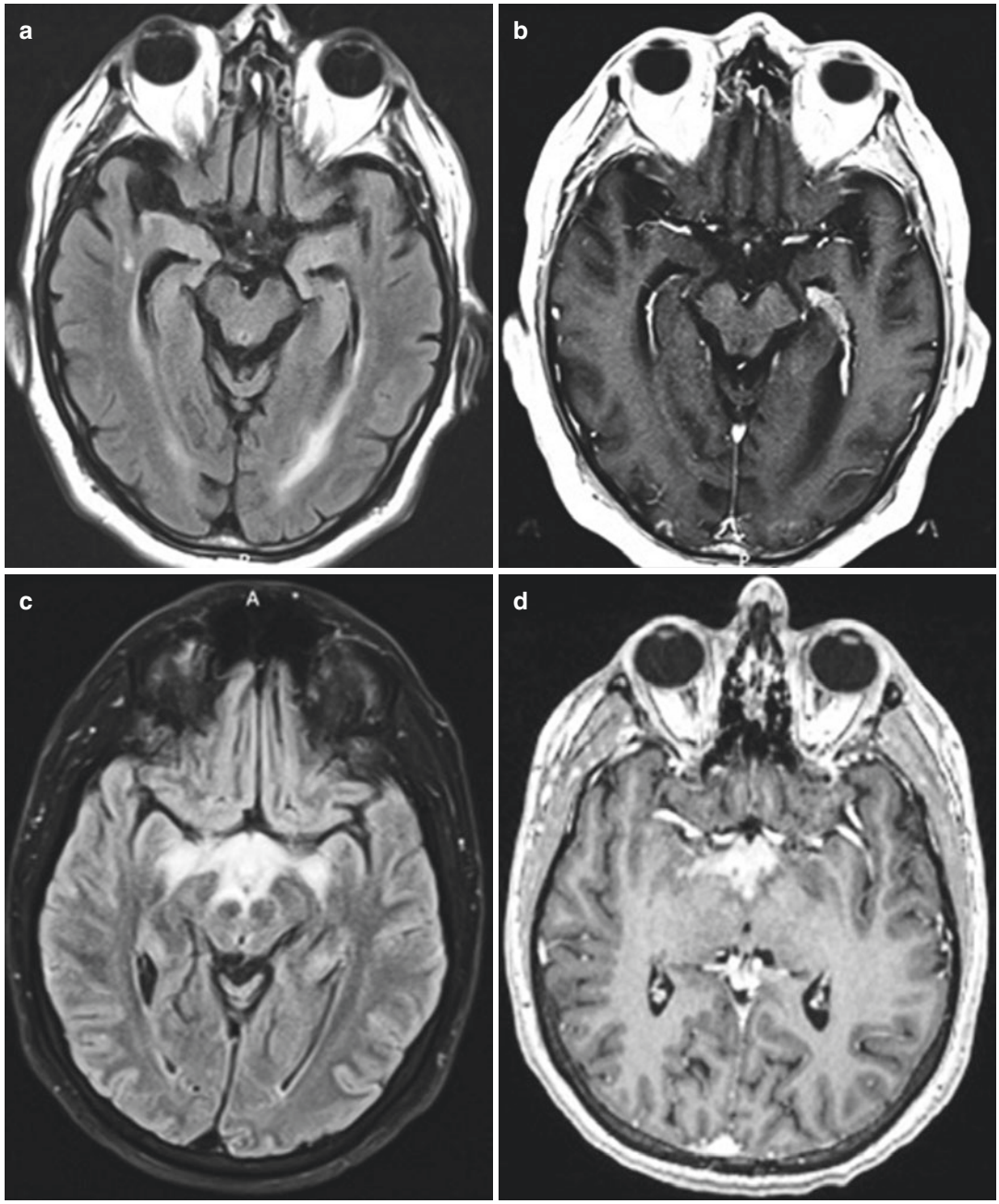

Fig. 13.2 MRI findings in paraneoplastic encephalitis and subacute cerebellar degeneration

(**a** and **b**) T2/FLAIR and T1 post-gadolinium brain MRI of a patient with anti-Hu limbic encephalitis demonstrating atrophy and non-enhancing T2 hyperintensities of the left more than the right hippocampus. (**c** and **d**) A patient with anti-Ma2 limbic encephalitis with T2 hyperintensities of the medial temporal lobe and hypothalamus as well as enhancement of the hypothalamus. (**e**) Acute-phase T2/FLAIR MRI of a patient with anti-NMDAR encephalitis with subtle T2 hyperintensities of the bilateral medial temporal lobes. (**f**) Convalescent-phase T2/FLAIR MRI of a patient with anti-NMDAR encephalitis demonstrating right hippocampal atrophy. (**g**) Acute-phase T2/FLAIR MRI of a patient with anti-LGI1 encephalitis demonstrating bilateral medial temporal lobe T2 hyperintensities. (**h**) Convalescent-phase T2/FLAIR MRI of the same patient demonstrating left hippocampal atrophy and persistent T2/FLAIR hyperintensities of the bilateral medial temporal lobes. (**i** and **j**) Axial T2/FLAIR and sagittal brain T1 MRI images of a patient with anti-P/Q calcium channel autoimmune cerebellar degeneration in the convalescent phase, demonstrating marked cerebellar atrophy

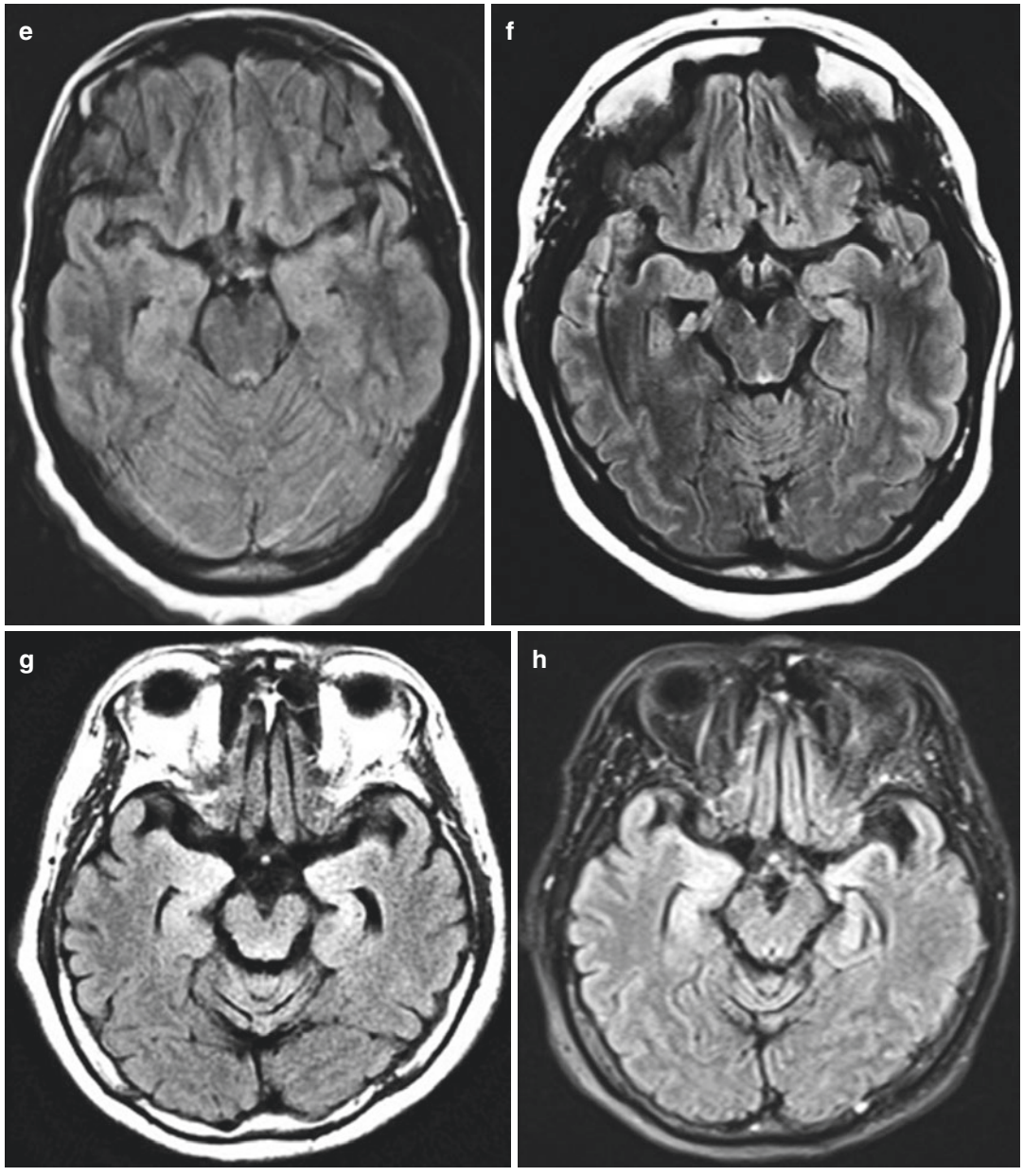

Fig. 13.2 (continued)

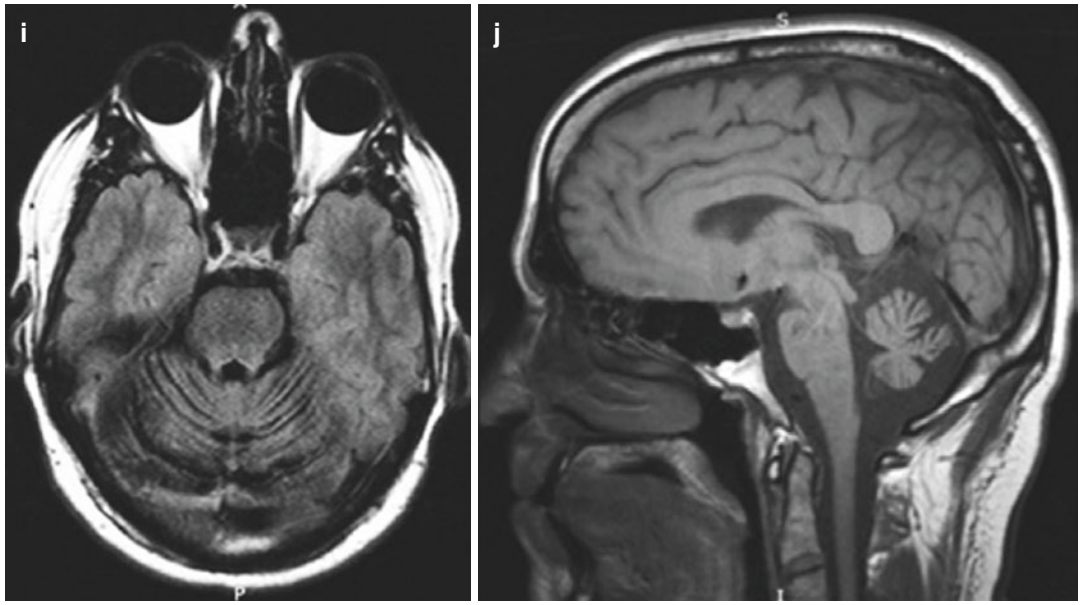

Fig. 13.2 (continued)

Encephalitis

Autoimmune encephalitis (AE) is a neurological disorder that is characterized by subacute development of short-term memory loss, confusion, hallucinations, mood changes, and/or seizures [43]. Limbic encephalitis (LE) is a subtype of autoimmune encephalitis that is confined to the limbic system including the hippocampus, hypothalamus, and amygdala and is considered a classical PND. Autoimmune encephalitis is a common non-prion cause of rapidly progressively dementia and can lead to irreversible dementia if it is not adequately treated [44].

It is important to note that paraneoplastic encephalitis can present with numerous other neurological and systemic findings such as extensive encephalomyelitis, sleep disturbances, hypothalamic-pituitary hormone deficits, and sensorimotor neuropathy. Proposed consensus clinical diagnostic criteria for possible autoimmune encephalitis incorporate subacute progressive memory deficits, altered mental status, and one of the three other supporting findings among the following: T2 hyperintense lesions on brain MRI possibly with associated enhancement, new-onset seizures, and/or CSF pleocytosis [43]. Thus, the typical workup includes imaging, EEG, and CSF analysis. Early in the disease course, MRI of the brain can be normal, but PET scan may show hypermetabolism in the mesiotemporal regions (which is included in the consensus clinical criteria for definite limbic encephalitis), or areas of hypometabolism, such as hypometabolism of the visual cortex in anti-NMDAR encephalitis [45]. MRI usually evolves and shows fluid-attenuated inversion recovery (FLAIR) or T2 sequence hyperintensity in the medial temporal lobes (Fig. 13.2). EEG studies may show irritability over the temporal lobes with foci of epileptic activity, seizures, or focal or generalized slow activity. CSF analysis is typically pursued and often shows mild pleocytosis, elevated protein, elevated IgG level, and possibly an onconeural autoantibody [43]. The CSF pleocytosis may only be present in the early stages of the disease and can resolve over the course of weeks to months [9].

Paraneoplastic encephalitis is often associated with onconeural antibodies, including antibodies that recognize intracellular neuronal antigens and cell surface antigens. Onconeural antibodies that recognize intracellular antigens are more closely associated with malignancies and include

anti-Hu, anti-collapsin response-mediator protein-5 (anti-CRMP5), anti-amphiphysin, and anti-Ma2 [4, 46] (see Table 13.1). Encephalitis is a common PND in small-cell lung cancer, and approximately 50% of patients with SCLC and limbic encephalitis have anti-Hu onconeural antibodies [47]. Anti-CRMP5 antibodies are associated with testicular germ-cell tumors in young men and with non-small cell lung cancer and breast cancer among older patients. These types of limbic encephalitis can be more difficult to treat as the T-cell-driven response causes irreversible neuronal damage [4].

Paraneoplastic encephalitis can also be associated with cell surface onconeural antibodies. Antibodies against cell surface onconeural antibodies include those directed against the VGKC complex proteins (such as anti-LGI1 and anti-CASPR2), anti-NMDAR, anti-alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (anti-AMPAR), and anti-gamma-butyric acid receptors (e.g., anti-$GABA_BR$) (see Table 13.1). The most well-studied is anti-NMDAR encephalitis. Anti-NMDAR encephalitis frequently starts with a viral-like prodrome followed by prominent psychiatric symptoms including psychosis, catatonia, and agitation in addition to memory loss, altered mental status, abnormal movements, and seizures [28]. An autoantibody targeting the NR1 (GluN1) subunit of the NMDA receptor causes functional disruption by cross-linking and catalyzing internalization of receptors [28, 29]. Anti-NMDAR encephalitis is associated with underlying tumor in 38% of patients, most commonly ovarian teratoma [4, 33]. Other tumors that can be associated include small-cell lung carcinoma, testicular teratoma, and sex cord-stromal tumors. Treatment of anti-NMDAR encephalitis is generally successful and involves removal/treatment of tumor if applicable and immunotherapy. Recovery is nearly complete in 75% of patients who receive timely treatment [33].

Although LE is a classical PND, approximately 70% of patients with limbic encephalitis do not have a malignancy diagnosed within 5 years. The differential for patients with malignancy presenting with a constellation of symptoms suggestive of encephalitis is broad. Other possible etiologies include infectious encephalitis such herpes simplex encephalitis, which can also trigger autoimmune anti-NMDAR encephalitis [48], as well as direct involvement of malignancy such as brain/leptomeningeal metastasis or low-grade glioma [4].

Subacute Sensory Neuronopathy

Subacute sensory neuronopathy is characterized by rapidly progressive asymmetric sensory deficits that progress to include all sensory modalities leading to rapid impairment of ambulation within 3 months. Initial symptoms include loss of vibration sense and joint position that is followed by pain and temperature sensory loss, typically more pronounced in the upper extremities than lower extremities. In addition to loss of sensation, patients also experience severe burning pain and hyperesthesia. Clinically, patients frequently have loss of sensation in all sensory modalities, sensory ataxia, and absent reflexes but preserved strength. Diagnostic workup includes nerve conduction studies that demonstrate reduced/absent sensory nerve action potentials and CSF analysis with pleocytosis and elevated protein [49].

Autoantibodies associated with subacute sensory neuronopathy include anti-Hu, anti-CRMP5, and anti-amphiphysin. Pathologically, there is destruction of sensory neuron cell bodies in the dorsal root ganglia with predominant $CD8^+$ T-cell infiltration [50, 51]. Malignancies that are typically associated include lung cancer (both small-cell lung cancer and bronchial carcinoma), breast cancer, ovarian cancer, and Hodgkin's lymphoma [52]. The differential diagnosis for subacute sensory neuronopathy includes other disorders that cause primary degeneration of sensory neurons in the dorsal root ganglia such as Sjögren's syndrome, HIV infection, cisplatin toxicity, and vitamin B6 toxicity [51].

Opsoclonus-Myoclonus Syndrome

Opsoclonus-myoclonus syndrome (OMS) is a classical PND that is characterized by opsoclo-

nus, myoclonus, ataxia, and behavioral and sleep disturbances [4]. Clinically, opsoclonus is characterized by oscillations of the eyes with horizontal, vertical, and torsional saccades. OMS is a clinical diagnosis and requires presence of at least three of the four clinical findings: opsoclonus, myoclonus and/or ataxia, behavioral/sleep disturbances, and presence of cancer or onconeural autoantibodies [53]. OMS is associated with malignancy in 39% of patients and idiopathic in 61%. Onconeural antibodies are found in 11% of patients, and humoral and cell-mediated immune mechanisms are both crucial for the pathogenesis of OMS. Onconeural antibodies that are associated with paraneoplastic OMS include anti-Ri, anti-Hu, anti-Yo, anti-Ma1/Ma1, anti-NMDAR, anti-amphiphysin, anti-CRMP-5/anti-CV2, and anti-Zic2. In adults, paraneoplastic OMS is most frequently associated with breast carcinoma, ovarian teratoma, and SCLC; in children, it is associated with neuroblastoma in 50% of patients [53]. Management focuses on identification and treatment of the underlying cancer as well as immunosuppressive therapies such as corticosteroids, adrenocorticotropic hormone (ACTH), intravenous immunoglobulin (IVIG), cyclophosphamide, and rituximab [53]. OMS can also be triggered as part of a parainfectious or postinfectious autoimmune response to infections like HIV, mycoplasma pneumonia, *Salmonella enterica*, rotavirus, cytomegalovirus, human herpesvirus 6, and hepatitis C [4]. OMS may present with ataxia alone and delayed opsoclonus, and thus patients may be misdiagnosed with subacute cerebellar degeneration [53]. Lastly, drug toxicity from lithium, phenytoin, or amitriptyline may present in a similar fashion and should be considered [4].

Lambert-Eaton Myasthenic Syndrome

First described in 1953, Lambert Eaton myasthenic syndrome (LEMS) is a rare classical PND, estimated to affect approximately 0.48 persons per million. LEMS is associated with tumors in 50–60% of cases, especially small-cell lung cancer (SCLC). LEMS is diagnosed based on clinical signs and symptoms, EMG/NCS studies, and autoantibody testing. Clinical findings include progressive proximal muscle weakness with autonomic dysfunction and areflexia. In contrast to myasthenia gravis, patients with LEMS typically first note proximal leg weakness that quickly progresses to involve the arms with later ocular and bulbar symptoms. Autonomic dysfunction is common in LEMS, manifesting as dry mouth and erectile dysfunction. Other autonomic findings such as gastrointestinal dysmotility, cardiovascular dysfunction, and bladder dysfunction are typically due to coexistence of autoimmune dysautonomia, which is probably paraneoplastic in origin. Patients have decreased or absent deep tendon reflexes. Unlike myasthenia gravis, strength and reflexes improve after muscle contraction and exercise (characteristic but not especially sensitive for diagnosis). Electrophysiological studies help aid diagnosis and can distinguish between closely related syndromes such as myasthenia gravis [54]. Autoantibodies recognizing P/Q-type VGCC are detected in greater than 85% of patients with LEMS, and some patients also have antibodies to N-type and L-type VGCC [30]. Other diagnostic considerations include myasthenia gravis, myopathies (such as inclusion body myositis), and Guillain-Barre syndrome [33].

It is important to note that specific onconeural antibodies can be associated with various clinical syndromes and cancers, and identification of >1 onconeural antibodies is associated with increased risk of malignancy [38]. Management is focused on treatment of the malignancy and disease sequelae as well as immunosuppression.

Treatment of Paraneoplastic Neurological Disorders

Treatment of PNDs first focuses on the evaluation for occult malignancy as PNDs present prior to diagnosis of cancer in approximately 80% of patients. The specific autoantibody detected can help guide the evaluation for occult malignancy (see Table 13.1), and malignancy

is more likely to be found in patients with a cluster of autoantibodies [38]. In patients with previously diagnosed malignancy, a PND may herald cancer relapse [23]. The screening for occult malignancy includes a careful physical exam as well as various diagnostic studies such as computed tomography (CT) imaging of the chest, abdomen, and pelvis. Gender-specific cancer screening including mammography and pelvic ultrasound in women and testicular ultrasound and prostate-specific antigen testing in men represent important adjunctive testing [1, 2]. Though considered a secondary or tertiary screening modality depending on the cancer of concern, FDG-PET imaging has a greater sensitivity for occult malignancy over CT if seropositive for a paraneoplastic autoantibody [55]. The development of a PND can precede the diagnosis of malignancy by several years (presumably because the immune response is effective at controlling the malignancy), so serial evaluation and close follow-up are crucial. Once a malignancy is identified, treatment of the detected cancer alone can have a dramatic effect on the PND and potentially lead to its stabilization. This is thought to be due to reduction of the theoretical antigen source as well as potentially the immunosuppressant effects of chemotherapy [1, 6].

As PNDs are triggered by the generation of immune responses to onconeural antigens of tumors leading to attack of neuronal cells, immunomodulatory therapy is an important component of treatment. Intravenous methylprednisolone is a typical first-line step for the treatment of many PNDs. In PNDs associated with intracellular antigens, cytotoxic and lymphocyte-specific medications (e.g., cyclophosphamide and mycophenolate, respectively) are used with the goal of reducing the cell-mediated immune response. Therapies aimed at depleting autoantibodies, such as plasmapheresis, are ineffective. Cell membrane protein-associated PNDs respond to antibody-directed first-line therapies such as intravenous immunoglobulin therapy and plasmapheresis. Other immunosuppressants such as rituximab, cyclophosphamide, mycophenolate, and azathioprine are used as second-line agents in the acute phase as well as for chronic management [1, 6]. Given the rarity of these syndromes, data from randomized controlled trials are not available.

Neurological Immune-Related Adverse Events Following Immune Checkpoint Inhibitor Therapy

Immune checkpoint inhibitors (ICIs) represent a major breakthrough in the treatment of several advanced cancers, and immune-related adverse events associated with their use are important to consider. Immune checkpoints are molecules that play a crucial role in maintaining self-tolerance, dampening excessive inflammation, and preventing autoimmunity (Fig. 13.3). By tipping the balance in favor of T-cell activation, ICSs improve tumor antigen presentation, amplify immune responses, and disrupt tolerance but can also cause autoimmunity involving any organ system [56, 57].

ICIs can cause neurological immune-related adverse events (nirAEs) by triggering the development of immune responses against neuronal antigens. NirAEs following immune checkpoint inhibitor (ICI) treatment for cancer are similar in many respects to PNDs [58]. NirAEs affect up to 1.5% of patients, with serious events in 0.2–0.8% of patients causing significant morbidity and mortality [39, 59, 60]. Neurological adverse events include both CNS complications such as encephalitis, aseptic meningitis, posterior reversible encephalopathy syndrome, and hypophysitis and peripheral nervous system complications like polyneuropathy, transverse myelitis, Guillain-Barre syndrome, myasthenia gravis, and myositis. The same autoantibodies can be found in nirAEs as in PNDs; however, in some cases the profile of autoantibodies may be different for nirAEs. Treatment of nirAEs focuses on early recognition, interruption of ICI treatment, and immunosuppression with high-dose steroids or other immunosuppressive medications [59]. Interestingly, the prognosis of nirAEs tends to be more favorable than the corresponding PNDs. Given the undisputed efficacy of ICIs and expanding indications for treatment, the number of patients exposed to ICIs will continue to increase, and nirAEs will likely become more common.

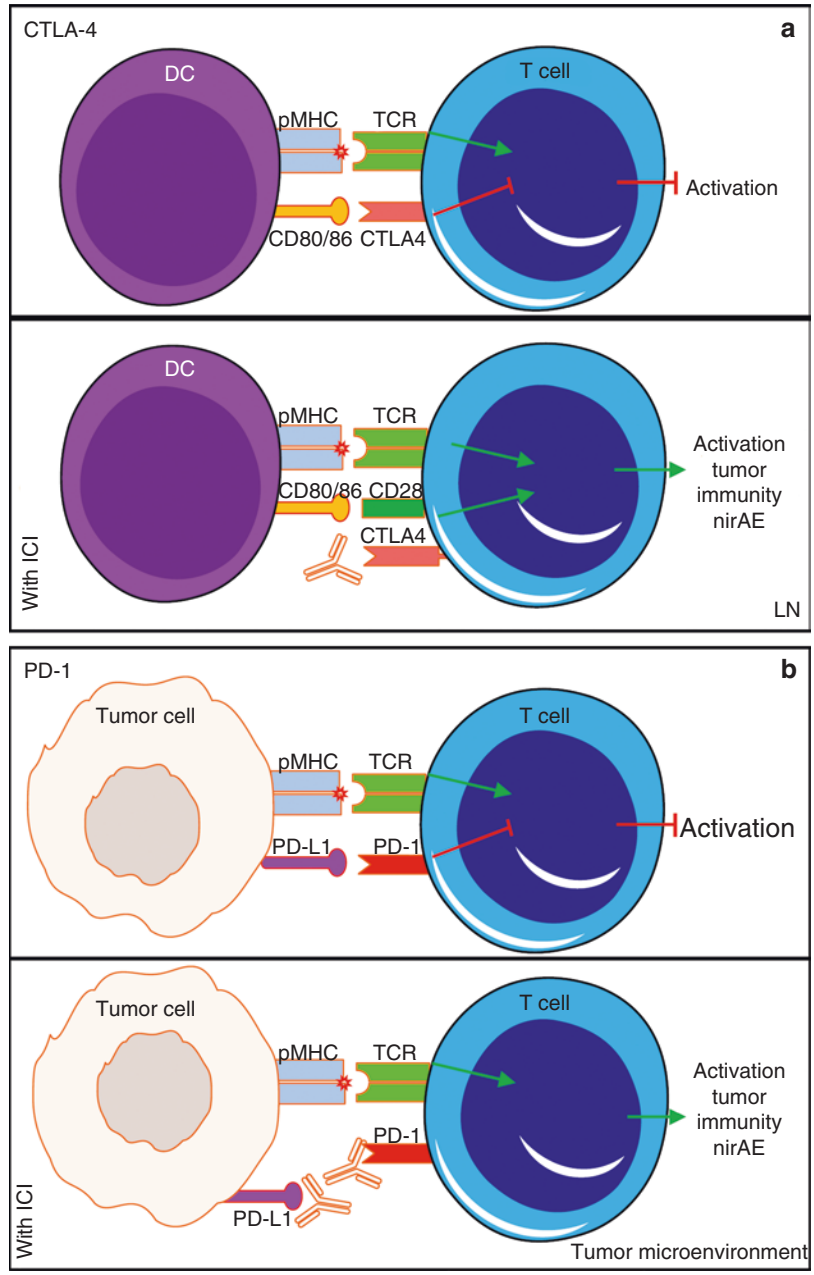

Fig. 13.3 Immune checkpoint inhibitors leading to T-cell activation

(**a**) CTLA-4 signaling is a negative regulator of T-cell activation and acts at the initial stage of T-cell activation in the LN. ICIs targeting CTLA-4 block interaction of CD80/86 with CTLA-4, allowing CD80/86 to bind with the costimulatory molecule CD28 and promote T-cell activation. (**b**) PD-1 signaling is a negative regulator of T-cell activation and acts at later stages of the immune response in peripheral tissues including in the tumor microenvironment. ICIs targeting either PD-1 or PD-L1 block the interaction of PD-1 and PD-L1, thus promoting T-cell activation

Summary

PNDs are rare, although likely under-recognized, complications of cancer. These disorders can occur at any stage of cancer and treatment; PNDs are often the first clinical manifestation of cancer and may herald a relapse in patients with known prior cancer history. They also share many symptoms with neurological immune-related adverse events related to immune checkpoint inhibitor therapy for a variety of cancers. PND syndromes involve multiple areas of the nervous system, and patients can present with a wide variety of symptoms and clinical signs. Investigations of PNDs continue to provide further insight into the immune system's response to cancer; how-

ever, much is still unknown regarding their exact mechanisms and the best diagnostic and treatment strategies.

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14 Systemic Therapy of Brain Metastases: Lung Cancer

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Introduction

Lung cancer is the most common cancer that results in the metastatic disease to the brain [1]. Small cell cancers are characterized by neuroendocrine feature and account for 15% of lung cancers seen [1–3]. Brain metastases from both non-small cell lung cancer (NSCLC) and small lung cancer are treated differently; small cell lung cancer is often treated with whole-brain radiation (WBRT) [4]. Both cancer types have a propensity for brain involvement—10–30% of NSCLC patients develop brain metastases during their course [5]. Ten to twenty-five percent of patients with stage IV NSCLC have brain involvement at presentation. Until recently, NSCLC brain metastases were managed with surgery and radiation therapy such as WBRT and increasingly stereotactic radiosurgery (SRS). With our improved understanding of the molecular underpinnings of NSCLC, there is a larger role for targeted agents and immunotherapy in the treatment of NSCLC brain metastases. Further, prognostication has evolved and the new Lung-molGPA (molecular graded prognostic assessment) includes molecular markers associated with NSCLC. The latest GPA incorporates molecular alteration data for patients with NSCLC and brain metastases; the clinical variables in the new model include patient age, performance status, extracranial metastases, number of brain metastases, and, in patients with adenocarcinoma, the presence of EGFR or ALK alterations [6].

Targeted Therapy

The identification of targetable gene alterations has transformed the management of lung cancer, allowing for personalized therapies with excellent response rates, including in the setting of brain metastasis. In the multicenter Lung Cancer Mutation Consortium, targetable oncogenic drivers have been identified in 64% of patients with non-small cell lung cancer (NSCLC) adenocarcinoma [7]. Within squamous cell carcinoma (NSCLC), up to 80% of tumors has a known oncogenic driver mutation; however, unlike in adenocarcinoma, targeted therapies to these oncogenic drivers have not reached the same level of clinical utility [8, 9]. The latest NSCLC

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guidelines published by National Comprehensive Cancer Network (NCCN), 2019 version 4, recommend that the nine genes should be tested, including EGFR, KRAS, HER2, ALK, ROS1, MET, BRAF, RET, and NTRK [10]. In patients with small cell lung cancer, where approximately 15–20% of patients present with brain metastases, a different set of genetic alterations is observed [11]. These include insulin-like growth factor-I receptor (IGF-IR), c-Kit overexpression, mutations in vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR) mutation and PTEN, as well as Myc overexpression [12]. However, none of the currently available targeted therapeutics agents have shown efficacy in small cell lung cancer. The remainder of this section will focus primarily on agents that target EGFR and ALK mutations, as they are the most clinically relevant and have the most data regarding intracranial efficacy. Although still limited, preliminary data suggest promising results in targeting ROS1, MET, BRAF, RET, and NTRK alterations as well.

Epidermal Growth Factor Receptor (EGFR)

EGFR belongs to a receptor tyrosine kinase family that also includes human epidermal growth factor receptor 2 (HER2, also known as ERBB2), HER3 (ERBB3), and HER4 (ERBB4). The receptor contains four extracellular domains, a transmembrane domain, a tyrosine kinase domain, and a carboxy tail. The binding of an activating ligand leads to EGFR dimerization and transphosphorylation, triggering a vast array of signaling pathways leading to cell growth, proliferation, survival, invasion, and angiogenesis [13].

EGFR is overexpressed in 15–50% of NSCLC and was viewed from the start as a promising therapeutic target; however, early trials with EGFR inhibitors in unselected populations demonstrated minimal clinical efficacy and no improvement over cytotoxic chemotherapies [14–17]. Three subsequent papers published in 2004 demonstrated that activating mutations in the EGFR gene were associated with sensitivity to the first-generation EGFR tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib [18–20]. The majority of these genetic aberrations are either exon 19 deletions (60%) or L858R missense substitutions (35%), which result in constitutive activation of the receptor without ligand binding [21]. EGFR mutations are more likely to be found in nonsmokers, and the incidence of EGFR mutations varies with ethnicity, with up to 50% frequency in adenocarcinomas in the Asian population compared to only 10–15% in Caucasians [20]. The IPASS trial was the first to confirm clinical efficacy of the targeted EGFR inhibitor gefitinib in a selected patient population with EGFR mutations [22].

Two retrospective studies published in the late 2000s provided the first evidence for the potential efficacy of EGFR inhibitors in NSCLC patients with brain metastases (NSCLCBM) harboring EGFR mutations [23, 24]. Both articles found that patients with NSCLC who received EGFR TKIs at any time after the diagnosis of BM survived longer than those that did not. In addition, other retrospective studies published around the same time found intracranial response rates ranging from 42% to 82% [25–27].

Failure to penetrate the blood-brain barrier (BBB) is often cited as one of the primary reasons for the lack of intracranial efficacy of cytotoxic chemotherapy in patients with NSCLCBM. Deng et al. found that the BBB penetration rate of erlotinib was 4.4% ± 3.2% and that the concentration of erlotinib was higher in patients with a partial response compared to stable or progressive disease [28]. Similarly, Zhao et al. found that gefitinib had a BBB permeation rate of 1.3% ± 0.7% and that the presence of brain metastases increased the BBB penetration (1.46% vs. 0.95%; *p*-value, 0.042) [29]. Pulsatile dosing is a strategy that has been proposed for increasing CSF concentration of TKIs. In one study testing this approach, an increased dose of 1500 mg of erlotinib allowed a CSF concentration that had been shown to inhibit the growth of cell lines harboring EGFR mutations in vitro [30, 31]. In a phase 1 study of twice-weekly pulse dose and daily low-dose erlotinib in patients with NSCLC, the authors noted stable disease in the

11 patients with brain metastases. In addition, of the 19 patients on trial that had systemic progression, none of these patients had any radiographic evidence of new or progressing brain metastases, suggesting that pulsatile dosing may improve intracranial efficacy of erlotinib [32].

Some of the first prospective data on the intracranial efficacy of first-generation EGFR TKIs originated from a phase 2 study in China that treated NSCLC patients with asymptomatic brain metastases with erlotinib. The authors found that patients with known EGFR mutations had increased survival compared to wild-type patients (18.4 months vs. 37.5 months, $p = 0.02$) [33]. Welsh et al. treated patients concurrently with erlotinib and WBRT and found that median survival time was greater in patients with EGFR mutations compared to wild-type EGFR [34]. In a prospective phase 2 clinical trial in 41 Japanese patients with EGFR-mutant NSCLCBM, gefitinib demonstrated a response rate of 87.8% with a PFS of 14.5 months (95% CI, 10.2–18.3 months) and OS of 21.9 months (95% CI, 18.5–30.3 months). Interestingly, this study found that exon 19 deletion was associated with better PFS and OS, when compared with L858R mutations [35]. Finally, a phase 2 trial of icotinib, a first-generation TKI approved in China for EGFR-mutated NSCLC, demonstrated a significantly increased OS in patients with EGFR mutations compared to wild-type EGFR (median OS 22 months vs. 7.5 months, respectively, $p = 0.0001$) when given concurrently with WBRT [36]. The best evidence for intracranial efficacy of first-generation TKIs came from a phase 3 study comparing icotinib alone vs. WBRT with or without chemotherapy. While there was a significantly improved intracranial PFS in the icotinib monotherapy group (HR 0.44, $p < 0.0001$), there was no difference in the overall survival between the two groups. However, a higher number of patients in the WBRT group crossed over to icotinib, making OS difficult to interpret [37]. Crossing over after progression has made it difficult to identify any statistically significant improvement in OS with TKIs vs. platinum-based chemotherapy. In a meta-analysis of almost 3000 patients from eight phase 3 clinical trials, there was no overall survival benefit of TKI vs. chemotherapy (HR 0.98, 95% CI 0.87–1.10); however, there was a vastly improved PFS in patients taking TKIs (HR 0.37, 95% CI 0.29–0.49).

Unfortunately, the response duration to first-generation EGFR TKIs is often limited due to a second EGFR mutation on exon 20, with a threonine-methionine substitution on codon 790 (T790M) [38, 39]. Other documented mechanisms of resistance include HER2 amplification; mutations to *MET*, *BRAF*, and *PIK3CA*; or transformation to small cell lung cancer [40]. The average patient will develop resistance within 12–16 months of starting treatment with a first-generation TKI [41].

First-generation inhibitors are reversible competitive ATP inhibitors that target only EGFR, while second-generation inhibitors such as afatinib, neratinib, and dacomitinib are irreversible inhibitors that also target HER2 and HER4. LUX-LUNG 3 and 6, both randomized phase 3 studies of afatinib, enrolled patients with asymptomatic brain metastases [42, 43]. Although a subgroup analysis of the two trials showed increased PFS compared to conventional chemotherapy (8.2 vs. 5.4 months; HR, 0.50; $p = 0.0297$), the field quickly progressed to using third-generation EGFR TKIs.

Osimertinib is a third-generation TKI that is effective against T790M mutations. The drug binds covalently to the cysteine on codon 797, overcoming the enhanced ATP affinity from T790M mutations [13]. Osimertinib is effective both as second-line treatment in patients who progressed after treatment with first-generation EGFR TKIs [44] and a first-line agent in EGFR-mutant disease [45]. In a trial comparing osimertinib to first-generation EGFR TKIs for first-line treatment, only 6% of patients had CNS progression in the osimertinib group compared to 15% in the standard EGFR TKI group. In the same trial, patients treated with osimertinib had significantly improved intracranial PFS (HR 0.48; 95% CI 0.26–0.86). In a subgroup analysis comparing osimertinib to pemetrexed plus carboplatin or cisplatin, the median PFS was longer in those receiving osimertinib, among the 144

patients with brain metastases (8.5 months vs. 4.2 months; HR 0.32; 95% CI 0.21–0.49) [46]. Together, this data consistently supports better intracranial activity with osimertinib compared to first-generation EGFR TKIs and cytotoxic chemotherapies.

Anaplastic Lymphoma Kinase (ALK)

The *ALK* gene was first discovered in 1994 in a subset of non-Hodgkin lymphoma where ALK was fused to nucleophosmin (NPM) as a result of a chromosomal translocation [47]. *ALK* encodes a transmembrane receptor tyrosine kinase that belongs to the insulin receptor superfamily; it comprises an extracellular domain, a single-pass transmembrane domain, and an intracellular kinase domain. In the normal physiology of human cells, ALK's function is unclear [48]. *ALK* rearrangements in the context of NSCLC were first identified in 2007, where it was found that a small inversion within chromosome 2p resulted in a fusion gene with echinoderm microtubule-associated protein-like 4 (*EML4*) gene (*EML4-ALK*) [49]. ALK translocations are found in approximately 3–7% of patients with NSCLC and cluster more commonly in non-smoker and light smokers [50–52]. Patients with *ALK* rearrangements treated with platinum-based chemotherapy had no overall survival difference compared to wild-type patients; however, outcomes of NSCLC patients with *EML4-ALK* positivity rapidly improved with the development of ALK inhibitors [51].

As discussed above, many of the initial clinical trials with first-generation EGFR inhibitors were agnostic to a patient's EGFR mutation status, slowing the implementation of these inhibitors in clinical practice. However, the lessons learned from these trials allowed for a more logical approach to ALK inhibitors, with many studies including prospective tumor genotyping. The first drug developed in this class was crizotinib, an oral small molecule inhibitor of ALK, MET, and ROS tyrosine kinases [53]. In a randomized phase 3 clinical trial of ALK-positive advanced NSCLC patients (PROFILE 1014), first-line crizotinib demonstrated superior intracranial activity compared to standard platinum-based chemotherapy [54–56]. Of the 79 patients with stable brain metastases enrolled, those treated with crizotinib had significantly better intracranial disease control at 12 and 24 weeks (12 weeks: 85% vs. 45%, $p < 0.001$; 24 weeks: 56% vs. 25%, $p = 0.006$). In a pooled analysis of PROFILE 1005 and 1007, 275 patients with asymptomatic brain metastases were analyzed, with a 56% intracranial disease control rate at 12 weeks and a median intracranial PFS of 7 months. However, progression of preexisting or development of new intracranial lesions while receiving crizotinib was a common manifestation of acquired resistance.

This led to the development of second-generation ALK inhibitors—ceritinib, alectinib, and brigatinib [57–59]. In a phase 1 clinical trial of ceritinib, of 14 patients with measurable intracranial lesions at baseline, 7 achieved an intracranial response and 3 had stable disease [60]. In ASCEND-2, a phase 2 study of ceritinib, of 100 patients with baseline brain metastases, there was a 45% intracranial response rate (95% CI, 23.1% to 68.5%) and 80% intracranial control rate. Alectinib has also shown promising intracranial activity. In the phase 1/2 study AF-002JG, patients with crizotinib-resistant ALK-rearranged NSCLC were given alectinib. Of 21 patients with CNS metastases at baseline, 11 had an objective response (6 complete, 5 partial) [61]. In the phase 3 J-ALEX trial, alectinib was compared to crizotinib in ALK inhibitor-naïve patients; alectinib was associated with significantly prolonged PFS (HR = 0.08, 95% CI, 0.01–0.61) [62]. In another multicenter phase 3 trial (ALEX) comparing alectinib and crizotinib, only 12% of patients in the alectinib group had CNS progression compared to 45% with crizotinib (HR = 0.16; 95% CI, 0.10–0.28; $p < 0.001$) [63]. In addition, complete CNS response was more likely in the alectinib group (45% vs. 9%, $p < 0.001$).

The third-generation inhibitor lorlatinib is the latest ALK inhibitor to demonstrate intracranial efficacy. Lorlatinib is a potent, brain penetrant inhibitor of ALK and ROS1 and has broad *ALK* mutational coverage. In a recently published

phase 2 clinical trial of patients treated with at least one prior ALK inhibitor, 51 of 81 of patients had an intracranial response (63%; 95% CI 51.5–73.4) [64]. The results of this trial ultimately led to accelerated approval of lorlatinib for patients that have progressed on another ALK inhibitor.

Kristen Rat Sarcoma 2 Viral Oncogene Homolog (KRAS)

KRAS belongs to a family of GTPases that transduce growth signals from multiple tyrosine kinases [8]. Activating KRAS mutations contribute to constitutive signaling and are present in about 30% of NSCLC adenocarcinoma; they are more commonly found in smokers [65, 66]. The presence of a KRAS mutation has been associated with worse prognosis compared to wild-type tumors [67]. Despite being one of the most common mutations and one of the first identified, effective targeting of KRAS mutations has been therapeutically challenging. Direct KRAS inhibition with salirasib was unsuccessful with no patients having any radiographic response [68]. Selumetinib, a MEK inhibitor, potentially inhibits and targets downstream of KRAS but demonstrated no additional efficacy in a phase 3 trial when added to docetaxel [69]. Our group has unpublished data suggesting the use of immunotherapy negates the poor outcomes traditionally seen in patients with NSCLC brain metastasis and KRAS mutations. Patients with KRAS mutations treated with immunotherapy had improved overall survival from the diagnosis of brain metastases compared to chemotherapy (unpublished Lauko and Ahluwalia). Although a similar result was seen in a recent meta-analysis, intracranial disease was not analyzed [70].

Immunotherapy in Brain Metastases from Lung Cancer

The advent of therapeutic strategies to aid the immune system in recognizing cancer cells as foreign and mounting a response against them has been a major milestone in oncology. The interaction between the T-cell and cancer cell is complex and involves MHC class 1 and T-cell receptors as well as additional co-stimulatory and co-inhibitory interactions. CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) and PD-1 (Programmed death-1) are two such co-inhibitory signals. Ipilimumab is an anti-CTLA-4 antibody which helps block the CTLA-4 co-inhibitory signals in the lymph nodes. There are several anti-PD-1 and PD-L1 antibodies including pembrolizumab and nivolumab, which block the PD-1/PD-L1 interaction in the tumor microenvironment. A phase 3 clinical trial of pembrolizumab has shown improved PFS in metastatic non-small cell lung cancer, with superior outcomes in patients with >50% tumor PD-L1 expression [71]. Nivolumab has been shown to be efficacious in cisplatin-resistant NSCLC [72]. Atezolizumab, another PD-L1 antibody, has been shown to add survival benefit to platinum-based chemotherapy in small cell lung cancer [73]. Several other studies have shown promising activity of immune checkpoint inhibitors in lung cancer.

Brain metastases from lung cancer express PD-L1, but the extent of this expression can be varied. A small study of 32 patients showed PD-L1 expression in 22% of brain metastases, and it was a predictor of poor overall survival [74]. In another study of brain metastases from small cell lung cancer, up to 75% were noted to have PD-L1 expression [75]. A larger study of 73 lung cancer patients with paired samples of primary and brain metastases evaluated the tumor and tumor microenvironment PD-L1 expression [76]. Tumor microenvironment PD-L1 and tumor cell PD-L1 expression were discordant between primary tumor and brain metastases in 14% (10/73) and 26% (19/73) cases, respectively. This suggested significant differences between brain metastases and the primary tumor. The density of T-cell infiltration may also vary considerably in brain metastases. The T-cells are usually a mixture of the exhausted and activated subtypes. In a study of 116 brain metastases (approximately 50% from NSCLC), 99% of the tumor microenvironment had T-cell infiltration [77]. There was no co-relation between T-cell infiltration and

PD-L1 expression or corticosteroid use. Dense T-cell infiltration was noted in more than 50% of all brain metastases samples, including effector CD3+ and CD8+ cells and memory cells. The density of T-cell infiltration had a positive impact on overall survival. Additionally, microglia and macrophages represent a unique and significant part of the tumor microenvironment in brain metastases [75, 78]. Tumor mutational burden is another important predictor of response to immunotherapy. A small study of 20 patients with lung cancer brain metastases showed an increase in tumor mutational burden compared to the corresponding primary site; however, the T-cell clones were less rich, suggesting a possible role of immune checkpoint inhibitors in activating the immune system [76]. In summary, the characteristics and tumor microenvironment of lung cancer make it a good target for immune checkpoint inhibitors.

The biggest challenge in drug delivery to brain metastases is the blood-brain barrier. In fact, the brain was historically thought to be an immune privileged site. Recent window of opportunity ("phase 0") studies have evaluated changes in T-cell activation and tumor microenvironment in high-grade glioma patients after administration of one dose of nivolumab or pembrolizumab [79, 80]. The surgical specimen obtained after exposure to either anti-PD1 antibodies showed upregulation of T-cell and interferon-Y gene expression, focal induction of PD-1 expression in the tumor microenvironment, and enhanced clonal T-cell expansion. This gives the best evidence of intracranial activity of anti-PD1 antibodies. The use of systemic high-dose corticosteroids in patients with symptomatic brain metastases is another potential hurdle for utilization of immunotherapeutic agents. This was demonstrated in a phase 2 clinical trial of ipilimumab in melanoma brain metastases, where patients receiving corticosteroids had a significantly lower intracranial disease control rate with ipilimumab (10% vs. 24%) compared to asymptomatic patients not on corticosteroids [81].

There are several retrospective series of nivolumab or pembrolizumab reported in the literature, often in the setting of expanded access programs (EAPs) for patients with mostly asymptomatic, stable brain metastases. One such large EAP was an Italian series of 409 patients with asymptomatic or previously treated non-squamous lung brain metastases who were treated with nivolumab [82]. The intracranial disease response rate was 40% with median overall survival of 8.1 months. In a French EAP of 409 non-small cell lung cancer patients receiving nivolumab, 130 had asymptomatic or stable treated brain metastases [83]. The intracranial partial response rate was 12% and the median overall survival was 6.6 months.

Most major clinical trials with immunotherapy excluded patients with active and progressive brain metastases. However, several allowed for inclusion of patients with stable and treated lesions. For example, the KEYNOTE 024 study was a phase 3 clinical trial of pembrolizumab compared to standard of care chemotherapy in newly diagnosed NSCLC with PD-L1 expression of at least 50% of the tumor [71]. This study showed significant improvement in progression-free survival in the entire cohort. The subgroup of patients with brain metastases was small—18 patients in the pembrolizumab arm and 10 in the standard chemotherapy arm; the survival was not significantly different between the groups. KEYNOTE 189, a clinical trial of the combination of pembrolizumab and chemotherapy in newly diagnosed NSCLC, enrolled the largest number of patients with brain metastases [84, 85]. The pembrolizumab plus chemotherapy combination arm had 73 patients with stable brain metastases, while the chemotherapy alone arm had 35 patients with stable brain metastases. With a hazard ratio of 0.36, the subgroup analysis noted improved overall survival with the combination of pembrolizumab and chemotherapy.

Another single center phase 2 trial evaluated the NSCLC brain metastasis response rates with pembrolizumab [86] and enrolled patients with asymptomatic but progressive or untreated, measurable (5–20 mm) brain metastases. A recently reported interim analysis described 39 patients treated with pembrolizumab (34 with PD-L1 > 50% expression in the primary tumor and 5 without PD-L1 expression). The intracranial

response rate in the cohort with increased PD-L1 expression was 29.4% (10 of 34 patients), while none of the patient in the PD-L1-negative group had an intracranial response. The median overall survival of the entire group was 8.9 months. The PFS among patients with an intracranial response or stable disease was 10.7 months, and 31% were alive at 2 years, suggesting a durable response. More studies like this are needed to better understand the intracranial activity of immunotherapy in brain metastases from lung cancer.

Combination of Radiation Therapy and Immunotherapy

Radiation therapy has long been the backbone of management of brain metastases. Stereotactic radiosurgery (SRS) has replaced whole-brain radiation therapy (WBRT) in a majority of patients, although there is still a role for the latter in patients with numerous symptomatic metastases. As initial studies with targeted and immunotherapy agents have shown intracranial efficacy, the clear next step is to consider combinations with radiation therapy. There are several theories suggesting synergy between radiation therapy and immunotherapy, such as the abscopal effect and release of neo-antigens with radiation. Numerous retrospective studies combining immunotherapy and radiation have been published in patients with brain metastases from melanoma and NSCLC. One retrospective, single center study compared the efficacy of SRS after traditional chemotherapy or immunotherapy in patients with NSCLC brain metastases. No differences in overall survival, progression-free survival, or response rates were between the groups (46 patients in the chemotherapy group and 39 in the immunotherapy group) [87]. A larger retrospective study of 260 patients, including 157 with NSCLC, evaluated the role of radiation therapy given concurrently or within 2 weeks of initiating immunotherapy; this combination was compared to SRS monotherapy and SRS with stereotactic body radiation [88]. Overall, there was no difference in overall survival between the groups. There are several ongoing clinical trials evaluating the optimal timing of radiation therapy and systemic therapy for patients with brain metastases. Targeted therapies are generally not combined with radiation therapy due to the possibility of worse cutaneous toxicities.

Conclusion

The management paradigm for brain metastases from lung cancer is rapidly evolving. The treatment plan must be customized and take into account each patient's overall prognosis, extracranial disease status, available systemic therapy options, neurologic symptoms, and brain metastasis burden. Surgery is an option for patients with solitary, large, and symptomatic brain metastases. Whole-brain radiation therapy is considered for patients with numerous symptomatic brain metastases and limited systemic options. SRS is utilized in patients with few brain metastases who are expected to live longer, in hopes of avoiding long-term cognitive decline from whole-brain radiation therapy. Novel systemic therapies, mainly targeted agents and immune checkpoint inhibitors, have shown promising intracranial activity in early studies. They are generally used in patients with predominantly extracranial disease and asymptomatic brain metastases. The combination and timing of immunotherapy with radiation therapy requires further investigation. Innovative research continues to identify pathways that drive metastatic growth with hopes of developing novel, effective agents to target them.

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15 Systemic Therapy of Brain Metastases: Breast Cancer

Leigh Klaus Swartz and Aki Morikawa

Introduction

Breast cancer is the most common malignancy diagnosed in women and remains a significant public health burden worldwide. Despite significant advances in the management of breast cancer that have improved overall survival, the prognosis of patients with breast cancer brain metastases (BCBM) remains poor [1]. Depending on a number of factors including tumor characteristics and performance status, the mainstay of treatment is neurosurgery and/or radiation therapy. Ongoing research has vastly accelerated the role for systemic therapy in the management of BCBM; however, effective therapies remain limited. Active research areas include investigating the underlying disease mechanisms, examining response to therapy, determining novel uses for systemic therapy, expanding targeted therapy, optimizing drug formulations for penetration across the blood-brain barrier/brain-tumor barrier (BBB/BTB), augmenting local therapy, researching screening strategies, and determining expanded outcome measures [2].

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Epidemiology

Among women in the USA, breast cancer is the most commonly diagnosed malignancy and the second most common solid tumor to metastasize to the brain [3]. In patients with breast cancer, the presence of brain metastases confers a poor prognosis. Population-based studies utilizing the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute (NCI) have shown that up to 8% of patients have BCBM at initial presentation [1]. The incidence of BCBM varies according to tumor subtype, based on human epidermal growth factor receptor 2 (HER2) receptor overexpression and/or gene amplification and the presence of estrogen receptor (ER), and progesterone receptor (PR) staining by immunohistochemistry (IHC). The highest incidence of BCBM is among patients with HER2-positive and triple-negative breast cancer (TNBC), which confer a respective 2.7- and 1.4-fold higher risk as opposed to patients with ER-positive/PR-positive/HER2-negative disease [4]. In fact, studies have demonstrated that up to 55% of patients with HER2-positive metastatic disease will develop BCBM [5]. Additional risk factors for developing subsequent BCBM include younger age at diagnosis (between the ages of 20 and 39), shorter time to development of first metastasis, higher number of non-brain metastatic sites of disease, and higher tumor grade [4, 6].

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Screening

Despite increased incidence in certain populations, screening for BCBM is not currently recommended at the time of breast cancer diagnosis in asymptomatic patients without suspicious neurologic exam findings. Clinicians are advised to have a low threshold to order brain imaging in HER2-positive metastatic breast cancer (MBC) patients with neurologic symptoms that may be clinically indicative of CNS involvement [7]. MRI is preferred over conventional CT, if not contraindicated [8]. Conversely, for stage IIIC or higher melanoma, stage II or higher non-small cell lung cancer (NSCLC), and any stage small cell lung cancer, the NCCN recommends screening MRI brain at the time of diagnosis given the propensity of these cancers to metastasize to the brain [9–11]. In a retrospective review comparing 659 patients with NSCLC to 349 patients with breast cancer, the study authors concluded that at time of diagnosis of brain metastases, breast cancer patients are more likely to have neurologic symptoms, seizures, leptomeningeal involvement, and brainstem involvement [12]. Patients with BCBM were also more likely to receive whole brain radiation therapy (WBRT) upfront and to die from neurologic causes compared to patients with NSCLC [12]. Another retrospective review of 100 patients with HER2-positive breast cancer demonstrated that diagnosing BCBM before development of symptoms was associated with increased survival, decreased use of whole brain radiation therapy (WBRT), and fewer brain lesions [13]. Additionally, surveillance for BCBM during treatment represents an ongoing research focus due to variable penetrance of systemic agents through the BBB/BTB. For example, in a retrospective review investigating the HER2-directed antibody-drug conjugate trastuzumab-emtansine (T-DM1), which is known to not adequately cross the BBB, authors demonstrated that the first site of progression was the brain in 56% of HER2-positive patients [14]. Such studies suggest the need for ongoing investigation into BCBM surveillance strategies in an effort to improve patient quality of life, treatment options, and survival.

Choice and Timing of Initial Therapy for BCBM

The decision to initiate therapy for BCBM is best approached with a multi-disciplinary team consisting of medical oncology, radiation oncology, neurosurgery, and palliative care. The standard approach for patients with limited and extensive brain metastases involves choosing among stereotactic radiosurgery (SRS), WBRT, neurosurgery, systemic therapy, best supportive care, and palliative care. The presence of symptoms related to BCBM is paramount to determining a treatment plan. Local therapy is preferred over initial systemic therapy for symptomatic BCBM. Per the NCCN guidelines, consideration should first be given to neurosurgery for biopsy purposes or for alleviation of mass effect or neurologic symptoms caused by brain metastases [15]. For patients who are not deemed neurosurgical candidates due to either patient or disease factors, SRS, WBRT, systemic therapy, and clinical trials should be considered. The principles of radiation and neurosurgery will be discussed elsewhere in this textbook.

Principles and Challenges of Systemic Therapy

Currently, there are limited systemic therapy options for patients with BCBM. Systemic therapy is only rarely employed in the first-line management of BCBM, as it has been traditionally reserved as salvage therapy following local therapy or to jointly control extra-axial disease. Ongoing research is opening doors to additional uses of systemic therapy including as upfront therapy, secondary prevention, radiosensitization, and treatment of side effects from local therapy. Systemic therapy does have advantages in that it can concurrently treat both CNS and non-CNS disease, and may postpone or potentially obviate the need for radiation therapy [2, 16–19]. The BBB/BTB also poses a significant clinical quandary, given limited penetration of many chemotherapies and lack of information regarding their CNS efficacy [20]. Many patients with BCBM will also present with brain metastases after extensive exposure to prior chemothera-

pies and radiation, which complicates the availability of additional systemic options. Consideration must also be given to HER2 status when selecting systemic therapy, given numerous advances in HER2-targeted therapy that have led to relatively longer overall survival coupled with high rates of CNS-only disease progression for patients who overexpress HER2 [5, 14].

Systemic Therapy for BCBM

The NCCN suggests several systemic therapy recommendations for recurrent BCBM including high-dose methotrexate, capecitabine, cisplatin plus etoposide, and capecitabine plus temozolomide [15]. Unfortunately, the data underlying these recommendations originates from generally weak studies consisting mostly of small single-arm prospective studies, retrospective reviews, and case reports. The paucity of evidence to support these therapies highlights the need for more clinical trials designed to advance care for patients with BCBM. The recommendation for high-dose methotrexate originates from a retrospective review of 32 patients with CNS metastases, of whom 29 (91%) had breast cancer; 94% of patients received high-dose 3.5 g/m^2 IV methotrexate [21]. Of all patients (including non-breast cancer patients), 56% had a partial response or stable disease in response to therapy. After excluding patients who also received concurrent radiation, systemic therapy with capecitabine, or intrathecal chemotherapy, 23 patients were evaluated and 57% had a partial response or stable disease after receiving solely high-dose IV methotrexate [21].

The combination of cisplatin plus etoposide for patients with recurrent BCBM was analyzed in two separate studies that were published in the 1990s [22, 23]. The first study evaluated 100 mg/m^2 platinum on day 1 and etoposide 1000 mg/m^2 on days 4, 6, and 8 of each 21-day cycle in a cohort of 22 patients with BCBM [23]. The overall response rate was 55%, with 5 (23%) patients achieving a complete response [23]. Hormone receptor and HER2 status were not reported for the cohort. The second study was a larger, prospective study of patients with brain metastases from breast cancer, non-small cell lung cancer (NSCLC), and malignant melanoma who had not received prior radiation therapy [22]. Similar to the first study, patients received 100 mg/m^2 cisplatin on day 1 and etoposide 1000 mg/m^2 on days 1, 3, and 5 or days 4, 6, and 8 of each 21-day cycle. Of the 56 patients with BCBM, 21 patients (37.5%) achieved either a complete or partial response.

The NCCN suggests the option of single-agent capecitabine in patients with recurrent HER2-negative BCBM, which is supported by drug uptake studies in BCBM tissue, limited case reports, and studies that use capecitabine in combination with other agents [24–29]. As an oral formulation, capecitabine represents a more convenient option than intravenous chemotherapy. In a retrospective review of seven patients with breast cancer, one of whom had leptomeningeal carcinomatosis (LC) and two of whom had both BCBM and LC, three patients had a complete response, and three patients had stable disease with capecitabine monotherapy [28]. From the time of initiation of capecitabine, progression-free survival (PFS) was 8 months and overall survival (OS) was 13 months [28]. Capecitabine plus temozolomide was investigated in a phase I trial of 24 patients with BCBM, with one complete response and three partial responses (18% CNS overall response rate (ORR)) [25]. Capecitabine plus lapatinib was also investigated in a multicenter phase II trial of 242 patients with progressive HER2-positive BCBM [30]. In the single-agent lapatinib arm, CNS response rate (RR) was 6%, while the lapatinib plus capecitabine arm demonstrated a CNS RR of 20% [30].

In addition to the systemic therapies suggested by the NCCN, a number of alternate systemic options are being investigated including combinatorial regimens, targeted therapy, novel formulations of chemotherapy, and new classes of therapeutics. The majority of published trials were designed for the treatment of recurrent BCBM after local therapy. Bevacizumab, a humanized anti-VEGF monoclonal antibody, was studied in various combinations in BCBM, including as part of a regimen with carboplatin and in the bevacizumab, etoposide, and cisplatin (BEEP) regimen consisting of bevacizumab, etoposide, and cisplatin. The combination of carboplatin plus bevacizumab was studied in a phase II trial—38 patients with progressive BCBM (30 HER-2 positive, 8 HER-2 negative)

were enrolled [31]. CNS ORR was 63%, and responses were observed in both HER2-positive and HER2-negative patients [31]. Another phase II study evaluated the bevacizumab, etoposide, and cisplatin regimen (BEEP) in patients with BCBM with any hormone receptor and HER2-status who had progressed after WBRT [32]. In the analysis, 12 patients were evaluable for response assessment, demonstrating 75% CNS ORR and PFS 6.6 months [32]. Temozolomide was also investigated as a single agent and in various combinations alongside capecitabine, cisplatin, and liposomal doxorubicin. As a single agent, temozolomide has shown poor CNS RR in BCBM. The CNS RR ranged from 0% to 4% in four phase II trials of temozolomide monotherapy in BCBM patients [33–36]. The combination of temozolomide with other systemic agents has yielded more promising results. A phase II study investigating temozolomide plus cisplatin in patients with BCBM demonstrated a 40% CNS RR [37]. Another phase II trial examined the combination of temozolomide plus liposomal doxorubicin in eight patients with BCBM and demonstrated a CNS RR of 66% [38].

Novel therapeutic agents are being investigated including ixabepilone, patupilone, and sagopilone of the epothilone class of microtubule inhibitors. Ixabepilone, alone or in combination with capecitabine, is currently approved for MBC that is resistant to anthracyclines and taxanes; however, patients with BCBM were excluded from the trials that led to FDA approval [39, 40]. Unfortunately, results from other trials of agents in the epothilone class have yielded discouraging results. Patupilone was studied in a multicenter phase II trial in patients with BCBM. Cohort A included patients who had received prior WBRT and cohort B included patients with untreated brain metastases or LC. Study authors concluded that patupilone was ineffective in treating BCBM with unacceptable GI toxicity [41]. Another drug of the same class, sagopilone, showed disappointing results in a phase II trial of 15 patients with BCBM. The study showed a CNS RR of 13.3% and PFS of only 1.4 months [42].

In order to effectively penetrate the BBB/BTB, novel formulations of existing therapies are being extensively studied through techniques such as liposomal drug delivery, pegylation, and nanoparticles [43]. Etirinotecan pegol (pegylated irinotecan) is an extended release formulation of the topoisomerase I inhibitor irinotecan that both increases exposure to and decreases the toxicity of the active metabolite of irinotecan, SN-38 [44]. The phase III BEACON trial compared etirinotecan pegol to physician's choice and demonstrated a significant improvement in OS of 10 months versus 4.8 months, respectively, in the BCBM subgroup [44]. Of 852 patients enrolled in the study, 67 (8%) had a history of BCBM [44]. Etirinotecan pegol is being actively studied in several BCBM clinical trials including the phase III ATTAIN study, which is designed to compare etirinotecan pegol to physician's choice in patients with stable BCBM who have been previously treated with an anthracycline, taxane, and capecitabine (NCT02915744). A phase II study examining the efficacy of etirinotecan pegol in patients with brain metastases from lung cancer and breast cancer is also ongoing (NCT02312622). Nanoliposomal irinotecan, a nanoparticle formulation that improves irinotecan pharmacokinetics, is also undergoing active clinical investigation in a phase II trial for patients with progressive HER2-negative BCBM after local therapy (NCT03328884) [45]. Novel drug conjugates, such as ANG1005, a novel paclitaxel-peptide conjugate, are being actively evaluated. In a phase II trial for patients with recurrent BCBM and LC, patients received an infusion of ANG1005 every 3 weeks; HER2-positive patients were allowed to continue trastuzumab and/or pertuzumab [46]. Seventy percent of patients demonstrated an intracranial clinical benefit by RECIST criteria [46]. Another phase II trial (publication pending) investigated ANG1005 as a single agent in HER2-negative disease and in combination with trastuzumab in HER2-positive disease (NCT01480583).

The portfolio of targeted therapy in BCBM is expanding to include inhibitors of CDK 4/6, poly-ADP ribose polymerase (PARP), and PIK3CA. The CDK 4/6 inhibitors palbociclib, ribociclib, and abemaciclib are currently approved to treat advanced ER-positive, HER2-negative breast cancer; however, the trials that led to FDA approval of ribociclib and abemaciclib excluded patients with CNS metastases

[47, 48]. The PALOMA-2 trial that led to the approval of palbociclib allowed for the inclusion of patients with stable BCBM, provided they had been treated with local, definitive therapy and were asymptomatic from brain metastases [49]. Abemaciclib is being actively investigated in a phase II trial in patients with brain metastases from breast cancer, NSCLC, and melanoma (NCT02308020). Abemaciclib has been showed to cross the BBB in xenograft models and has potential efficacy in BCBM [50]. Iniparib was originally promoted as a PARP inhibitor but then was shown to lack clinically relevant PARP inhibition [51]. The combination of iniparib and irinotecan was studied in a failed phase II trial of BCBM in patients with TNBC and demonstrated CNS RR of 12%, TTP 2.1 months, and OS 7.8 months [52]. An alternate PARP inhibitor, veliparib, is currently being studied in combination with cisplatin in patients with TNBC or BRCA-mutated breast cancer with or without BCBM (NCT02595905). PI3K (phosphoinositide 3-kinase) inhibitors represent another area of active research, with ongoing trials for advanced breast cancer [53]. The phase III SANDPIPER trial is studying the PI3K-inhibitor, taselisib, plus fulvestrant in patients with advanced breast cancer; however, patients with active or untreated BCBM are excluded from study participation (NCT02340221) [54]. Buparlisib (BKM120) plus capecitabine is being investigated in a phase II study designed for patients with BCBM (NCT02000882) (Tables 15.1 and 15.2).

Table 15.1 Selected phase II trials of systemic therapy alone

Drug	Combination	BCBM patients	Comments	Result
Afatinib	A: Afatinib B: +Vinorelbine C: +Choice	A: 40 B: 38 C: 43	3 arm, randomized	CNS RR A: 30%, B: 34.2%, C: 41.9% [55]
Bevacizumab	Carboplatin	38	–	CNS RR 63% (composite) [31]
	Etoposide and cisplatin	16 (12 evaluable)	Progression after WBRT	CNS RR 75% [32]
Capecitabine	Lapatinib	50	Prior RT and trastuzumab	CNS RR 20% [30]
Capecitabine	Lapatinib	45	LANDSCAPE trial, first-line, no prior RT	CNS RR 66% (volumetric), TTP 5.5 mos, OS 17 mos, Time to RT 8.3 mos [16]
Cisplatin	Temozolomide	15	–	CNS RR 40% [37]
	Lapatinib	22, 50	Prior RT	CNS RR 20–38% [30, 56]
Iniparib	Irinotecan	34	TBCRC 018, TNBC only	CNS RR 12%, TTP 2.1 mos, OS 7.8 mos [52]
Lapatinib	–	39, 242	–	CNS RR 2.6–6%, OS 6.4 mos [30, 57]
	Topotecan	22	Closed due to toxicity and lack of efficacy	CNS RR 0% [56]
Neratinib	–	40	For recurrent brain mets	CNS RR 8%, PFS 1.9 mos, OS 8.7 mos [58]
Patupilone	–	55	Group A: progressive BCBM after WBRT Group B: LC or untreated BCBM	Group A: CNS PFS 27% at 3 mos, OS 12.7 mos, ORR 9% Group B: CNS RR 0% [41]
Sagopilone	–	15	For recurrent brain mets	CNS RR 13.3%, PFS 1.4 mos, OS 5.3 mos [42]
Temozolomide	–	4, 10, 19, 51	For recurrent brain mets	CNS RR 0–4% [33–36]
	Pegylated liposomal doxorubicin	8	–	CNS RR 66% [38]

RR response rate, *ORR* overall response rate, *OS* median overall survival, *PFS* progression-free survival, *TTP* time to progression, *LC* leptomeningeal carcinomatosis

Table 15.2 Selected ongoing clinical trials

Intervention	Drug	Phase	Clinical trial ID
Systemic therapy alone	ARRY-380, anti-HER2, trastuzumab	I	NCT01921335
	Autologous activated dendritic cells for intratumoral injection	I	NCT03638765
	T-DMI, T-DMI + metronomic temozolomide	I, II	NCT03190967
	Abemaciclib	II	NCT02308020
	Atezolizumab + pertuzumab + trastuzumab	II	NCT03417544
	BKM120 (buparlisib) + capecitabine	II	NCT02000882
	Cabozantinib	II	NCT02260531
	Cisplatin ± veliparib	II	NCT02595905
	Eribulin	II	NCT03637868, NCT02581839, NCT03412955
	Etirinotecan	II	NCT02312622
	ANG1005 (paclitaxel-peptide conjugate) ± trastuzumab	II	NCT01480583
	HKI-272 (neratinib)	II	NCT01494662
	Nanoliposomal irinotecan	II	NCT03328884
	Palbociclib	II	NCT02774681
	Pertuzumab + high-dose trastuzumab	II	NCT02536339
	Pyrotinib + capecitabine	II	NCT03691051
	Tucatinib + capecitabine + trastuzumab	II	NCT02614794
	T-DMI	II	NCT03203616
	Proteome-based immunotherapy	II/III	NCT01782274
	NKTR-102 (etirinotecan pegol) versus physician's choice	III	NCT02915744
Concurrent with SRS	Sunitinib Pembrolizumab	I I, II	NCT00981890 NCT03449238
	Afatinib	I, II	NCT02768337
	Atezolizumab	II	NCT03483012
Concurrent with WBRT	Sorafenib	I	NCT01724606
	Bevacizumab + etoposide + cisplatin	II	NCT02185352
	Lapatinib	II	NCT01622868

Source: clinicaltrials.gov, last accessed October 2018

HER2-Positive Therapy Considerations in BCBM

HER2 overexpression is present in the tumors of 15–20% of patients with breast cancer, and approximately half of these patients will develop brain metastases [7, 59]. The most widely used HER2-directed agent, trastuzumab, has demonstrated poor penetration into the CNS, which may partially account for the increased incidence of HER2-positive BCBM. Prior to the discovery of HER2-directed therapy, HER2-positive breast cancers carried the worst prognosis among breast cancer patients [60]. Timing and consideration of initial therapy are similar to patients without HER2 overexpression; however, there are numerous additional considerations in recurrent disease and with regard to systemic therapy. The nature of HER2-positive disease, the BBB/BTB, and HER2-targeted treatment necessitates consideration of the brain and body as separate compartments. Per ASCO HER2-positive guidelines, systemic therapy should not be changed if systemic disease is controlled at the time of BCBM diagnosis [7]. In this scenario, local therapy should be employed to treat newly diagnosed BCBM. If systemic disease is not controlled at the time of BCBM diagnosis, standard HER2-directed therapy should be employed to treat disease in the body and brain in addition to local therapy for treating CNS disease [7]. The NCCN guidelines recommend the following HER2-

targeted systemic therapy regimens for HER2-positive recurrent BCBM: capecitabine and lapatinib, capecitabine and neratinib, or paclitaxel and neratinib [15]. Lapatinib is an oral, reversible dual tyrosine kinase inhibitor (TKI) that blocks HER1/EGFR1 and HER2. Neratinib is an oral, irreversible TKI with activity against HER1, HER2, HER4, and EGFR.

Lapatinib has been shown to have drug uptake in BCBM tissue [29]. Lapatinib was initially investigated as a single-agent after prior radiation therapy in multiple BCBM trials with discouraging results. Single-agent lapatinib only achieved a CNS RR of 2.6–6.6% in two phase II trials [30, 57]. The LANDSCAPE trial (Lapatinib Plus Capecitabine in Patients with Previously Untreated Brain Metastases from HER2-Positive Metastatic Breast Cancer) was a single-arm phase II trial that enrolled 45 patients who had not received WBRT, capecitabine, or lapatinib and had at least 1 CNS lesion measuring 10 mm or greater in diameter [16]. Forty-three percent of patients in the study were asymptomatic at the time of the radiologic assessment which led to BCBM diagnosis [16]. Ninety-three percent of patients had received trastuzumab-based chemotherapy prior to study enrollment [16]. Per the study protocol, patients were given lapatinib 1250 mg daily and capecitabine 2000 mg/m^2 days 1–4 of each 21-day cycle. The study demonstrated a 65.9% CNS objective response rate at 21 months; however, 49% of patients experienced grade 3–4 toxicity [16]. The most common toxicities were diarrhea, palmar-plantar erythrodysesthesia, fatigue, and rash [16]. Based on the results of the LANDSCAPE trial, ASCO suggests that initial therapy with lapatinib and capecitabine may be considered in patients who have low-volume, asymptomatic BCBM who have not received prior radiation therapy [7]. Due to concerns regarding inferior BTB penetration of lapatinib and overlapping toxicity of lapatinib and capecitabine, a phase I study was initiated to investigate intermittent high-dose lapatinib alternating with capecitabine in HER2-positive CNS metastases [61]. Results suggested that intermittent high-dose lapatinib at a dose of 1500 mg BID 3 days on, 11 days off sequentially with capecitabine 1500 mg BID 7 days on, 7 days off was a tolerable regimen with potential benefit [61]. In order to investigate prevention of BCBM, the CEREBEL study (A Phase III, Randomized, Open-Label Study of Lapatinib Plus Capecitabine Versus Trastuzumab Plus Capecitabine in Patients with Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer) was designed to compare the incidence of BCBM between patients receiving lapatinib plus capecitabine and trastuzumab plus capecitabine [62]. After enrollment of 540 patients, the study was terminated early and was inconclusive in regard to the primary endpoint [62]. The study did not show a difference in BCBM incidence between the treatment arms [62].

The NCCN recommendation for capecitabine and neratinib for recurrent HER2-positive BCBM derives from the Translational Breast Cancer Research Consortium (TBCRC) 022 trial, which is pending final publication [63]. This non-randomized phase II trial enrolled 39 patients with HER2-positive BCBM who had not previously received capecitabine or lapatinib [63]. Patients were required to have at least 1 CNS lesion measuring 10 mm or greater in diameter prior to enrollment. At baseline, 65% of patients had received prior WBRT [63]. Patients received neratinib 250 mg daily by mouth and capecitabine 750 mg/m^2 by mouth on days 1–14 of each 21-day cycle. The final results of the trial have not yet been published, but results from the preliminary abstract indicate 49% of patients achieved VORR (≥50% reduction in volumetric sum of CNS target lesions) [63]. As such, neratinib plus capecitabine represents a promising systemic therapy regimen for patients with HER2-positive BCBM.

The NCCN provides a category 2B recommendation for paclitaxel and neratinib for recurrent HER2-positive BCBM [15]. This is based on the NEfERT-T randomized clinical trial (Neratinib Plus Paclitaxel vs Trastuzumab Plus Paclitaxel in Previously Untreated Metastatic ERBB2-Positive Breast Cancer) that enrolled 479 women with locally recurrent or metastatic HER2-positive breast cancer [64]. The study uses ERBB2 nomenclature as the equivalent of HER2. Patients were randomized in 1:1 fashion to receive neratinib 240 mg orally daily plus 80 mg/m^2 IV paclitaxel

on days 1, 8, and 15 of each 28-day cycle or 4 mg/kg followed by 2 mg/kg IV every week of trastuzumab plus paclitaxel [64]. Notably, paclitaxel is known to have poor penetration into the BBB [65]. The trial excluded patients with active BCBM, but did allow enrollment of patients with CNS metastases or spinal cord involvement if they were asymptomatic, had been previously treated with definitive radiation and/or neurosurgery, and were not taking steroids or anticonvulsants for 4 weeks prior to the study [64]. Like the CEREBEL study, NEfERT-T can be viewed as a BCBM prevention trial. Of the 479 patients enrolled in the study, 18 had BCBM at the time of study enrollment [64]. The study demonstrated a significant reduction in symptomatic or progressive CNS events in the neratinib plus paclitaxel arm (8.3%) compared to the trastuzumab plus paclitaxel arm (17.3%) which remained significant after adjusting for baseline BCBM [64]. Similarly, study authors estimated 2-year incidence of CNS recurrence to be significantly decreased in the neratinib plus paclitaxel arm compared to the trastuzumab plus paclitaxel arm (relative risk of 0.45) [64]. As demonstrated in prior studies, the most common side effect of neratinib was diarrhea, which occurred in 92.5% of patients in the neratinib plus paclitaxel arm, and can be managed with primary diarrheal prophylaxis [64]. Given these data, it is reasonable to consider neratinib plus paclitaxel for systemic therapy in patients HER2-positive MBC, as it may delay onset of CNS metastases.

A number of other notable therapies for HER2-positive BCBM warrant further discussion. Tucatinib is an oral TKI with selective activity against HER2, which has been studied in two phase Ib trials in patients with HER2-positive MBC with or without BCBM [66, 67]. One study combined tucatinib with capecitabine and trastuzumab, and the other investigated the combination of tucatinib with T-DMI. Both combinations demonstrated acceptable toxicity and promising efficacy [66, 67]. A phase II trial is ongoing, investigating the combination of tucatinib versus placebo with capecitabine plus trastuzumab in a randomized, double-blind approach (NCT02614794).

Although trastuzumab has not been shown to have adequate BBB penetration, T-DMI has shown activity in HER2-positive BCBM in case reports [68, 69]. In a retrospective analysis of the phase III EMILIA trial, authors examined the incidence of CNS metastases in the T-DMI cohort versus the capecitabine plus lapatinib cohort [70]. Despite increased incidence of CNS metastases and CNS progression in the T-DMI cohort, a significant improvement in OS was observed in the T-DMI cohort in patients who had asymptomatic, previously treated CNS metastases at baseline [70]. This analysis supports the concept of separate brain and body compartments in HER2-positive disease.

Finally, alternate dosing strategies of existing HER2-targeted agents are being studied. Similar to the phase I high-dose lapatinib study, a trial is investigating the combination of pertuzumab plus high-dose trastuzumab in patients whose CNS disease has progressed after radiation therapy (NCT02536339) [71]. Inadequate BBB penetration of trastuzumab may be due to inadequate dosing, and an impaired BBB after radiation therapy has been shown to increase CNS concentrations of trastuzumab [71].

Systemic Therapy Concurrent with Radiation

Numerous trials have studied the use of systemic therapy in conjunction with radiation therapy in BCBM. Due to high recurrence rates after local therapy, research has focused on improving initial therapy through immunotherapy, radiosensitization, adjuvant RT after surgical resection, and alternative local techniques. Additional areas of active research include secondary chemoprevention after local therapy in an effort to prevent recurrence, as demonstrated in the CEREBEL and NEfERT-T trials [62, 64].

Earlier trials of chemotherapy with WBRT were not as promising as newer studies with targeted therapeutics. For example, a phase II trial investigating cisplatin and vinorelbine given concurrently with 30 Gy WBRT showed a 3.7-month PFS and 6.5-month OS [72]. However, CNS

response rate of 76% was consistent with contemporary trials [72]. Sorafenib, an oral TKI with anti-VEGF activity, is being actively investigated as a radiosensitizer when used concurrently with both SRS and WBRT. In a phase I trial of sorafenib with SRS for the treatment of 1–4 brain metastases, investigators demonstrated a 46% CNS PFS at 1 year and median OS of 11.6 months [73]. The trial enrolled 23 patients, of which 5 had breast cancer (22%). Another study designed to investigate sorafenib with concurrent WBRT for BCBM is actively recruiting patients (NCT01724606) [74]. A novel PET tracer (FLT: 3′deoxy-3′-fluorothymidine) will be used to improve response assessment.

Lapatinib has also been investigated in conjunction with WBRT with promising results in early phase trials [75, 76]. In a phase II trial evaluating lapatinib with WBRT in patients with brain metastases from breast cancer and NSCLC, patients with BCBM fared significantly better than those with NSCLC. Breast cancer patients accounted for 22% of trial subjects and demonstrated an 11.8-month median OS and 5-month time to progression (TTP), compared to 4.2-month median OS and 2.9-month TTP in patients with NSCLC [75]. The difference in median OS, but not TTP, was statistically significant between cohorts. An ongoing phase II trial is currently investigating concurrent RT (WBRT or SRS) with or without lapatinib in HER2-positive BCBM (NCT01622868).

Due to their ability to cross the BBB/BTB, PARP inhibitors are also being evaluated in conjunction with RT. A phase I trial examined veliparib in combination with 30 or 37.5 Gy WBRT for brain metastases from a variety of solid tumors [77]. Of 81 patients enrolled in the study, 25 had BCBM with median OS of 7.7 months [77]. When compared to WBRT, no additional toxicity was identified with the addition of veliparib [77].

In an effort to expand the portfolio of secondary chemoprevention after SRS, a phase II trial of sunitinib was completed in 14 patients (21% with BCBM) with 1–3 brain metastases [78]. Sunitinib, a TKI with anti-VEGF activity, was employed as an alternative to consolidation with WBRT after SRS. Study authors demonstrated 6-month CNS PFS of 43% [78]. Another secondary chemoprevention trial is underway investigating T-DMI alone versus T-DMI plus metronomic temozolomide after SRS in HER2-positive BCBM (NCT03190967).

Immuno-oncology (IO) represents an area of active BCBM research, with many trials examining the combination of immunotherapy and radiation. Although studies in melanoma and NSCLC have demonstrated CNS responses to IO agents as monotherapy, breast cancer studies have so far failed to show improved outcomes [79]. Current studies are investigating pembrolizumab or atezolizumab given concurrently with SRS in BCBM (NCT03449238 and NCT03483012) (Table 15.3).

Table 15.3 Selected completed trials of systemic therapy with concurrent radiation therapy

Drug	Phase	RT	Result
Bevacizumab	I (65% BC)	30 Gy WBRT	OS 13.3 mos, TTP 7.1 mos [80]
Capecitabine + sunitinib	II	WBRT (dose unspecified)	42% of pts removed from study due to toxicity, PFS 4.7 mos, OS 10 mos [81]
Cisplatin + vinorelbine	II	30 Gy WBRT	CNS RR 76%, PFS 3.7 mos, OS 6.5 mos [72]
Lapatinib	I	37.5 Gy WBRT	CNS RR 79% [76]
Lapatinib	II (26% BC)	30 Gy WBRT	CNS RR 71%, OS 11.8 mos, TTP 5 mos [75]
Sorafenib	I (22% BC)	SRS	OS 11.6 mos, CNS progression 10 months [73]
Sunitinib	II (21% BC)	SRS	CNS PFS 6-mos after SRS 43% [78]
Veliparib	I (31% BC)	30 Gy or 37.5 Gy WBRT	OS 7.7 mos [77]

BC breast cancer, *RR* response rate, *OS* median overall survival, *PFS* progression-free survival, *TTP* time to progression

Complications of BCBM Therapy

In addition to well-reported side effects from individual systemic therapies, additional complications from therapy include radiation necrosis and cognitive impairment. WBRT is notably associated with well-reported neurocognitive side effects and fatigue. In a randomized, placebo-controlled, double-blind trial of memantine started within 3 days of radiation initiation, Brown et al. found that the memantine cohort showed less decline in executive function, memory impairment, and processing speeds and better overall cognitive function [82].

Another growing area of research is the relationship between systemic therapy and the incidence of radiation necrosis [83]. Cerebral radiation necrosis may present in an asymptomatic patient as simply an imaging finding or as a serious, potentially life-threatening complication that can occur at any time up to years after radiation treatment. The diagnosis of radiation necrosis can be difficult due to the complexity of distinguishing between tumor progression and radiation necrosis on imaging. Biopsy remains the gold standard but is not a feasible option in many patients. In a retrospective review of 12 BCBM patients, the incidence of radiation necrosis was 50% in those patients treated with T-DMI simultaneously with SRS compared to 28.6% if T-DMI was given sequentially with SRS [84]. In a smaller retrospective review, four of seven patients treated with SRS prior to T-DMI developed clinically significant radiation necrosis [85]. Bevacizumab remains the most evidence-based option to treat radiation necrosis due to VEGF dysregulation in radiation necrosis; however, bevacizumab cannot be used in patients with acute cerebral hemorrhage [86]. Bevacizumab can be a safe and effective therapy for radiation necrosis that reduces steroid requirements [87, 88].

Future Directions

Many active trials have been specifically designed to advance the care of patients with BCBM. A number are investigating systemic therapy concurrent with radiation, with a novel focus on immunotherapy. The efficacy of immunotherapy with radiation is not clear. Systemic monotherapy is also being evaluated in in the prevention, first-line, and recurrent settings. Promising therapeutics include CDK 4/6 inhibitors, HER2-targeted therapy, cytotoxic therapy, TKIs, PARP inhibitors, and estrogen modulator therapy. Novel mechanisms to deliver drugs to the brain through the restrictive BBB/BTB are being pursued including liposomal drug delivery, pegylation, and use of nanoparticles [43]. In addition to discrete, clinical endpoints, quality of life measures are being incorporated into trial designs.

As more patients undergo genetic tissue typing of their tumors, precision medicine will continue to move to the forefront in many cancers, including breast cancer. Precision medicine may pave the way for a more tumor agnostic approach, in that the genomic features of the tumor impact treatment decision-making more than the tumor type itself. Such an approach is being actively investigated in the ASCO TAPUR (Targeted Agent and Profiling Utilization Registry Study) and NCI MATCH (Molecular Analysis for Therapy Choice) trials [89, 90]. However, both the TAPUR trial and MATCH trial exclude patients with active, symptomatic brain metastases [89, 90].

Traditional clinical trials generally excluded patients with active CNS disease. A 2017 meta-analysis which reviewed phase I, II, and I/II trials for MBC concluded that only 29% allowed patients with CNS metastases [91]. The 2018 guidelines by the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) working group stipulate clear recommendations for inclusion and exclusion of patients with brain metastases in an effort to safely advance research for this challenging and underrepresented patient population [92]. The RANO-BM working group postulates clinical trial designs based on the understanding of the potential CNS activity of an experimental drug to recommend exclusion or inclusion of patients with brain metastases into a particular clinical trial [92]. With updated guidelines for inclusion of patients with BCBM and numerous novel therapeutics to investigate, progress is anticipated in the treat-

ment of this challenging patient population. This will require well-designed clinical trials and collaboration between specialties across multiple institutions.

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16 Systemic Therapy for Brain Metastases: Melanoma

Sarah Weiss and Harriet Kluger

Introduction

Melanoma is the third most common cancer to metastasize to the brain after lung cancer and breast cancer, but it has the highest propensity to spread to the brain [1]. Brain metastases occur in over 30% of patients with metastatic melanoma [2], and the incidence is even higher in autopsy series [3, 4]. Risk factors for development of melanoma brain metastases include primary melanomas greater than 4 mm in size, location on the scalp, and nodular histology [5]. Once brain metastases have developed, factors such as older age, elevated lactate dehydrogenase, more than three brain metastases, poor performance status, and neurologic symptoms are predictive of worse outcomes [3, 6]. Patients with leptomeningeal disease and those who develop brain metastases after receiving systemic therapy for extracranial metastases also do poorly [3]. Historically, the median overall survival (OS) from the time of diagnosis of melanoma brain metastases was less than 6 months [7]. Treatment approaches for melanoma brain metastases typically focused on local therapies such as whole brain radiotherapy (WBRT), stereotactic radiosurgery, or surgical resection. Until recently, the impact of systemic therapies on melanoma brain metastases was understudied because few clinical trials allowed for inclusion of these patients.

Several recent clinical trials have demonstrated activity of contemporary immune checkpoint inhibitors and *BRAF* and *MEK* inhibitors in untreated melanoma brain metastases. This data has impacted current brain metastasis treatment paradigms, as local therapy may not be necessary upfront in select patients. Even patients who achieve disease control with systemic therapy for extracranial metastases may relapse with CNS metastases. It will be important to develop effective second-line therapies for these patients. Moreover, combinations of local and systemic therapies have proven to be effective, but the optimal sequencing of treatments remains unclear, and there may be higher risk for chronic neurologic toxicity. Research is underway to understand how to sequence and combine systemic and local therapies for maximal activity with minimal toxicity and how to select patients most likely to benefit from each treatment. Other important challenges to be addressed include accurately assessing radiographic response to treatment, managing radiation necrosis, and treating leptomeningeal disease, for which no effective therapy currently exists. In this chapter, we discuss systemic therapy approaches for the management of melanoma brain metastases, current therapeutic challenges, and new approaches being investigated.

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Historic Systemic Therapy Approaches

There were essentially no effective systemic therapies for metastatic melanoma prior to the advent of contemporary immunotherapy and targeted therapies. Historically, chemotherapy including temozolomide, fotemustine, and several other combination chemotherapies was studied in the setting of brain metastases without evidence of substantial activity [8–10].

Temozolomide is an oral alkylating agent that was found to have equivalent efficacy to intravenous dacarbazine in a phase 3 trial of patients with advanced extracranial melanoma [11]. Due to the good CNS penetration of temozolomide, a phase 2 study enrolled 155 advanced melanoma patients with asymptomatic brain metastases not requiring immediate radiation therapy. Intracranial disease benefit was achieved in 36% of patients who were chemotherapy-naïve, including 1 complete response (CR) (1%), 7 partial responses (PR) (6%), and 34 with stable disease (SD) (29%). Patients who received prior chemotherapy had much lower intracranial response rates (1 PR (3%) and 6 SD (18%)). Responses did not last for meaningful periods of time. Median progression-free survival (PFS) in the brain was only 1.2 months for chemotherapy-naïve patients and 1 month who had already received chemotherapy [12]. OS was also poor at 3.5 months and 2.2 months, respectively [11].

Other studies using chemotherapy had equally disappointing results. For example, a phase 2 study of fotemustine included a small cohort of patients with melanoma brain metastases and initially reported a 25% intracranial response rate [13]. However, a follow-up phase 3 trial of fotemustine versus fotemustine with whole brain radiation therapy in patients with melanoma brain metastases showed no significant differences in intracranial response rates (7% vs 10%), which were much lower than that reported in the earlier phase 2 study. OS was brief, with no significant difference between the two groups (86 vs 105 days) [14].

Targeted Therapy

BRAF V600 mutations are the most common targetable driver mutations identified in melanoma. *BRAF* is a serine/threonine protein kinase that activates the MAP kinase/ERK signaling pathway and when mutated becomes constitutively activated, increasing melanoma cell proliferation and survival [15]. In small series, melanoma brain metastases have an estimated 44–55% rate of *BRAF* V600 mutations; *BRAF* status in melanoma brain metastases has been shown to be generally concordant with that of matched extracranial metastases [16, 17]. Additional molecular profiling of small cohorts of melanoma brain metastases have shown a 23% rate of *NRAS* mutations [18] as well as a significantly higher degree of PI3K/AKT pathway activation, PTEN loss, and increased expression of proteins such as STAT3 or SOCS1, compared to other metastatic sites [19–22].

Vemurafenib, one of the earliest mutant BRAF inhibitors, was FDA approved in 2011 for patients with *BRAF* V600E mutant melanoma and was the first to be studied specifically in melanoma brain metastases. In one pilot study, 24 patients with *BRAF* V600-positive melanoma with unresectable, previously treated, symptomatic brain metastases were treated with vemurafenib 960 mg twice a day. Median treatment duration was only 3.8 months (range 0.1–11.3) limited mostly by disease progression, but 3/19 (16%) patients had a PR, demonstrating some intracranial activity in previously treated patients; this set the foundation for further investigation of targeted approaches for melanoma brain metastases [23].

A phase 2 study (BREAK-MB) used dabrafenib, a *BRAF* inhibitor FDA approved in 2013, to treat patients with V600E or V600K *BRAF*-mutant melanoma with at least one asymptomatic brain metastasis (Cohort A included patients with no prior therapy, while Cohort B was comprised of patients with progression of brain metastases after prior local therapy). The intracranial response rate for patients with V600E mutations was 39% (29/74) in Cohort A and 31% (20/65) in Cohort B. Far fewer patients with

V600K mutations were enrolled as this mutation is much less frequent than V600E, but intracranial response rates were also lower than those seen for V600E-mutant patients: 7% (1/15) in Cohort A and 22% (4/18) in Cohort B [24]. This study further confirmed the safety and activity of *BRAF* inhibitors for melanoma patients with treated or untreated brain metastases.

After combined *BRAF* and *MEK* inhibition was found to be superior to *BRAF* inhibition alone in advanced melanoma [25], the phase 2 COMBI-MB trial studied dabrafenib 150 mg orally twice daily with trametinib 2 mg orally daily in treatment-naïve melanoma patients with brain metastases. Patients were divided into four cohorts: Cohort A (asymptomatic, V600E mutant, no prior local therapy, ECOG performance status 0–1), Cohort B (asymptomatic, V600E mutant, prior local therapy, ECOG performance status 0–1), Cohort C (asymptomatic, V600E/D/K/R mutant with or without prior local therapy, ECOG performance status 0–1), and Cohort D (symptomatic, V600E/D/K/R mutant with or without prior local therapy, ECOG performance status 0–2). Intracranial response rates were 58%, 56%, 44%, and 59% in Cohorts A, B, C, and D, respectively [26]. Despite the encouraging response rates, the duration of response was brief. For example, median PFS in Cohort A was less than 6 months, with a 1-year PFS rate of 19%. This is much lower than the PFS of over 11 months and a 3-year follow-up PFS rate of 22% for dabrafenib and trametinib in advanced melanoma patients without brain metastases [25, 27]. These results suggest that resistance to BRAF/MEK inhibition may occur more quickly in the brain compared to extracranial sites. Additional studies are necessary, but this may be related to insufficient drug delivery or to development of distinct resistance pathways [28]. For example, in vitro studies have demonstrated that the addition of cerebrospinal fluid to melanoma cell lines reduced the cell death response to *BRAF* inhibition, which was restored with addition of a PI3K inhibitor [29].

There are multiple active clinical trials using targeted approaches for melanoma brain metastases. Use of other available BRAF/MEK inhibitors such as vemurafenib and cobimetinib is being studied after radiosurgery to brain metastases in patients with *BRAF*-mutant melanoma (NCT03430947). Other targeted therapies being investigated include inhibitors of JAK2 (NCT01904123), MEK (NCT03332589), and PI3K (NCT02452294).

Immune Checkpoint Inhibitors

The CTLA-4 inhibitor ipilimumab was the first immune checkpoint inhibitor that was FDA approved for the treatment of advanced melanoma in 2011, followed by the PD-1 inhibitors pembrolizumab and nivolumab in 2014, and combination regimen of ipilimumab and nivolumab in 2015. Immunotherapy has the potential to induce durable responses in patients with advanced melanoma. Historically, most clinical trials studying these agents excluded patients with brain metastases so their impact on the CNS was initially unclear.

Initial data on checkpoint inhibitors in melanoma brain metastases came from a retrospective analysis of a phase 2 study of ipilimumab in patients with advanced melanoma. Twelve out of the 115 patients enrolled in the trial had stable brain metastases at baseline. Of the 12 patients, 2 had a PR and 3 had SD with treatment, with 3 of these patients surviving beyond 4 years, suggesting activity and potential for durable responses in the brain [30]. A subsequent phase 2 trial studied ipilimumab 10 mg/kg once every 3 weeks for four doses followed by maintenance every 12 weeks in brain metastasis patients, including those who received prior WBRT or stereotactic radiosurgery, as long as at least one untreated target lesion was present. The majority of patients had received prior systemic therapy for melanoma, including interferon, interleukin-2, or chemotherapy. Two cohorts were studied: patients with asymptomatic brain metastases not requiring corticosteroids (Cohort A) or symptomatic patients on a stable dose of steroids (Cohort B). CNS objective response rates were 16% and 5%

in Cohorts A and B, respectively. PFS was less than 2 months for both cohorts and median OS was 7 months and 3.7 months, respectively. This trial did not demonstrate unexpected adverse events in the CNS and suggested modest activity for ipilimumab, particularly for small, asymptomatic brain metastases in heavily pre-treated patients [31].

Anti-PD-1 therapy with or without ipilimumab has since become the backbone for frontline melanoma therapy and has recently been investigated in several clinical trials specific to melanoma brain metastases. Pembrolizumab 10 mg/kg every 2 weeks was studied in a phase 2 trial of 23 melanoma patients with asymptomatic brain metastases measuring 5–20 mm. At 24-month follow-up, the brain metastasis response rate was 26%, and at follow-up the 2-year OS rate was 48%. Intracranial and extracranial responses were concordant [32, 33]. Although neurologic adverse events occurred in 65% of patients, almost all instances were grade 1 or 2. The most common neurologic adverse events included gait disturbance (22%) and headache (17%). Three patients developed seizures which were controlled with antiepileptics, and four patients developed neurologic symptoms related to perilesional edema. Radiation necrosis occurred in seven patients (30%), which was higher than expected. Based on these results, a trial of pembrolizumab in combination with bevacizumab is underway (NCT02681549) in patients with untreated melanoma brain metastases to determine if bevacizumab can mitigate perilesional edema and radiation necrosis while also enhancing T-cell migration and thus antitumor immune responses.

Combined treatment with ipilimumab and nivolumab has also been studied in two clinical trials. The first was a phase 2 randomized study by Long et al. assessing the safety and efficacy of ipilimumab plus nivolumab (Cohort A) compared to nivolumab monotherapy (Cohort B) in patients with asymptomatic melanoma brain metastases measuring 5–40 mm without prior local therapy. Nivolumab was also administered to a third cohort of patients who had progression in the brain after prior therapy, neurologic symptoms, or leptomeningeal disease (Cohort C). At 17-month follow-up, intracranial responses were seen in 46% (16/35), 20% (5/20), and 6% (1/16) of patients in Cohorts A, B, and C, respectively. Intracranial complete responses were seen in 6 (17%) and 3 (12%) patients in Cohorts A and B, respectively, and none in Cohort C [34]. Adverse events were similar to those seen in prior trials of ipilimumab and nivolumab in melanoma patients without CNS disease, and there were no unexpected neurologic toxicities.

Another phase 2 trial by Tawbi et al. evaluated the safety and efficacy of combined ipilimumab and nivolumab in patients with asymptomatic melanoma brain metastases measuring 5–30 mm, without prior local therapy. At 14-month follow-up of 94 patients, the intracranial response rate was 57% (CR 26%, PR 30%, SD 2%) and was concordant with the extracranial response rate of 56%. Grade 3 or 4 adverse events occurred in 55% of patients which is again consistent with expected rates and is similar to Long et al. Adverse events specific to the CNS occurred in 36% (34/94) of patients, and only 7% (7/94) were grade 3 or 4. The most common CNS adverse event was headache which occurred in 21 patients (almost all grade 1 or 2). Only four patients had cerebral edema, three had intracranial hemorrhage, and two had seizures [35].

These studies demonstrate the intracranial safety and efficacy of immune checkpoint inhibitors for treatment of untreated melanoma brain metastases. Historically stereotactic radiosurgery or resection has served as the initial therapy of melanoma brain metastases. New data suggest that it is safe to start with upfront immunotherapy in select patients with close monitoring of intracranial disease. However, stereotactic radiosurgery remains an important component, particularly for large lesions or lesions in neurologically sensitive sites, and its use in combination with systemic therapies is discussed below. Data demonstrate a higher rate of intracranial response with combined ipilimumab with nivolumab compared to anti-PD-1 therapy alone. Also, available evidence suggests that the durability of response is longer with immunotherapy compared to targeted therapy.

As new systemic therapy approaches become available and/or demonstrate efficacy for extracranial disease, their efficacy is also likely to be tested in the setting of melanoma brain metastases. Clinical trials are now often including patients with small, asymptomatic, untreated brain metastases. Combination studies are also underway that focus specifically on enrolling patients with melanoma brain metastases—examples include the previously mentioned trial of pembrolizumab and bevacizumab and another investigating the use of atezolizumab with bevacizumab (NCT03175432).

Systemic Therapy Combined with Radiation

Prior to the advent of stereotactic radiosurgery (SRS), patients with brain metastases were treated with whole brain radiation therapy (WBRT). The most commonly used WBRT regimen is 3 Gy daily over 10 days, for a total of 30 Gy, although various alternative strategies have been utilized that spare sensitive parts of the brain [36, 37]. This modality is only minimally effective, and the median survival in melanoma patients treated with WBRT has ranged from 2 to 4 months [38]. In recent years, SRS is being used with increasing frequency. The delivery of 22 Gy in a single fraction has proven to be highly effective for melanoma, a disease which is only modestly sensitive to radiation [39]. The incorporation of SRS into standard treatment paradigms over a decade ago increased median overall survival to 8 months, which has fortunately improved with the advent of immunotherapy and targeted agents [40]. Initially SRS was reserved for patients with a small number of metastases (up to 4), but with improved technology, it is now feasible to treat a larger number of lesions [41]. Many institutions now forgo WBRT, given limited efficacy and potential neurocognitive toxicities, and patients are often treated with a combination of systemic therapy and SRS. However, WBRT is still widely used for diffuse intracranial and/or leptomeningeal disease.

Combination of Immune Therapy with SRS

There is limited clinical trial experience regarding the combination of immunotherapy with SRS. The bulk of our current knowledge is from retrospective analyses, which are often single institution in nature. In one example, Knisely et al. demonstrated prolonged overall survival with ipilimumab and SRS in a series of patients at Yale University [41]. In another series, Silk et al. evaluated outcomes of melanoma patients with brain metastasis treated at the University of Michigan with radiation, some of whom also received ipilimumab, and survival was similarly improved in the ipilimumab-treated group [42]. Additional studies have been published regarding PD-1 inhibitors, demonstrating enhanced activity in combination with SRS [43, 44].

A phase 1 trial of ipilimumab in combination with SRS or WBRT in melanoma brain metastasis patients (NCT01703507) has been completed [45]. Patients were assigned to one of two treatment groups (SRS vs WBRT) based on tumor burden, and the dose of ipilimumab was escalated from 3 mg/kg in the first cohort in each treatment group to 10 mg/kg. Expected toxicities of ipilimumab were observed—although one patient experienced a grade 3 neurotoxicity, most were relatively minor. Results regarding efficacy are still pending.

Another clinical trial of pembrolizumab with SRS is currently accruing patients at Emory University (NCT02858869). Patients with metastatic melanoma or non-small cell lung cancer to the brain are being treated with standard pembrolizumab dosing and escalating doses of radiation (6, 9, and 18–21 Gy). The primary endpoint is to determine the safety of the combination. A similar trial assessing SRS with nivolumab is being conducted at Johns Hopkins University (NCT02716948). A study evaluating the combination of SRS, ipilimumab, and nivolumab is being planned in Australia (NCT03340129), building on the high intracranial response rate observed with this systemic therapy regimen in prior trials [34, 35].

Sequencing and Timing of Immune Therapy and Radiation Therapy

The timing of SRS relative to immune therapy appears to affect outcome. For example, in an institutional series published by Qian et al., administration of CTLA-4 or PD-1 inhibitors within 4 weeks of SRS resulted in improved response of melanoma brain metastasis, compared to waiting longer to initiate immunotherapy [46]. Further, preclinical studies have suggested that concomitant therapy may be superior to stepwise treatment [47]. In theory, intermittent radiation could increase tumor infiltration by T cells and ultimately improve antitumor activity by avoiding exhaustion of intra-tumoral T cells. As murine models of melanoma brain metastases improve, preclinical studies may be able to address the optimal sequence and timing of combined modality therapy.

Targeted Therapy in Combination with Radiation Therapy

Case reports and case series have described institutional experiences of the combination of BRAF inhibitors with radiation therapy, summarized by Anker et al. [48]. An ongoing clinical trial is studying the activity of dabrafenib in combination with SRS (NCT01721603). The primary endpoint of this study is 6-month distant brain metastasis-free survival. A trial of cobimetinib and vemurafenib after SRS is ongoing (NCT03430947). Toxicities associated with the combination of BRAF/MEK inhibitors in combination with radiation can be severe, leading to the establishment of treatment guidelines [48]. Specifically, for brain metastases, the Eastern Cooperative Oncology Group recommends holding BRAF and/or MEK inhibitors for at least 3 days before and after WBRT and at least 1 day before and after SRS.

Challenges of Systemic Therapy for Melanoma Brain Metastasis

Response Criteria for Brain Metastasis

Accurately assessing responses to systemic therapy can pose a challenge. In general, radiographic responses to systemic therapy in extra-cerebral sites are determined by RECIST criteria, which utilize the sum of the largest single dimension of target lesions over 1 cm in size. The minimal size criterion was determined as double the distance between slices on CT. Brain lesions are typically imaged by high-resolution MRI with slices that are 1–2.5 mm apart, allowing for reliable assessment of differences in smaller lesions; response criteria for brain metastasis were recently standardized. The international Response Assessment in Neuro-Oncology (RANO) Working Group developed response criteria for brain metastases (RANO-BM) [49]. Given the potential for initial tumor inflammation in patients on immunotherapy, the RANO group also developed the iRANO criteria [50]. Other groups have used modified RECIST criteria for brain metastasis trials, allowing for lesions $\geq$5 mm to be used as target lesions—overall, differences between these modified RECIST criteria and the RANO-BM are minimal, and both allow inclusion of patients with smaller lesions into clinical trials [51]. All of these criteria require further prospective validation and standardization.

Radiation Necrosis

Radiation necrosis is becoming an increasingly frequent challenge with the increasing utility of SRS. Radiation necrosis is a delayed complication of SRS, occurring months to years after treatment. It appears to occur more frequently in the brain than in other organs. Some studies have suggested increased incidence in patients treated with combination SRS and immune therapy,

either concurrently or sequentially, compared with the combination of SRS and other forms of systemic therapy [52]. A recent clinical trial of pembrolizumab in patients with untreated brain metastases reported radiation necrosis in over 30% of patients [33].

Radiation necrosis can sometimes be managed by observation alone in patients with asymptomatic lesions that do not grow or regress. However, surgical intervention such as resection or laser interstitial thermocoagulation therapy is required in over half of cases for symptom control [53–56]. Glioblastoma patients similarly develop radiation necrosis, which sometimes responds to bevacizumab [57]. This practice is being adopted in brain metastasis patients as well, although the true efficacy of bevacizumab in either treating or preventing radiation necrosis is unknown [58–60].

Leptomeningeal Disease

Despite the progress in treating parenchymal brain metastasis, leptomeningeal disease (LMD) remains a major challenge. The median survival for LMD from melanoma is still dismal [61]. Patients with LMD have almost universally been excluded from clinical trials, and the few small trials that have been conducted for this disease population have not yielded promising results. Standard treatment includes supportive care, clinical trials when available or whole brain radiation therapy for symptom palliation. Given the lack of prospective randomized data for treating these patients, a number of groups have published their institutional experience suggesting that contemporary targeted or immune therapies may improve survival with LMD. For example, one retrospective analysis of 39 metastatic melanoma patients with LMD reported a median survival of 21 weeks in 21 patients treated with targeted/immune therapy and radiotherapy, compared to 4.3 weeks in patients treated with radiation therapy alone [62]. Of note, approximately one third of the patients in this series had disease progression that was too rapid for any further intervention—median survival in this group was only 2.9 weeks.

Intrathecal drug administration is an interesting alternative approach for patients with LMD, as it overcomes concerns about limited drug penetration into the cerebrospinal fluid. Glitza et al. recently reported results for over 100 melanoma patients with LMD who were treated with intrathecal interleukin-2 over two decades [63]. The 43 cases in this series treated between 2006 and 2014 showed 1-, 2-, and 5-year survival rates of 36%, 26%, and 13%, respectively, from the start of treatment. However, intrathecal IL-2 administration is often poorly tolerated due to increased intracranial pressure, indicating an urgent need for newer approaches for LMD patients. Limited ongoing clinical trials for melanoma LMD include NCT03025256 (combined systemic and intrathecal nivolumab) and NCT02939300 (ipilimumab and nivolumab, both systemic). Additional approaches are sorely needed.

Conclusions

Improved systemic therapies for metastatic melanoma have resulted in superior outcomes for patients with melanoma brain metastases. Increased enrollment of patients with brain metastases in clinical trials has enhanced our understanding of the efficacy of systemic therapies in the CNS. Brain metastasis response rates to immune therapies are similar to response rates in other advanced (stage M1C) melanoma patients, while responses to targeted therapies in the brain appear to be shorter than in extracranial sites. Further investigation is necessary to determine whether this reflects limited drug penetration into the CNS or other local factors. SRS remains an important component of treatment of brain metastases, as response rates to all current regimens are <60%, and large lesions or lesions in neurologically sensitive sites such as the brain

stem, speech area or motor strip may require local intervention. The combination of SRS with immune therapy may improve outcomes but may also be associated with increased risk of radiation necrosis, a phenomenon that is rarely seen outside the brain. Patients with leptomeningeal disease have very limited options with poor outcomes, highlighting the need for further clinical trials in this population. In conclusion, while outcomes of patients with melanoma brain metastasis have significantly improved, additional preclinical and clinical studies are required to increase survival while minimizing CNS toxicity.

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17 Systemic Therapy for Brain Metastases in Other Primary Cancers (Genitourinary, Gastrointestinal, Gynecology, Head/Neck)

Karishma M. Parikh and Rajiv S. Magge

Introduction

Brain metastasis (BM) is most common in lung and breast cancers and melanomas; BM in these malignancies tends to make up 75% of all brain metastases [1, 2]. Metastatic disease from renal cell carcinoma and colorectal carcinoma makes up a large portion of the remainder.

In most cases, there is no standardized treatment for BM; the treatment approach for BM tends to be customized for each patient and often involves multiple modalities of treatment [3, 4]. Patients with isolated, symptomatic, and accessible lesions are usually offered surgical resection, while stereotactic radiosurgery (SRS) and whole brain radiation therapy (WBRT) are used in the setting of multiple lesions.

Systemic therapy for BM has been challenging due to limited CNS penetration of traditional chemotherapy—if drugs are only effective with non-CNS disease, the brain may become a sanctuary site for metastases [5–7]. Efficacy of systemic therapy is dependent on both the intrinsic sensitivity of the primary malignancy and the ability of the agent to pass the blood-brain barrier (BBB), which can have heterogeneous breakdown within lesions [6].

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With our rapidly growing understanding of genetics and molecular phenotypes, novel systemic options are now available. Immunotherapy, such as checkpoint inhibitors, has shown exciting efficacy in specific malignancies. Interestingly, some agents with minimal CNS penetration may still play a role in both preventing and treating BM [6].

Gastrointestinal Cancers

Colorectal

Gastrointestinal malignancies are some of the most common in the United States, with colorectal cancer (CRC) being the most frequent type [8]. Colorectal cancer (CRC) is the third most common cancer worldwide [9] and third most common cause of cancer death in the United States [8], with improving survival due to better screening and available treatment options [10]. About 5% of CRC patients have an underlying genetic disorder that predisposes them to the development of colon cancer, such as familial adenomatous polyposis (FAP) and Lynch syndrome (hereditary nonpolyposis colorectal cancer (HNPCC)) [11–13]. They are both associated with the development of brain tumors—typically, patients with FAP can develop medulloblastomas, while those with Lynch syndrome have an increased risk of glioma [14–16].

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About 20% of patients diagnosed with CRC have metastatic disease at baseline; 25% of patients have systemic metastases during the disease course, most commonly to the liver, lung, and lymphatic tissue. BM occurs in approximately 1–4% of patients [17], often concomitant with other metastases [18]. Cerebellar lesions are seen in up to 33–55% of the patients [19]. Patients often present with headache, hemiparesis, dizziness, ataxia, and/or seizures [20].

Curative treatment for localized CRC is usually surgical resection. The mainstay for metastatic CRC (mCRC) treatment is generally cytotoxic chemotherapy, including irinotecan or oxaliplatin, combined with 5-FU and leucovorin or capecitabine [21]. These drugs are generally considered ineffective for BMs as they have limited CNS penetration [22].

Outcomes have improved with the addition of targeted therapy with monoclonal antibodies (mAbs) against vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR). EGFR mAbs cetuximab and panitumumab have been approved for use in patients with RAS wild-type tumors. For RAS-mutant disease, the VEGF mAb bevacizumab, anti-VEGF receptor 2 (VEGFR2) mAb ramucirumab, recombinant fusion protein ziv-aflibercept, and multikinase inhibitor regorafenib have been approved [21]. RAS mutations have been associated with increased incidence of brain and lung metastases [23–27]. There are no established associations between BM and alterations in PIK3CA, BRAF, EGFR, and CXCR4 or changes in tumor markers CA19.9 and CEA [23–25, 28–33] (Fig. 17.1).

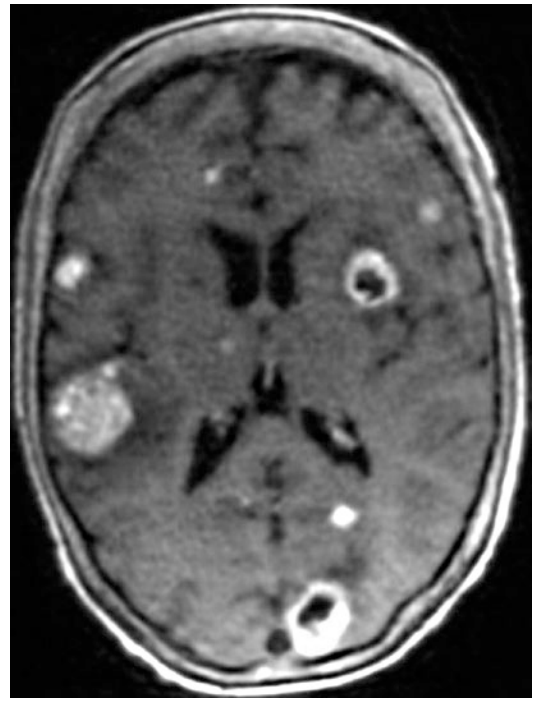

Fig. 17.1 T1-weighted post-contrast MRI demonstrating brain metastases from colon adenocarcinoma. Post-contrast T1 MRI image of brain metastases in a 54-year-old patient with metastatic colon adenocarcinoma

Esophageal

Esophageal cancer is the eighth most common cancer worldwide and the sixth leading cause of cancer death due to its aggressiveness [34]. Approximately 40% of patients with esophageal cancer present with metastatic disease at diagnosis, usually to the lymph nodes, liver, peritoneum, lung, and adrenal glands [8].

BM is rare, with incidence ranging from 0% to 6% [35, 36], with 75–80% of patients presenting with neurological symptoms at the time of presentation [37, 38]; some report that BM has been associated with poorer prognosis than BM from other solid tumors [39]. No clear distribution pattern for brain lesions has been found, with patients presenting with both supratentorial and infratentorial metastases [36]. Spread to the brain may occur via Batson's vertebral venous plexus, which allows vascular communication between the brain and esophagus. It was traditionally thought that brain metastases were more common with adenocarcinoma histology; one study [40] found adenocarcinoma as the primary histology for all BM in their series. However, a later 2017 study by Welch et al. observed no statistically significant differences between the adenocarcinoma and squamous cell carcinoma groups, supporting no difference in neurotropism [36]. On average, median survival for these patients with BM was 3.8–10.5 months [37, 41].

Due to the aggressive nature of esophageal cancer, most patients receive trimodality therapy

with chemotherapy (carboplatin, paclitaxel, and 5-FU) alongside radiation therapy and surgical resection when indicated [42]. Carboplatin has incomplete CNS penetration, but there is no evidence yet of clear efficacy with esophageal BM.

Abu et al. retrospectively looked at 142 cases of esophageal cancer over a 10-year period and found that HER2 overexpression correlated with postoperative BM [43]. Similarly, Preusser et al. described 21 patients with esophageal BM with good concordance of HER2 and EGFR expression between the primary tumor and brain metastasis; however, unlike the earlier study, HER2 positivity did not seem to increase risk of BM [44]. Ongoing investigation is required to determine the role of HER2 [41].

Gastric

Gastric cancer is the second most common cause of cancer-related death worldwide [45]. Adenocarcinoma is the most common subtype, and surgical resection is quite effective for early stage cancer. Postoperative chemoradiation is often considered for patients with at least stage IB disease. There are multiple regimens utilized worldwide based on heterogeneous populations; in the United States, docetaxel tends to be the drug of choice added to a regimen with cisplatin and 5-fluorouracil [16, 46].

With the rare incidence of less than 1% (range: 0.16–0.69%), there are only a few reported studies characterizing gastric BM [47]. In one study, York et al. described 0.7% of their patients to have BM with all of them having concomitant systemic metastatic disease, with a median survival of 2.4 months [48]. The usual clinical presentation tends to be headache, muscular weakness, and visual difficulties [20].

Lemke et al. reported that surgical resection provided the best chance of improved survival in these patients [49]. In a study by Kasakura et al., 11 of 2322 Japanese patients with gastric cancer had BM (0.47%); patients that received both surgical resection and WBRT lived longer than patients who had surgery or WBRT alone [50]. Jun et al. [51] found that BM from advanced gastric cancer was associated with VEGF expression, and based on a preclinical model proposed that reducing VEGF expression may decrease metastatic capacity, by using metformin to reduce VEGF expression and blocking epithelial to mesenchymal transformation.

Hepatocellular Carcinoma

Hepatocellular carcinoma is the most common primary hepatic malignancy worldwide with increasing prevalence [52]. The dominant risk factor for HCC in North America is hepatitis C-related cirrhosis, while in Africa and Asia, HCC incidence is associated with hepatitis B infection [53].

HCC has a low affinity for the CNS, with studies indicating an incidence of around 1% (range of 0.2–2.2%) [54]. Reports mostly describe a solitary intracranial metastasis to the parietal or frontal lobes [55]. In addition to hepatic encephalopathy, patients may develop intracranial hypertension and focal neurologic symptoms [56]. Of significant concern is that a reported 70% of HCC BM is associated with intracerebral hemorrhage [55]. In one study, patients with a single BM, Child-Pugh grade A, had the best prognosis with median overall survival of 27 weeks [57].

As is the case with other primary tumors, WBRT, SRS, and surgical resection are commonly used, with improvements in survival noted with combination of both surgery and RT [57, 58]. Sorafenib, an oral multi-kinase inhibitor that induces tumor stasis and inhibits tumor angiogenesis, has been theorized to reduce intracranial disease, but its use has been limited by concern that it may increase risk of intracranial hemorrhage [59, 60]. Targeted agents often only provide partial inhibition of a signaling pathway, so combinatory regimens may be necessary [61–65]. Unfortunately, there is no evidence yet to support systemic therapy for HCC BM.

Pancreatic Cancer

Pancreatic cancer is one of the most lethal cancers with a 5-year survival of <5% [9, 66, 67], in large

part due to its diagnosis at an advanced disease stage [68]. The incidence of BM in pancreatic cancer remains poorly understood and is extremely rare (0.33–0.57%) [39, 69]. No clear brain regional preference for metastases has been described [20]. Gemcitabine monotherapy is often used as the first-line treatment for resected disease and has only limited BBB penetration. Other regimens include FOLFIRINOX (fluorouracil, folinic acid (leucovorin), irinotecan, and oxaliplatin) and gemcitabine plus nanoparticle albumin-bound paclitaxel (nab-paclitaxel) and similarly do not have any clear efficacy in the brain [70]. Lemke et al. described extended survival after surgical resection of solitary brain metastases in two post-pancreatectomy patients [49].

Gallbladder Cancer

Gallbladder cancer is rare but rapidly fatal with about 5000 cases diagnosed annually in the United States. Most cancer is primarily adenocarcinoma and most commonly linked to chronic gallbladder inflammation due to gallstone, gallbladder polyps, and chronic infection. Initial symptoms can be nonspecific, contributing to late diagnosis and subsequent treatment difficulty [71].

BM from primary gallbladder carcinoma is extremely rare, with an incidence of <0.5% [72]. Surgical resection offers the best chance of cure in patients with localized gallbladder cancer. There is no definitive standard regimen for adjuvant or palliative chemotherapy for gallbladder cancer, but gemcitabine has been used in most adjuvant/palliative regimens [73]. As noted above, gemcitabine has only limited BBB permeability. Few cases have been reported, and subsequently no clear efficacy of systemic therapy has been established.

Head and Neck

Squamous Cell Carcinoma

Head and neck squamous cell carcinoma (HNSCC) is the sixth leading cancer worldwide [74], found to be linked to both tobacco and alcohol exposure and separately with a distinct pathophysiology to infection by the human papillomavirus (HPV). Overall, HNSCC is an aggressive epithelial malignancy associated with lymph node metastasis and immunosuppression [75, 76].

BM for patients with head and neck malignancies is extremely rare [1, 77]; there are primarily only case reports in setting of an untreated primary cancer.

The treatment for early stage HNSCC is usually surgery or radiotherapy; localized advanced HNSCC often requires combination regimens, such as surgery followed by postoperative radiation and/or chemoradiation, including with cisplatin or sequential induction chemotherapy.

Immunotherapy agents such as pembrolizumab or nivolumab, humanized monoclonal antibodies targeting PD-1, have been approved by the FDA for platinum-refractory recurrent/metastatic HNSCC. There is no data to support their efficacy in patients with BM; however, some brain lesions from primary melanoma and lung cancer do respond to systemic immunotherapy, indicating potential utility in the future. Several clinical trials evaluating other immune checkpoint inhibitors are ongoing including for HPV-associated HNSCC, which tends to be more immunogenic and responsive [78].

The rare case of brain metastasis from head and neck malignancy is usually treated with SRS. One study by Patel et al. reported similar outcomes to other cancers with SRS for BM from head and neck carcinomas, without the neurotoxicity seen with WBRT [79].

Paraganglioma (Carotid Body Tumor)

Paragangliomas of the head and neck are rare vascular neuroendocrine tumors derived from the paraganglia tissues originating from the neural crest, comprising 0.6% of head and neck tumors [80]. Up to 40% of paragangliomas are hereditary, and there are well-known tumor syndromes associated with the same, including multiple endocrine neoplasia type 2 (MEN 2), von Hippel-Lindau (VHL), and neurofibromatosis (NF-1).

Paragangliomas can also occur in familial forms, which tend to present at a younger age and at multiple sites compared to sporadic paragangliomas. Paragangliomas are associated with PGL1 genes, with a mutation of the SDHB protein being involved in head and neck paragangliomas [81]. Carotid paraganglioma or carotid body tumors (CBTs) represent 60–70% of paragangliomas of the head and neck [82]. Preferred method of treatment and management of CBT involves surgical excision, often times difficult due to size and vascular involvement of these tumors, with a high risk of cranial nerve damage and resultant neurological dysfunction [83].

Paragangliomas may arise at the skull base with local invasion and involvement of cranial nerves, but brain parenchymal metastasis is very uncommon. Wang et al. [84] described a 53-year-old woman with right limb weakness associated with dizziness and vomiting who presented with intracranial metastasis from a carotid body paraganglioma, one of few cases in the literature. She recovered without reported neurological deficits following surgical resection of the brain tumor.

GYN

Choriocarcinoma

Choriocarcinoma is the most aggressive type of gestational trophoblastic disease (GTD), arising from the placental trophoblastic tissue after fertilization. It usually occurs after a molar pregnancy but may present prior to a full-term/ectopic pregnancies or abortion [85]. Worldwide incidence is variable mostly because of differences in reporting and diagnostic criteria. The incidence in the United States is 2–7 per 100,000 pregnancies [86]. Choriocarcinoma is quite aggressive, notably with rapid vascular invasion and diffuse systemic metastases.

CNS metastases are seen in up to 40% of choriocarcinoma patients [87]. Choriocarcinoma BM often causes elevated intracranial pressure contributing to subsequent headache, vision changes, nausea, vomiting, tinnitus, hemiparesis, and seizures, especially with cortical lesions [88–90]. The most common presentation is unfortunately intracerebral hemorrhage; metastatic choriocarcinoma should be on the differential for any woman of reproductive age with a new hemorrhagic brain lesion [90]. Most CNS metastases are discovered alongside concurrent lung involvement—a chest CT should be routinely performed as part of the workup [88].

The use of systemic chemotherapy for metastatic choriocarcinoma is a well-accepted practice, particularly with EMA-CO (etoposide, methotrexate, and actinomycin-D, alternating weekly with cyclophosphamide and vincristine). Methotrexate dosing in this regimen is lower than commonly used for other types of CNS malignancy but higher than established for other metastatic sites in choriocarcinoma. Patients with high burden of CNS disease may receive low-dose etoposide and cisplatin before the EMA-CO regimen, even though they have limited CNS penetration [91]; in one study employing EMA-CO along with EMA-EP by Savage et al., 85% of the 27 patients with BM had an overall cure [91], with previous earlier and smaller studies having cure rates ranging from 35% to 100% [89, 90, 92–95]. Additionally, utilizing the presence of multidrug-resistant-associated protein 1 (MRP1) in the uterus and choroid plexus epithelium, one study using triple-knockout and double-knockout mice for MRP1 was able to enhance the delivery of etoposide tenfold through the BBB with lack of the MRP1 protein; the utility and optimization of drug delivery through the CSF in this regard are being investigated [96, 97].

There is no established management with surgery, radiotherapy, or intrathecal chemotherapy for BM in choriocarcinoma; the benefit of WBRT and chemotherapy is not clearly established.

Ovarian/Fallopian Tube Cancer

Ovarian cancer is the second most common gynecological cancer after endometrial cancer and a leading cause of mortality in women [98]. Globally, it is the seventh most common cancer and the eighth most common cause of cancer death among women [99, 100].

BM is a rare and late manifestation of ovarian cancer, with an incidence ranging from 0.3% to 1.2% [101]. According to a review by Pakneshan et al., most patients with brain metastases present with sensory/motor disturbances, ataxia, seizures, and altered consciousness; the cerebellum was the common site of parenchymal metastasis. Most patients diagnosed with BM have stage III or stage IV cancer when diagnosed, but BM can occur both in the setting of disseminated or isolated disease; 30–44% of patients in one study were reported to have isolated CNS relapse [100, 101]. Patients with concurrent extracranial disease had a median overall survival of 9 months compared to 21 months in patients with isolated CNS metastases [102].

Patients with high-grade (stage 3 or more) disease usually receive adjuvant systemic chemotherapy consisting of a platinum (carboplatin or cisplatin) and taxane (paclitaxel or docetaxel). BBB penetration of these drugs, especially taxanes, is limited, and thus significant CNS activity may not be expected.

Most cases of ovarian BM are treated with surgical resection and/or SRS. In one study by Niu et al., Gamma Knife radiotherapy and surgical excision contributed to extended survival [103]. Another study by Kwon et al. found significantly prolonged survival after surgical resection for single or symptomatic BM [104]. There are no novel systemic treatments identified for the use of BM in ovarian cancer.

Cervical

Cervical cancer is the third most common cancer in women and the fourth major cause of mortality in women worldwide.

The development of BM is rare in uterine cervical cancer, with an incidence of 0.4–1.2% [105, 106]. Most brain metastases tend to be supratentorial without a propensity for a specific lobe [107]. Median survival is 2.3–8 months [105, 106, 108].

Metastatic cervical cancer can be managed with the use of recurrent surgery or radiation therapy if the disease is more limited; however, in most cases, patients will receive a platinum-based agent like cisplatin with bevacizumab, an anti-VEGF monoclonal antibody that acts as a tumor angiogenesis inhibitor.

There is no established chemotherapy regimen for patients with BM. There is no standardized treatment for BM from cervical cancer, and most patients will undergo resection, SRS, and/or WBRT [109].

Endometrial

Endometrial carcinoma is the most common gynecological malignancy in the United States and the fourth most common malignancy in women, with an overall increasing incidence due to improved survival as well as higher rates of obesity [74, 110, 111].

BM is exceedingly rare with primary endometrial cancers, with incidence of 0.3–0.9% of patients based on case reports [112, 113]. The cancer may first metastasize to the lungs and subsequently disseminate to the CNS hematogenously; papillary serous, clear cell, and poorly differentiated histologic subtypes carry higher risk of BM [112, 114]. Cybulska et al. described 23 of the total 3052 patients who developed BM in the setting of low-grade endometrial carcinoma [113]. No specific neurological symptoms or predilection of certain areas in the brain have been described.

Total hysterectomy with bilateral salpingo-oophorectomy is the primary treatment for patients with endometrial cancer followed by XRT or chemotherapy. The combination of cisplatin, doxorubicin, and paclitaxel is the most active regimen for advanced or recurrent endometrial cancer [115]. In one retrospective study from Gien et al., 8 of 1295 women developed BM; brain involvement was diagnosed an average of 2 months following completion of primary tumor treatment [114], indicating likely poor efficacy of the chemotherapy regimen for brain disease. No effective systemic treatment for endometrial BM has been fully identified [116].

Genitourinary Cancers

Prostate

Prostate cancer is the second most common cancer in men after lung cancer and the third leading cause of malignancy in the United States [117].

BM is extremely uncommon with an incidence of 0.2–2.0% [118–122]—most are solitary metastases that are usually supratentorial. BMs are present with concurrent osseous, lymph node, liver, and/or lung metastases [122, 123]. Additionally, prostate cancer more commonly spreads to the calvarium and dura, which can be seen in 2–8% of patients. Calvarial metastases are usually asymptomatic but can exert mass effect on venous structures leading to increased ICP or venous infarcts [124–126]; dural metastases can mimic meningiomas or hematomas [122, 127].

Patients with clinically localized disease may be treated with a combination of radiation, androgen deprivation therapy, or bilateral orchiectomy and radical prostatectomy [128, 129]. Treatment of metastatic disease is focused on androgen deprivation therapy for castration-sensitive disease; castration-resistant disease warrants androgen inhibition with agents like abiraterone or enzalutamide alongside chemotherapy including docetaxel, cabazitaxel, and mitoxantrone [130]. As brain lesions are relatively uncommon, no systemic treatment has shown definitive efficacy.

Renal Cell Carcinoma

Renal cell carcinoma (RCC) accounts for about 1% of systemic cancers [131, 132]; clear cell carcinoma is the most common histological subtype (70–80%). Frequently seen sites of distant metastasis include the lungs, lymph nodes, liver, and bone.

BM occurs in about 3.5–17% of patients [133]. RCC brain metastases have a tendency to be hemorrhagic [134], leading to complications of intracerebral hemorrhage and extensive peritumoral edema [132, 135, 136]. Often BM can present as a solitary lesion [137].

There have been ten FDA-approved systemic therapies in the last decade for the treatment of mRCC, including agents that target vascular endothelial growth factor receptor (VEGFR), mammalian target of rapamycin (mTOR), and immune checkpoint inhibitors [138]. Of the approved VEGFR tyrosine kinase inhibitors (TKI), most have not shown promising responses for BM. One such drug, sunitinib, did not show significant efficacy in patients with BM in RCC [139]; similar results were seen with cabozantinib, which has additional targeting activity against c-MET, AXL, and RET [140]. Immunotherapy with checkpoint inhibitors has changed the face of RCC treatment; nivolumab has had objective positive responses for BM [138, 141]. A case report by Rothermundt et al. described a patient being treated with pembrolizumab, another PD-1 inhibitor, which with steroids contributed to regression of BM from renal cell carcinoma [142].

Bladder

Bladder cancer accounts for approximately 4.5% of malignancies in the United States and is the fifth leading cause of cancer and one of the most common malignancies seen in men [117]. Bladder cancer usually spreads through local invasion as well as hematogenous dissemination, usually involving the liver, lung, and bone [143, 144].

BM in bladder cancer is rare, with incidence reported as 0–7% [145]. In a study by Mahmoud-Ahmed et al., headache and motor weakness were the most common symptoms seen with bladder cancer BM [146].

Localized, non-muscle-invasive tumor can be responsive to transurethral resection and intravesical delivery of chemotherapy and immunologic therapy. For invasive tumors, adjuvant chemotherapy with cystectomy is often required. The most common chemotherapy regimen is MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin); none of these drugs cross the blood-brain barrier, potentially allowing for brain metastasis development late in the disease and/or CNS relapse [146, 147].

Testicular

Testicular cancer is the most common solid malignancy diagnosed in men less than 40 years of age but is one of the most curable solid tumors in the United States [117]. More than 95% of testicular cancer is testicular germ-cell tumor (TGCT), classified as seminomas and nonseminomatous germ-cell tumors. Seminomas usually are not aggressive and present with localized disease, while nonseminomatous germ-cell tumors carry a worse prognosis and can metastasize. TGCT are usually chemotherapy responsive, with up to 70–80% survival rates [148].

BM of TGCT is relatively uncommon, with an incidence ~1% (range of 0.4–4%) [149, 150], and usually carries a poor prognosis. The International Germ Cell Cancer Collaborative Group reported incidence of BM at the initial diagnosis of all advanced TGCT to be 10–15% and 1–2% of all TGCT cases in general [151].

For stage I seminomas, orchiectomy is usually curative; for stage II, it is dependent on lymph node involvement, so it can include radiotherapy or cisplatin-based chemotherapy. The usual regimen for nonseminomatous germ-cell tumors and more aggressive seminomas involves triple combination of bleomycin, etoposide, and cisplatin (BEP). Ginsberg et al. described that cisplatin and etoposide can cross the BBB such as in the presence of CNS tumors or previous radiation to that area, so presumably high-dose chemotherapy could work and improve outcomes in these patients [152]. In general, due to the penetration of the chemotherapy in the BBB, BM from TGCT generally is sensitive and can have survival rates of 45% but much poorer prognosis of 12% if BM and/or relapses present during or after chemotherapy [153].

Summary

In conclusion, brain metastases continue to be much more common than primary brain tumors and are a significant cause of morbidity and mortality in cancer patients. Although outcomes are improving, they are often associated with a poor prognosis, particularly because of the incomplete understanding of the various molecular mechanisms and genetic phenotypes of these metastases, making the creation of standardized therapies extremely difficult. Additionally, many systemic therapies do not cross the BBB. Although brain metastases are rare in gastrointestinal, head/neck, genitourinary, and gynecological malignancies, they remain a significant challenge. Further research into targeted therapies, immunotherapy, and better surgical and radiation techniques may improve patient outcomes in the future.

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18 Management of Solid Tumor CNS Metastases in Children

Whitney E. Parker, Shahiba Q. Ogilvie, Lily McLaughlin, and Mark M. Souweidane

Introduction and Epidemiology

Essential differences between adult and pediatric solid tumors suggest that the two ought to, in many regards, be considered distinct pathological entities. This distinction is particularly profound in the case of central nervous system (CNS) metastases. While adult solid tumor brain metastases occur in approximately 20–40% of primary tumor cases, the frequency of solid tumor brain metastases reported in children is only 1–10%, or 6–13% reported at autopsy [1–14]. In adults, CNS metastases occur most frequently in cases of lung, breast, and gastrointestinal primary tumors and melanoma [1, 15]. In contrast, the most common solid primary tumor types to present with CNS metastases in the pediatric population are sarcomas (including soft tissue, Ewing, and osteosarcoma), melanomas (up to 18% prevalence), retinoblastomas, neuroblastomas, kidney tumors [including Wilms tumors and clear cell sarcomas of the kidney (CCSK), the latter of which have been found to have a 5–11% incidence of CNS metastases], and germ cell tumors (with a particularly high rate of CNS metastases in choriocarcinoma, up to 43%), reflecting an increased representation of undifferentiated tumor types [3, 16–18]. Additionally, rare lung tumors in children have been reported to have an increased incidence of CNS metastases, including pleuropulmonary blastoma (PPB), with up to 25% incidence, and alveolar soft part sarcoma, with 15–29% incidence [6, 19, 20].

Pediatric solid tumors can enter the CNS space via one of two mechanisms—direct extension, as with sinonasal tumors, or hematogenous metastatic spread which necessitates penetrating the blood-brain barrier (BBB). Treatments for CNS metastases tend to vary based upon primary tumor type, extent of intra- and extracranial disease, and goals of care. Decreased prevalence of CNS metastases in pediatric versus adult tumors suggests a difference in the BBB—the pediatric BBB may be less permeable to tumor cells or, more likely, have increased permeability to systemic therapies used to treat the primary tumor or extracranial metastatic spread. Additionally, since tumor-instigated myeloid precursor cells are believed to play a role in metastasis, the increased tendency of children to receive myeloablative therapy for high-risk primary tumors, particularly in the neuroblastoma population,

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may contribute to a reduction in CNS spread [21–23]. Similarly to adult cases, however, pediatric solid CNS metastases are generally associated with a very poor prognosis, with survival times of typically less than 1 year after diagnosis [17].

Tumor Characteristics and Pathophysiology

The majority of pediatric solid tumor brain metastases are solitary (approximately 60–90% of cases), in contrast to adult cases where multiple CNS metastases are common. Pediatric brain metastases are supratentorial in 85–100% of cases in recently published series, in contrast to primary pediatric brain tumors which present with an infratentorial predominance [3, 4, 6, 10]. Solid brain metastases tend to most commonly be located in the cerebral hemispheres (less frequently in the cerebellum and basal ganglia), presenting at the gray matter-white matter junction, as in adults, or in border zones between major cerebral vascular territories, suggesting an arterial delivery mechanism [17, 24]. Interestingly, in our surgical experience at Memorial Sloan Kettering Cancer Center (MSKCC), we have found numerous brain metastases at the pial interface, such as at the depth of a sulcus, suggesting a possible venous or cerebrospinal fluid (CSF) mechanism of tumor cell seeding (Fig. 18.1, unpublished observations).

Although the CNS is a common site of extramedullary spread in pediatric leukemia, it is rarely seeded by solid tumors in children [6, 25]. Because the occurrence of pediatric solid tumor CNS metastases is so infrequent, surveillance imaging in children diagnosed with a primary solid tumor is not routinely performed. Thus, most CNS metastases are diagnosed from imaging in the setting of presenting symptoms such as headache, nausea, vomiting, seizures, aphasia, visual field deficits, focal motor or sensory deficits, cranial neuropathies, ataxia, and altered mental status. These symptoms reflect the location and size of the tumor, extent of edema, presence of intratumoral hemorrhage, and occurrence of obstructive or communicating hydrocephalus [3–7, 9–11, 17]. Pediatric solid tumor CNS metastases are rarely the sole or initial metastases and, when they occur, are often a late disease finding.

Multiple retrospective studies have suggested that there may be a direct correlation between the occurrence of pulmonary metastases and brain metastases, across several different primary tumor types, with up to 70% of cases having a known pulmonary metastasis at the time of brain metastatic diagnosis [2–4, 6, 9, 13, 26]. Mechanistically, it is plausible that tumor cells shed into the pulmonary circulation from a lung metastasis have a direct route to the brain via the left atrium, with a subsequent direct arterial conduit to brain circulation; this is supported

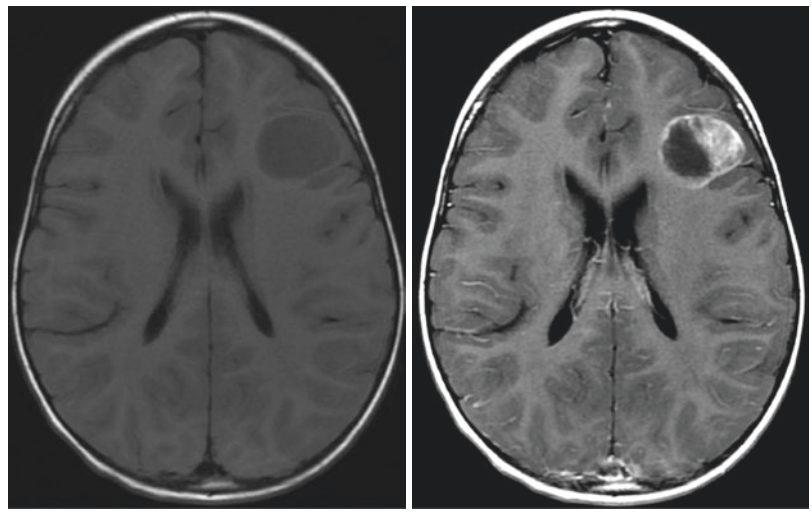

Fig. 18.1 T1-weighted MRI demonstrating a left frontal neuroblastoma metastasis at the pial interface. Pre- (left) and post-contrast (right) T1 MRI images of a neuroblastoma metastasis in a 7-year-old male patient illustrate the presence of tumor along the pial margin, a pattern commonly manifested in our cohort

by the presence of parenchymal metastases in major cerebral arterial border zones [2, 24]. Additionally, Kramer and colleagues at MSKCC found in their review of neuroblastoma cases with bone marrow involvement an association of lumbar punctures (LP) performed near the time of primary disease diagnosis with the development of CNS metastases, suggesting a possible direct hematogenous to CSF seeding mechanism [8].

Cumulatively across all histological subtypes, solid brain metastases in the pediatric population occur at a median age between 11 and 13 years and at a median interval of 8–16 months following the diagnosis of the primary tumor (Table 18.1) [2, 3, 6]. It has been suggested in multiple prior studies that the incidence of pediatric solid tumor CNS metastases is increasing [3, 6, 8]. However, the largest case series reported to date by Suki and colleagues from MD Anderson Cancer Center found that the proportion of patients with primary solid tumors developing CNS metastases remained relatively low at 1.4%, which was consistent with previously reported values from earlier studies [3]. Since pediatric CNS metastases are so rare and case studies have been limited to small cohorts, it has not yet been determined whether patients with this diagnosis have experienced an overall improvement in survival over time.

Treatment Options

Largely limited by small cohort sizes, evidence for the efficacy of different treatment regimens for pediatric solid tumor metastases remains sparse. Treatment options generally include surgical resection, radiation, chemotherapy, or primary tumor-specific immunotherapy. Brain edema can usually be managed with steroids during treatment.

Surgical Considerations

Surgical treatment depends upon multiple considerations, including tumor size, presence of hemorrhage, the type of primary tumor (specifically, whether it is radiosensitive or radioresistant), location, and neurologic symptoms. Surgical options for brain metastases can include resection, debulking (as with lesions extending into eloquent areas or deep brain structures), CSF diversion with shunting or endoscopic third ventriculostomy (ETV), or implantation of an intraventricular reservoir for therapeutic delivery. Long-term use of ventricular access reservoirs has been found to be safe—a recent study from our center reported a 4% rate of acute and relatively minor complications, including catheter migration and pericatheter cyst formation [28]. As some of these patients may develop hydrocephalus and require conversion of the intraventricular reservoir to a shunt, a programmable shunt can be implanted for both therapeutic CSF diversion and drug delivery (by increasing shunt resistance to the highest setting and thus effectively turning it "off" during the time of drug infusion).

Radiation

Radiation treatment may serve as a monotherapy or supplement surgical resection and/or systemic therapy; however, this is avoided if possible in children under 3 years of age, due to the likelihood of disruption of normal neurocognitive function during this critical period of brain development and the possibility of developing latent radiation-induced tumors such as meningiomas, gliomas, or sarcomas [29]. Whole brain radiation therapy (WBRT) remains the most common radiation treatment, delivered in fractionated doses, often totaling 10–50 Gy [2].

Stereotactic radiosurgery (SRS), however, is increasingly used and commonly preferred at our institution even for multiple metastases, offering the option of effective focal treatment while minimizing side effects, particularly in this vulnerable population. Recent studies have suggested that there is little to no survival benefit of WBRT over SRS, and in fact, that SRS alone may improve survival in select patient populations under 50 years of age and with less than four brain metastases [2, 30, 31]. This may be

Table 18.1 Case series of solid tumor CNS metastases in the pediatric population

Study reference	Institution	Primary cancer type	Years	Number of patients	Patient age at CNS diagnosis	Incidence of CNS metastases	Interval: primary diagnosis to CNS metastasis	Survival after primary diagnosis	Survival after CNS metastasis
Suki et al. [3]	MD Anderson	Mixed	1990–2012	54	11.37 years, median	1.4%	17 months, median	29 months, median	9 months, median
Wiens and Hattab [4]	Indiana University	Mixed, germ cell tumor predominance	1981–2011	26	10.6 years, median	2.2%, excluding germ cell primary tumors	18 months, median	34.8 months, median	12.5 months, median
Gobel et al. [32]	Ludwig Maximilians University (Munich, Germany)	Germ cell tumors	1982–2009	9	NR	1.1%	NR	NR	NR
Stefanowicz et al. [6]	Medical University of Gdansk (Poland)	Mixed	1992–2010	10	13.8 years, median	2%	8 months, median	NR	NR
Hauser et al. [7]	Semmelweis University (Budapest, Hungary)	Mixed	1989–2002	14	NR	3.4%	11.4 months, mean	21.9 months, mean	10.4 months, mean
Kebudi et al. [5]	Istanbul University (Turkey)	Mixed	1989–2002	16	10.5 years, median	1.45%	20 months, median	NR	2 months, median
Spunt et al. [11]	St. Jude	Germ cell tumors	1962–2002	16	NR	7.8%	NR	NR	NR
Paulino et al. [10]	University of Iowa	Sarcoma, neuroblastoma, Wilms tumor	1965–2000	30	14 years, median	4.9%	5 months, median	NR	4 months, median
Postovsky et al. [33]	Rambam Medical Center (Haifa, Israel)	Sarcoma	1990–2001	18	17.4 years, mean	4.3%	NR	NR	5.03 months, mean (death or last follow-up)

Kramer et al. [8]	MSKCC	Neuroblastoma	1980–1999	11	NR	6.3%, varying by study protocol	12.2 months, median	NR	6.7 months, median
Parasuraman et al. [34]	St. Jude	Ewing sarcoma (ES), rhabdomyosarcoma (RMS)	1962–1998	21	NR	ES: 3.3%, RMS: 2.4%	ES: 22 months, median; RMS: 12 months, median	NR	2.7 months, median
Lowis et al. [35]	UK Children's Cancer Study Group	Wilms tumor	1980–1995	7	NR	0.6%	19 months, median	NR	NR
Bouffet et al. [9]	Centre Leon Berard (Lyon, France)	Mixed	1987–1995	12	9 years, median	7.4%	15 months, median	NR	3 months, median
Rodriguez-Galindo et al. [16]	St. Jude	Melanoma	1962–1995	8	NR	18%	20 months, median	NR	5 months, median
Tasdemiroglu and Patchell [12]	University of Kentucky	Mixed	1982–1994	12	NR	7.8%, 4.5% parenchymal	327 days, mean	NR	5.2 months, mean
Weyl-Ben Arush et al. [36]	Rambam Medical Center (Haifa, Israel)	Mixed	1986–1990	6	NR	9.8%	13 months, median	NR	9.8 months, median
Marina et al. [27]	St. Jude	Osteosarcoma	1962–1989	13	NR	5.1%	3 months, median	NR	16 months, median
Baram et al. [37]	MD Anderson	Osteosarcoma	1980–1986	5	NR	5.7%	12 months, median	NR	NR
Graus et al. [13]	MSKCC	Mixed	1973–1982	31 (including postmortem diagnosis)	NR	22.3%, with 13% diagnosed at autopsy	Median ranges 8.5 months (rhabdomyosarcoma) to 22 months (osteosarcoma)	NR	NR
Vannucci and Baten [14]	MSKCC	Mixed	1951–1972	13 (including postmortem diagnosis)	NR	6%	23 months, median	NR	1 month (31.5 days), median

Characteristics of patients reported in case series of pediatric solid tumor metastases are summarized, including primary study center, dates, tumor subtype, number of patients included, average patient age, incidence of CNS metastasis, time interval between diagnosis of primary tumor and diagnosis of CNS metastasis, survival time after primary diagnosis, and survival time after CNS diagnosis. Averages are reported in each study, as either means or medians, as specified

due in part to the fact that SRS allows delivery of higher focal doses of radiation, rather than fractionated or hypofractionated doses, overcoming the radioresistance of certain primary cancer subtypes such as melanomas and sarcomas [2, 38, 39]. Importantly, SRS may be associated with fewer neurocognitive side effects than WBRT. In a Phase 3 randomized control trial comparing the outcomes of SRS alone to those of SRS plus WBRT, Chang and colleagues demonstrated decreased deficits in learning and memory in the group treated with SRS alone [40].

To date, the efficacy of SRS for metastases in the pediatric population has not been reported outside of case reports; however, this technique has been evaluated and found to be likely effective in cases of pediatric arteriovenous malformations (AVMs) and primary brain tumors, such as juvenile pilocytic astrocytomas (JPAs), recurrent ependymomas, and pineocytomas [2, 41–43]. The development of frameless, optically guided stereotactic systems has helped to overcome many of the difficulties of SRS in the pediatric population, such as intolerance of the headframe and the risk that movement could result in off-target effects, making this now a much more palatable treatment option [42].

Proton Therapy

Though not yet widely described for use in pediatric CNS metastases, proton therapy has been shown to be effective in both pediatric primary brain tumors (including astrocytic, embryonal, and ependymal tumors) and adult CNS metastases [44–46]. Characteristics of proton delivery optimize the risk-benefit profile, particularly for the pediatric population. Compared to photon therapy, protons can deposit more precisely at a desired depth in the oncologic target, reducing entry and exit doses and thus sparing surrounding normal tissues and enabling treatment of targets adjacent to critical structures [45]. Additionally, comparisons of proton therapy-treated primary pediatric CNS malignancies to historical photon beam-treated cohorts have shown non-inferiority or superiority in local control, progression-free survival, and overall survival while minimizing side effects, particularly in medulloblastoma patients receiving craniospinal irradiation (CSI) [46–50]. Given the reduction in the risk of neurocognitive deficits associated with proton therapy, it is a particularly appealing option in the susceptible pediatric population. With a favorable risk-benefit profile of proton versus photon beam therapy, proton therapy appears promising for the treatment of pediatric CNS metastases as well and will likely become more popular as a treatment option as specialized proton centers become more widespread.

Multimodal Treatment

Although pediatric solid tumor CNS metastases generally confer a grim prognosis, with survival in case studies described in months (Table 18.1), there are rare reports of long-term survivors, usually with patients who have received aggressive multimodal therapy incorporating surgical resection, radiation (often focal combined with craniospinal), chemotherapy, immunotherapy, and/or stem cell transplantation. Osawa and colleagues reported two cases of rhabdomyosarcoma achieving disease freedom at 8 and 10 months, respectively (whereas most rhabdomyosarcoma CNS cases succumb in under 1 year), through a combination of surgical resection, radiation to the tumor bed, ifosfamide/carboplatin/etoposide (ICE) chemotherapy, and additional CSI and allogenic stem cell transplantation in one of the patients [51]. Hauser and colleagues also reported a case of long-term survival of 44.8 months after CNS diagnosis in a patient undergoing surgery and receiving radiation, high-dose chemotherapy, and stem cell transplantation [7]. Notably, this was the patient in their reported cohort of 14 cases who received the most aggressive treatment regimen. Additionally, a few cases of long-term survivors with CNS osteosarcoma metastases treated with multimodal therapy have been reported to survive beyond 5 years (this disease is otherwise associated with a 6-month survival) [4, 27, 52]. Rare long-term survival with multimodal therapy has also been reported in

cases of CNS metastases from germ cell tumors, hepatoblastoma, melanoma, Wilms tumor, clear cell sarcoma of the kidney, and neuroblastoma [4, 11, 16, 53–56]. Croog and colleagues from our center demonstrated a survival advantage for CSI and intraventricular radio-immunotherapy in neuroblastoma patients with CNS relapse, postulating that neuroblastoma cells disseminate through CSF along the neuraxis, necessitating full craniospinal radiation [55]. Specifically, they advocate for simultaneous radiation of cranial and spinal fields to avoid potential reseeding and for treatment with either intrathecal or intraventricular delivery of therapeutics or systemic delivery of BBB-penetrating compounds such as irinotecan or temozolomide. With the advent of increasingly effective biological therapies for metastatic disease (such as the combination of nivolumab and ipilimumab checkpoint inhibitors), multimodal treatment options must always be considered [57].

Consideration of Prophylaxis

In contrast to the adult tumor and pediatric liquid tumor populations, pediatric solid tumors rarely develop CNS metastases, and thus, prophylaxis is generally not considered and is of unknown efficacy. Interestingly, in a comparison of Ewing sarcoma patients who received CNS prophylaxis (n = 92, WBRT and a single dose of intrathecal methotrexate) to those who did not (n = 62), Trigg and colleagues found no significant difference in the incidence of developing CNS metastases between the cohorts, suggesting prophylaxis may not be effective in preventing CNS spread, at least in this primary tumor type [58]. However, specific risk factors, such as a breach in the BBB, may render CNS prophylaxis warranted in certain cases. As mentioned, Kramer and colleagues found that prior LP in a neuroblastoma population was significantly associated with the development of CNS metastases; it may be beneficial to prophylactically treat such cases (undergoing LP for primary tumors known to have high risk of hematogenous spread and CNS seeding) with intrathecal chemotherapy [8].

Predicting the Occurrence of Pediatric CNS Metastases

While rare in incidence, pediatric solid tumor metastases tend to be associated more frequently with certain primary subtypes and metastatic disease characteristics. Certain rare primary tumors such as PPB, CCSK, and alveolar soft part sarcoma have been reported to have a higher incidence of CNS metastasis, approximately 25%, 5–11%, and 15–29%, respectively [18–20]. Additionally, although cases of choriocarcinoma comprised a small subset of their cohort, Suki and colleagues found that these were associated with a 43% incidence of brain metastases, suggesting that this germ cell subtype may have a particular predilection for the CNS [3]. Furthermore, as pulmonary metastases often predate or co-occur with CNS metastasis (as described previously), they appear to be a risk factor for CNS disease.

It remains to be determined whether there may be a role for CNS screening imaging in diagnosed pediatric solid tumor cases. This consideration remains controversial, as previous studies have found a high rate of false positives with computerized tomography (CT) imaging to survey for brain metastases in the melanoma population [59]. Risk factors such as primary tumor type (as those listed above are more neurotropic) and presence of pulmonary or other visceral metastases should be taken into account in determining whether CNS screening is warranted [16]. Although CNS metastasis has generally been considered a late-stage finding, continuing development of novel biological treatments, chemotherapies, and radiation regimens yields hope for combatting metastatic disease. With this, CNS screening should be performed for primary malignancy subtypes that have an effective systemic therapy, like melanoma [57].

Conclusions

CNS metastases in pediatric solid tumors remain a relatively rare and late-stage occurrence. This may reflect, in part, the early use of myeloablative therapy for pediatric primary

tumors, depleting the myeloid precursor pool, or an increased permeability of the pediatric BBB, thus facilitating delivery of systemic therapy into the brain. However, certain primary tumor subtypes, as well as the presence of pulmonary metastases, are associated with increased incidence of CNS pathology in the pediatric population. Previous studies have suggested that aggressive multimodal therapy may confer a survival advantage. Taken together, we propose that careful screening of select cases with risk factors for CNS metastasis, particularly in certain tumor subtypes and those with effective therapies available for metastatic disease, may enable better outcomes.

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Part III

Radiation Therapy of CNS Metastasis

Basic Radiobiology and Radiation Physics Primer

19

Emily S. Lebow, Marc R. Bussière, and Helen A. Shih

Radiobiology

The DNA-Damage Response

Radiation therapy treats cancer through damaging DNA, exerting its most potent effects through double-strand DNA breaks which are challenging to accurately repair. Cells have a complex set of mechanisms to detect and repair DNA damage collectively called the DNA-damage response [1–3]. Some types of DNA damage are more readily repairable, including damage to individual DNA bases or single-strand DNA breaks. In these cases, the opposite, intact strand of DNA serves as a template. This allows for a high-fidelity repair through processes including base excision repair, nucleotide excision repair, and mismatch repair [4]. In contrast, homologous recombination and non-homologous end joining are both utilized to repair double-strand breaks. However, these mechanisms are error-prone with potential for mutations (including deletions and translocations) that are propagated in future cellular divisions.

Radiation-induced DNA damage, particularly double-strand breaks, may be so deleterious to cellular function that cell death results. One form of cell death following radiation therapy is mitotic catastrophe, which occurs as a cell attempts to divide in the presence of significant chromosomal aberration. Cells may also activate a highly organized cell death in response to irreparable DNA damage, termed apoptosis. During apoptosis, cellular content including DNA is divided into membranous apoptotic bodies which are digested by phagocytes to prevent leakage of damaging cellular proteins. A third theory of cell death following ionizing radiation is the bystander effect, in which cancerous cells are killed due to irradiation of neighboring cells. Irradiated cells may release danger signals or other cytotoxic molecules inducing cell death of nearby cells that were not directly irradiated. Mitotic catastrophe, apoptosis, and the bystander effect may induce cell death weeks to months following irradiation [1].

Inherited mutations in the DNA-damage response are associated with a profound cancer predisposition, demonstrating the extraordinary role of DNA repair on organismal function (Table 19.1). Xeroderma pigmentosum (XP) is caused by deficient nucleotide excision repair. XP is associated with marked ultraviolet radiation sensitivity, such as to sunlight. Individuals with XP have a significant cancer risk in sun-exposed

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Table 19.1 Cancer syndromes secondary to inherited defects in DNA repair

	Genetic etiology	Functional deficiency	Cancer phenotype
Ataxia telangiectasia	*ATM*	Signal transduction	Lymphoma, breast
BRCA1 and BRCA2, DNA associated	*BRCA1*, *BRCA2*	Homologous recombination	Breast, ovarian
Hereditary non-polyposis colorectal cancer (Lynch syndrome)	*MSH2*, *MSH3*, *MSH6*	Mismatch repair deficiency	Colon, gastric, gynecologic
Li-Fraumeni syndrome	*p53*	Signal transduction	Sarcoma, breast, brain
Xeroderma pigmentosum	*XPA-XPG*	Nucleotide excision repair	Melanoma and non-melanoma skin cancer

areas, including a 10,000-fold increase in risk for non-melanoma skin cancer, 2000-fold increased risk of melanoma skin cancer, and a 3000-fold increased risk in intraoral cancers, most commonly on the tip of the tongue and the dorsal tongue [5, 6]. Inherited mutations in *BRCA1* or *BRCA2* result in impaired homologous recombination and confer an increased risk of breast, uterus, ovarian, fallopian tube, prostate, and pancreatic cancers [7, 8]. Hereditary non-polyposis colorectal cancer (Lynch syndrome) is caused by deficient mismatch repair and confers a predisposition to colorectal, gastric, endometrial, and ovarian cancers [9]. Inherited mutations in *p53* and *ATM*, both critical components of signal transduction, cell cycle regulation, and promoting conditions for repair of DNA and other cellular damage, also result in hereditary cancer predispositions [10–12].

It is hypothesized that robust DNA repair capacity also confers resistance to the effects of ionizing radiation, providing a potential explanation for why some cancer subpopulations are more radioresistant. High-grade gliomas are aggressive tumors that have a propensity to recur even with adjuvant radiation therapy [13]. Recurrence is hypothesized to be secondary to subpopulations of glioma stem cells in which cell cycle checkpoints are readily activated following radiation-induced DNA damage, halting division, creating an effective DNA repair, and conferring a net relative resistance to radiation therapy. In contrast, glioma cells with less robust pathways supporting DNA repair are more likely to undergo apoptosis in the setting of radiation-induced DNA damage [14]. While there are likely a complex set of mechanisms contributing to a radioresistant phenotype, evidence suggests that DNA damage repair is an important component to this phenomenon.

Tumor Hypoxia

Tumor hypoxia is a common feature of solid tumors. Rapidly proliferating tumors frequently outgrow their neovascular supply, which tends to be chaotic and poorly developed. The result is a state of diffusion-limited chronic hypoxia in which some cells are too far away from the vasculature to be adequately oxygenated. Hypoxia may also develop acutely, as blood vessels are temporarily obstructed or have variable blood flow, resulting in perfusion-limited hypoxia [15]. Tumor hypoxia is associated with radioresistance, requiring up to three times the dose of radiation to achieve the equivalent cell-killing effect. Hypoxic radioresistance is due to inefficient production of reactive oxygen species, a dominant mechanism of radiation-induced DNA damage. Furthermore, in response to a hypoxic microenvironment, cells activate hypoxia-inducible transcription factors to promote anaerobic metabolism, invasion, and angiogenesis. These changes result in a more aggressive and radioresistant phenotype [16]. Hypoxia within solid tumors is heterogeneous, with some areas of the tumor well oxygenated (e.g., cells near the blood vessels) and others hypoxic. Hypoxic niches within solid tumors support radioresistant cancer stem

cells that can repopulate the tumor following irradiation, accounting for local recurrence after treatment [17].

When the total dose of radiation is divided into many smaller doses delivered over days or weeks (termed fractionation), oxygenation may be improved, thereby increasing the efficacy of radiation therapy. Reoxygenation between fractions of radiation therapy may occur quickly via reperfusion through vessels that were temporarily closed, reoxygenating the tumor within minutes. Reoxygenation may also occur over days or weeks as tumor cells die secondary to effects of radiation therapy, thereby shrinking the size of the tumor and decreasing the distance between blood vessels and surviving tumor cells. These mechanisms of reoxygenation provide a fundamental rationale for fractionating radiation delivery.

Cell Cycle and Redistribution

The cell cycle is comprised of a series of phases as it goes through its process of growth, replication, and division to produce two daughter cells. Radiosensitivity varies depending on the phase of the cell cycle. Cells during the phases of mitosis and G2 (the gap immediately prior to mitosis) are more radiosensitive. In contrast, cells during S phase (DNA duplication) are more radioresistant. Tumor cells grow in an asynchronous manner, present at various phases of the cell cycle at any point in time. The first few fractions of a course of radiation therapy will preferentially kill cells in the radiosensitive phases (mitosis and G2) while killing fewer cells in radioresistant phases (S phase). However, surviving cells will continue to transition through the cell cycle and will redistribute to more sensitive phases of the cell cycle during subsequent fractions of a course of radiation therapy. Cells in the S phase during the first fraction of radiation therapy may transition to the G2 or M phase for a subsequent fraction, thereby becoming more sensitive to the effects of ionizing radiation. As a result, fractionated radiation therapy is considered to be more effective than delivery of a single, large dose in some circumstances [1].

Accelerated Repopulation

Accelerated repopulation is an important source of treatment failure following radiation therapy. During the course of fractionated radiation therapy, surviving tumor cells may proliferate, replacing tumor cells already killed by radiation therapy. The rate of tumor cell repopulation accelerates during the course of radiation therapy, with growth occurring increasingly quickly after the start of radiation therapy. Accelerated repopulation has been observed in several types of malignancy, including head and neck squamous cell carcinoma, cervical cancer, and bladder cancer [18]. Because of accelerated repopulation, prolonging overall treatment time results in a larger number of tumor cells that need to be eradicated to achieve local control. This necessitates a higher total dose of radiation therapy. One method to counter the effects of repopulation is accelerated radiotherapy, where radiation is delivered over fewer days giving tumor cells less time to repopulate. However, this strategy also reduces the opportunity for normal tissue repair from radiation injury, thereby increasing risk of toxicity of treatment. It also leaves less opportunity for tumor cell reoxygenation and transition through the phases of the cell cycle, both of which increase radiosensitivity.

Radiosensitizers

Radiosensitizing drugs decrease the proportion of cells that survive after radiation therapy (Fig. 19.1). There are multiple mechanisms by which classes of systemic therapies increase the efficacy of radiation therapy. Many classes of systemic therapies may do so through more than one mechanism (Tables 19.2 and 19.3). Antimetabolites increase radiation-associated DNA damage by incorporating itself into the cell's DNA and by inhibiting DNA repair processes, thereby making the cell more susceptible to DNA damage [19]. The antimetabolite 5-fluorouracil blocks the synthesis of the pyrimidine thymidine (a nucleoside required for DNA

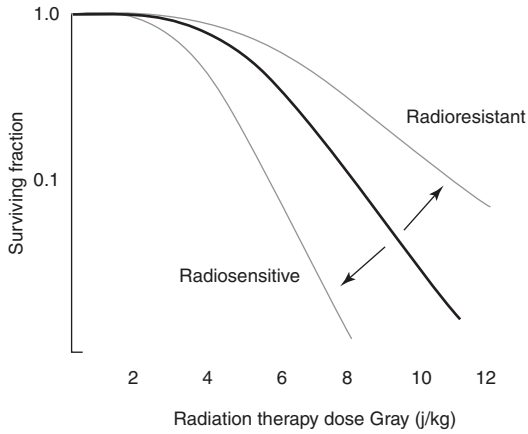

Fig. 19.1 Radiosensitization decreases the proportion of surviving cells for any given dose of radiation therapy resulting in a leftward shift of the curve. Radioresistance, in contrast, results in a greater proportion of surviving cells for any given dose of radiation, resulting in a rightward shift of the curve. Many factors are known to impact sensitivity or resistance of cells to radiation therapy, including radiosensitizing drugs, hypoxia in the tumor microenvironment, cell cycle phase, and DNA repair capacity

Table 19.2 Classes of systemic therapy

	Selected examples
Antimetabolites	5-Fluorouracil
	Gemcitabine
	Pemetrexed
Alkylators	Cyclophosphamide
	Temozolomide
Platinum agents	Cisplatin
	Carboplatin
Microtubule stabilizers	Vincristine
	Docetaxel
Topoisomerase inhibitors	Etoposide
	Doxorubicin
Molecularly targeted agents	Bevacizumab (VEGF)
	Trastuzumab (HER2-neu)
	Gefitinib (EGFR)
Immunotherapeutic checkpoint inhibitors	Pembrolizumab (PD-1)
	Nivolumab (PD-1)
	Ipilimumab (CTLA-4)

replication) through inhibition of thymidylate synthase. Without thymidine, DNA replication or repair from radiation-associated damage is impaired and preferentially affects cancer cells that are actively dividing and thus preferentially undergo cell death. The addition of 5-fluorouracil to radiation therapy has been demonstrated to improve survival in squamous cell carcinoma of the head and neck compared to radiation therapy alone [20].

Table 19.3 Mechanisms of drug-radiation interactions

Mechanism	Selected examples
Increased radiation-associated DNA damage and/or impaired DNA repair	Antimetabolites, alkylators, platinum agents, topoisomerase inhibitors
Redistribution of cells to more radiosensitive phases of the cell cycle	Antimetabolites, topoisomerase inhibitors
Cytostatic agents that reduce accelerated repopulation after radiation therapy	Molecularly targeted agents, most classical chemotherapy
Tumor microvasculature normalization that reduces hypoxia-associated radioresistance	VEGF-targeted agents
Release of immunogenic tumor antigens, induction of pro-inflammatory signaling pathways	Immune checkpoint inhibitors

Temozolomide is an alkylating agent with greater efficacy in the subset of glioblastoma patients with epigenetic silencing of O-6-methylguanine-DNA methyltransferase (*MGMT*), a gene critical in DNA repair. A randomized controlled trial demonstrated that the addition of temozolomide to radiation therapy preferentially improved survival among glioblastoma patients with *MGMT* silencing versus patients without *MGMT* silencing (21.7 months versus 15.3 months, $p = 0.007$). The *MGMT* protein removes temozolomide-induced methyl groups from the DNA base guanine to prevent errors during DNA transcription and replication. *MGMT* promoter methylation causes *MGMT* silencing, and those tumors harboring *MGMT* promoter hypermethylation are thus more sensitive to the effects of concurrent radiation therapy and temozolomide [21, 22].

There are several additional mechanisms of radiosensitizing drugs. Any therapy that slows or halts proliferation of cancer cells will mitigate accelerated repopulation of tumors associated with radiation therapy [19]. This includes many classes of systemic therapy, including molecularly

targeted agents. VEGF-targeted systemic therapy normalizes chaotic, tortuous, and dilated tumor neovasculature. This process of vascular normalization improves tumor oxygenation, thereby reducing hypoxic radioresistance [23]. Interaction between radiation therapy and enhancement of the immune system is an area of active investigation, with some successful approaches either enhancing tumor cell recognition by increased release of tumor-associated antigens and other approaches enhancing pro-inflammatory signals [24].

Normal Tissue Side Effects

The goal of radiation therapy is to deliver highly conformal radiation that maximizes dose delivered to the tumor while minimizing toxicity to normal tissues. Modern advances in radiation therapy have resulted in significant strides toward achieving this objective. Nonetheless, a number of early and late radiation-related toxicities are still commonly observed in patients treated with radiation therapy.

Early radiation effects occur during or within weeks of radiation therapy in highly proliferative tissues and are likely to be reversible. Proliferative tissues have a precise balance between cell loss and cell production. Radiation impairs cell division while accelerating the rate of cell loss, disrupting this equilibrium. Examples of common early toxicities include mucositis of the upper and lower gastrointestinal tracts, bone marrow hypoplasia, and hair loss. With cessation of radiation treatment, the balance between cell replication and cell loss is eventually restored. Tissues heal and return to essentially normal function with few or no long-term sequelae of treatment.

Late radiation effects, in contrast, occur within months or years of radiation therapy and tend to be permanent and progressive. Historically late radiation effects were thought to occur secondary to functional deficiency caused by depletion of organ parenchymal cells, called the target-cell hypothesis [25]. However, more recent understandings of late toxicity incorporate complex interactions between organ parenchymal cells, fibroblasts, vascular endothelial cells, and macrophages. Ionizing radiation induces pro-fibrosis signaling and growth factor cascades (such as TGFβ) that result in progressive deposition of extracellular matrix and collagen. Fibrosis is associated with organ loss of function (such as bowel malabsorption) as well as other symptoms such as pain, neuropathy, decreased strength, and reduced joint range of motion. Higher radiation doses decrease the latency between irradiation and the onset of late toxicity [1].

Radiation exposure also harbors a low but real risk of developing a secondary primary cancer, a distinct type of late adverse effect. Ionizing radiation can cause genomic instability or the acquisition of a mutator phenotype through mutations in genes critical for efficient and high-fidelity DNA replication and repair. As a result, cells will more readily acquire additional mutations that are oncogenic and may result in transformation to a malignancy [26]. The risk of secondary malignancy is inversely related to the age at treatment, with patients treated in childhood at the highest risk of secondary malignancy. For example, children treated with cranial irradiation have between an 8.1 and 52.3 times higher risk of developing subsequent central nervous system malignancies compared to the general populations [27]. There are other risk-modifying factors as well, including the site of irradiation, the size of the radiation field, radiation dose, systemic therapy, and environmental exposures, such as cigarette smoking [28].

Radiation Physics

Ionizing Radiation

Therapeutic radiation therapy takes advantage of the portion of the electromagnetic spectrum with sufficient energy capable of creating ionizations. Radiowaves and microwaves represent low energy, whereas visible light represents mid-energy range of the electromagnetic spectrum. X-rays are in the high-energy range of the electromagnetic spectrum and are capable of ejecting orbital electrons and thereby creating

highly reactive oxygen species which can damage DNA. This form of electromagnetic radiation – high-energy X-rays that are capable of ionizing atoms – is utilized in therapeutic radiation. The dose of radiation used to treat cancer is measured in Gray, representing the energy deposited by ionizing radiation per unit mass of the material [29].

Linear energy transfer (LET) describes the amount of energy that is transferred from an energy source to another material, measured by the amount of ionizations created. LET depends on the radiation source. Photons and protons produce few ionizations and are low LET, whereas neutrons and carbon are examples of radiation with high-density ionizations and are high LET. In general, high-LET radiation is more biologically effective (produces more DNA damage) per dose of radiation than low-LET radiation. This concept is quantified by relative biological effectiveness (RBE). As LET increases, RBE also increases in a nonlinear manner until reaching a maximum (at approximately 100 keV/μm) after which point RBE decreases with increasing LET. Photons produced by cobalt-60 are considered to have a low LET and are an established reference with an RBE of 1. Protons have an RBE of 1.1. Thus, for a given dose of radiation, protons have a 10% greater biological effect than photons. In fact, this is an oversimplification as the RBE of protons and all other particle beam profiles is variable, but the estimation of 1.1 is the currently accepted convention until its effects are better understood. However, the net effect of radiation includes the fractionation (how many sessions the radiation course is delivered in and the dose given with each treatment) and the intrinsic tumor radiosensitivity [30].

Photon Radiation

Photons are the most common source of radiation therapy utilized for treatment of cancer. In the setting of radiation therapy, photons interact with matter predominantly via the Compton effect. As a high-energy photon travels though matter, it eventually collides with an orbital electron. The collision ejects an electron from its atomic orbit, thereby leaving behind an ion (an atom with a net positive electric charge, from which the designated ionizing radiation originates). The photon, now decreased in energy, scatters and continues to travel through the material along an altered pathway. The ejected electron gains energy from its collision with the photon. Cells are mostly comprised of water, and therefore photons are most likely to interact with water molecules and produce reactive oxygen species, most importantly the hydroxyl radical. Reactive oxygen species are highly electron-affinic and damage nearby DNA, producing DNA base damage, single-strand breaks, and double-strand breaks. As previously discussed, the double-strand break is most difficult to repair and deleterious to cellular function.

There are two primary sources of photons utilized for radiation therapy: radioactive decay and linear acceleration. Radioactive decay is the process by which elements with unstable nuclei emit energy, thereby increasing their nuclear stability. Cobalt-60 has been a key source of therapeutic radiation for many decades. Cobalt-60 undergoes beta decay to produce high-energy photons called gamma rays, in the process becoming Nickel-60. Linear accelerators are now the most common source of high-energy photons. Linear accelerators use microwaves to accelerate electrons that collide with a heavy metal target to produce high-energy X-rays, interchangeably called photons. This process is called *bremsstrahlung*, "braking radiation" or "decelerating radiation," since the photon is produced by the braking or deceleration of a high-energy electron as it collides with a heavy metal nucleus. The kinetic energy of the electron is converted into radiation in the form of a high-energy X-ray. The only difference between the X-ray and gamma ray is the means of production, with gamma rays produced from radioactive isotope decay and X-rays produced from electron collisions. All photon beams, whether gamma rays produced from radioactive decay or X-rays produced from a man-machine, must be precisely regulated for clinical use to deliver a desired dose to a desired target [29].

As photons move through the patient, energy is deposited in a characteristic pattern called a depth-dose curve (Fig. 19.2). Within the first few

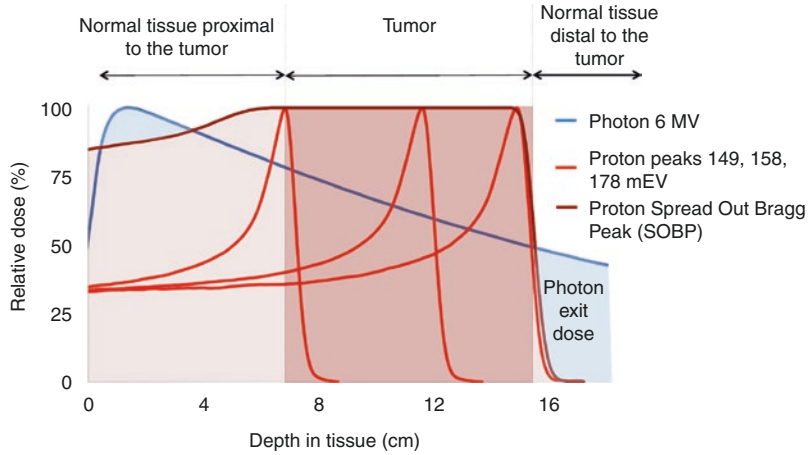

Fig. 19.2 Comparison of relative depth-dose distribution of photons versus protons. The blue line demonstrates the photon's deposition of energy as a function of depth. After entering the patient, photon dose deposition increases and peaks and then steadily decreases. Because photons deposit energy during its entire pathway, tissue both proximal to tumor and distal is exposed to relatively high radiation dose. The red lines demonstrate three examples of proton dose deposition. Protons also deposit energy during the entire pathway, but travel only a finite distance and rapidly increase in dose deposition near its end of range, reaching a maximum dose transfer at the Bragg peak followed by an extremely rapid drop-off in energy. Multiple proton beams are summed together to form the spread-out Bragg peak (SOBP) to provide coverage to the entire depth of the tumor

millimeters of entering the patient, photon dose deposition increases and peaks and then steadily decreases in energy deposition until exiting the body. Because photons deposit energy during their entire pathway through the body, tissue both proximal to the treatment target and distal to the target inevitably receives some radiation dose. The shape of the depth-dose curve is dependent on the photon energy. Higher-energy photons more effectively spare the skin but have less attenuation of dose deposition after passing through the target, increasing the dose deposition distal to the target. Despite advances in radiation delivery techniques that allow high-precision targeting of the intended volume, dose deposition distal to the target is a physical limitation of the photon beam. This dose to nontarget tissue contributes to radiation-associated toxicities [31].

Proton Radiation

Proton radiation consists of hydrogen atoms (composed of one proton and one electron) stripped of their electron. Most common proton accelerators are cyclotrons or synchrotrons which accelerate protons to therapeutic energy levels using magnetic fields [11]. Protons have a distinct pattern of energy deposition as they travel through tissue. Protons enter tissue with a high energy but relative low dose deposition. Protons decelerate quickly and eventually stop. Just before reaching its end of range, the proton beam transfers the great bolus of dose known as the Bragg peak and then abruptly stops. By modulating the energy of protons, a spread-out Bragg peak (SOBP) can be generated to treat a range of depths. Relative to photons, protons offer the advantage of decreased dose to both proximal and distal normal tissues within a given beam, offering a theoretic advantage of reduced toxicity including risk of secondary malignancy. Dose reduction to normal adjacent tumor also allows for dose escalation to the tumor, potentially improving disease control [31].

The dosimetric superiority of proton therapy relative to photon therapy is well-established, but whether there is also a clinical benefit is only widely recognized in a few conditions and otherwise largely remains an area of active inquiry for most types of benign and malignant diagnoses. Widely recognized uses of proton therapy include many childhood malignancies such as medulloblastoma, ependymoma, craniopharyngioma, and

rhabdomyosarcoma. Because many of these pediatric diseases are highly curable, these children are particularly susceptible to late effects of radiation therapy that may develop over many decades such as secondary malignancy, endocrinopathy, and cognitive dysfunction. Several studies suggest a decreased risk of secondary malignancy among children treated with proton radiation compared with photon radiation [32, 33]. Proton therapy is also commonly utilized for ocular melanoma, skull base malignancies, and sinonasal malignancies. In contrast, the uncertain benefit of proton therapy for other disease sites remains an area of active investigation, including for prostate cancer (NCT01617161, NCT01352429) and breast cancer (NCT02603341).

The primary disadvantage of proton radiation therapy is the high cost and complexity of construction and operating a proton facility, which have historically limited the availability of proton therapy. As technology has advanced, more cost-effective and user-friendly facilities have been designed; approximately 30 proton centers are operational in the United States alone in 2018, and this number is actively increasing. The historically limited availability of proton therapy has led to several important attempts to best ration this resource. Considerations include the degree of dosimetric and clinical benefit of proton therapy (versus the next best option, typically photon therapy), patient age (prioritization for pediatric patients), resource equity (no penalty for lifestyle-associated cancers), advancement of medical research (treat patients on research protocols), and the financial reality of operational cost and thus ability to pay [34, 35].

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Role of Whole-Brain Radiotherapy

20

Connor Lynch, Jeffrey P. Gross, and Vinai Gondi

Introduction

Whole-brain radiotherapy (WBRT) has been integral to the management of brain metastases for several decades. Early studies demonstrated the efficacy of WBRT in relieving neurologic symptoms related to intracranial disease and improving survival for patients with brain metastases. However, concerns over cognitive side effects with conventional WBRT and improvements in local treatment techniques have led to a shifting dynamic in how and when WBRT is used [1]. As a result, focal therapies involving stereotactic radiosurgery (SRS) with or without surgical resection have been increasingly used as an alternative to conventional WBRT in patients with limited brain metastases at a cost of increased risk of distant brain relapse and use of salvage therapies. Subsequent trials demonstrating cognitive preservation using neuroprotective strategies of prophylactic memantine and hippocampal avoidance have led to efforts seeking to redefine the role of WBRT, especially since prior trials comparing cognitive outcomes between focal therapy and WBRT did not include these neuroprotective strategies and no longer apply in the modern WBRT era.

In recent years, multiple attempts have been made to optimize the efficacy of WBRT. The most common dose prescription for WBRT is 30 Gy in 10 fractions, though other dosing regimens have been studied without proven superiority. The use of systemic agents during and following WBRT has also been studied extensively. Although enthusiasm for radiosensitizers was sparked by studies of motexafin gadolinium showing benefits in non-small cell lung cancer, other radiosensitizers have failed to show added value. The use of targeted agents and immune checkpoint inhibitors with WBRT remain areas of active study.

Radiation-related toxicity secondary to conventional WBRT manifests as early, early-delayed, and late delayed forms, with the last one being the most permanent. This toxicity ranges from mild cognitive impairment to rarely dementia and can be a concern for patients and clinicians alike. However, practice-changing clinical trials have demonstrated that prophylactic memantine, combined with minimal radiation

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dose to the hippocampal neural stem cell compartment (hippocampal avoidance), prevents cognitive toxicity in patients undergoing WBRT. This chapter traces the course of the research that established the use of WBRT and discusses the evolving role and delivery of WBRT in contemporaneous management of brain metastases. In order to improve care for patients requiring WBRT, knowledge of the optimal candidates for WBRT and techniques for safer delivery of WBRT are important.

The efficacy of WBRT was noted as early as 1954 when Chao et al. published a case series of 38 patients with symptomatic brain metastases treated with two opposed lateral x-ray fields targeting the whole brain. Chao started with doses of 0.5 Gray (Gy) per fraction and eventually increased to 4 Gy per fraction to deliver total dose up to 35 or 40 Gy. Of these patients, 63% experienced improvement of a variety of symptoms related to tumor shrinkage in the brain. Incontinence, aphasias, and hemiplegia improved or resolved in many of these patients. At least one returned to work and another was able to play the piano again [2]. While limited in many respects, this foundational study was the largest series to date demonstrating the palliative benefit of WBRT and prompted further study to define the role of WBRT. In 1980, Borgelt et al. published the results of two phase III trials—Radiation Therapy Oncology Group (RTOG) 6901 and 7361—demonstrating symptomatic improvement in 43–64% of patients with brain metastases at 2 weeks following WBRT, and noted a threefold increase in median survival time compared to standard supportive care (3–6 months vs 1–2 months). These studies evaluated five different dose schedules ranging from hypofractionated regimens (e.g., 10 Gy in one fraction or 12 Gy in two fractions) to more conventional schedules of 20–40 Gy in 5 to 20 fractions. They did not identify significant differences in outcomes between the different dose schedules [3].

More contemporary studies have confirmed these findings as well. RTOG 9104 assessed 1-year survival and acute toxicity in patients receiving either accelerated fractionation (30 Gy at 3 Gy daily) or accelerated hyperfractionation (54.4 Gy at 1.6 Gy BID). The authors found no difference in survival or toxicity between the two groups [4]. Rades and colleagues retrospectively compared 30 Gy in 10 fractions to either 40 Gy in 20 fractions or 45 Gy in 15 fractions. The alternative dose-escalated schedules did not significantly improve survival or local control [5]. Neider and colleagues demonstrated a 25% complete and 39% partial radiographic response at 3 months after WBRT with 30 Gy in 10 fractions. Radiographic response was associated with improved survival across multiple cancer histologies [6, 7]. Likewise, tumor shrinkage in those with favorable response following WBRT was associated with preserved neurocognitive function relative to those with poor response in both mini mental status exam and specific tests of executive function and fine-motor skills [8, 9].

These seminal studies established WBRT as the standard of care for management of brain metastases and support 30 Gy in 10 fractions as the most standard regimen. More recently, concerns over the neurocognitive sequelae of WBRT have prompted a reevaluation of the technique. Recognizing the connection between memory formation and the production of neural progenitor cells (NPCs) in the subgranular zone (SGZ) of the hippocampal dentate gyrus, a technique was devised that would avoid this highly radiosensitive region [10]. Termed hippocampal avoidance (HA), results from a single-arm phase II trial and subsequently a randomized phase III trial combining this strategy with the neuroprotective agent memantine (NRG-Oncology CC001) showed significant prevention of cognitive toxicity and better preservation of patient-reported quality of life (QoL) [11, 12]. Prior research comparing WBRT to focal therapy modalities, particularly SRS, does not account for these neuroprotective strategies, which is crucial to bear in mind when considering the differences in cognitive toxicity between WBRT and SRS presented below. Though SRS is considered to have a more favorable side effect profile, future trials are being designed to reevaluate this in light of these trials' practice-changing findings.

Conventional Whole-Brain Radiotherapy

Approach

Conventional WBRT is administered through parallel-opposed lateral portals. The inferior field border should be inferior to the cribriform plate, the middle cranial fossa, and the foramen magnum, all of which should be distinguishable on simulation or portal localization radiographs (Fig. 20.1). The safety margin depends on penumbra width, head fixation, and anatomic factors, but should be at least 1 cm, even under optimal conditions. A special problem arises anteriorly because sparing of the ocular lenses and lacrimal glands may require blocking with <5-mm margins at the cribriform plate.

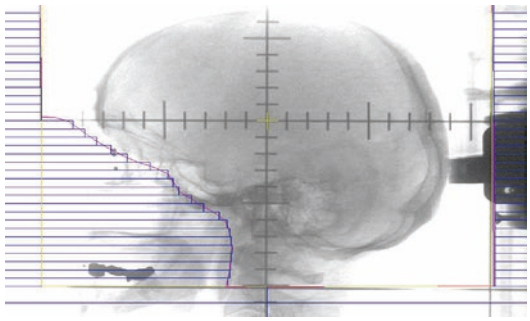

Fig. 20.1 Lateral portal of conventional whole-brain radiotherapy (WBRT) treatment. Conventional WBRT is administered through parallel-opposed lateral portals. The inferior field border should be inferior to the cribriform plate, the middle cranial fossa, and the foramen magnum

The anterior border of the field should be approximately 3 cm posterior to the ipsilateral eyelid for the diverging beam to exclude the contralateral lens. However, this results in only approximately 40% of the prescribed dose to the posterior eye. A better alternative is to angle the beam approximately 3 degrees or more (100- or 80-cm source-to-axis distance midline, but also field size dependent) against the frontal plane so that the anterior beam border traverses posterior to the lenses (approximately 2 cm posterior to eyelid markers). Placing a radiopaque marker on both lateral canthi and aligning the markers permits individualization in terms of the couch angle. This arrangement provides full dose to the posterior eyes. However, the eyelid-to-lens and -retina topography is individually more constant than the canthus, and lateral beam eye shielding is better individualized with the aid of computed tomography (CT) or magnetic resonance imaging (MRI) scans. When in doubt about tumor coverage or lens sparing for tumors in a subfrontal or middle cranial fossa location, CT-based contouring and planning should be considered (Fig. 20.2a).

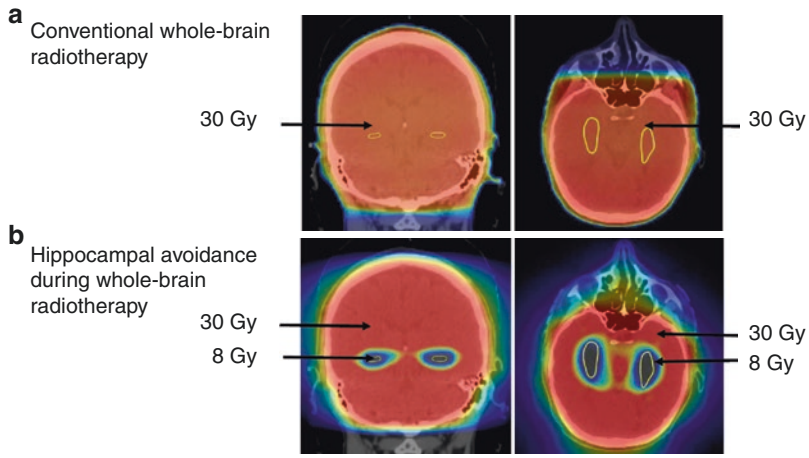

Fig. 20.2 Comparison of treatment plans between (**a**) conventional whole-brain radiotherapy (WBRT) and (**b**) hippocampal avoidant WBRT. Hippocampal avoidance using intensity-modulated radiotherapy during WBRT achieves several-fold reduction in radiation dose to hippocampi (yellow). (Adapted with permission from Brown et al. [12])

Acute, Early-Delayed, and Late-Delayed Complications

Toxicity following conventional WBRT may be categorized as acute, early-delayed, or late-delayed depending on the time of presentation. Acute effects of radiation manifest during the course of treatment or shortly after completion. Common complications include those associated with increased intracranial pressure such as headache, fatigue, nausea, and dizziness. These side effects may be due to interruption of the blood-brain barrier and the development of cerebral edema immediately following radiation exposure. These symptoms generally respond well to corticosteroids [13]. Patients may also acutely experience mild, self-limited dermatitis, and hair loss. Early-delayed toxicity appears weeks to months following treatment and is thought to arise due to transient demyelination. It manifests as weakness, headache, and fatigue [13]. Additional non-neurological side effects include serous otitis media, dry sinuses, and lacrimal gland dysfunction. Lhermitte's sign may be present in some of these patients, identified as the sensation of a shock spreading down the neck and upper limbs with flexion of the neck. Radiation somnolence syndrome is a rare early-delayed complication of central nervous system (CNS) radiation characterized by extreme somnolence accompanied by anorexia, apathy, and headache. The syndrome is commonly associated with prophylactic cranial irradiation in pediatric patients with acute lymphocytic leukemia, but has been described in adult patients undergoing radiation therapy for primary CNS tumors. Management and prevention involve administering corticosteroids during radiation treatment [14].

Late-delayed toxicities appear beginning at 6 months after radiation but can present many years later. They are often the most debilitating and the least likely to improve with time. Permanent neurocognitive dysfunction following conventional WBRT ranges from mild impairment in most cases to severe dementia in rare cases (<5%) [13]. For instance, in the previously mentioned NCCTG N107C/CEC.3, which assessed the impact of adjuvant WBRT after SRS, deterioration of immediate memory, delayed memory, processing speed, and executive function were associated with conventional WBRT [15]. Radiation necrosis is another late complication of WBRT. Necrosis may result in mass-effect-related symptoms that make these lesions difficult to distinguish from tumor recurrence. These lesions can require surgical intervention if unresponsive to corticosteroids. Radiation-related leukoencephalopathy is seen in rare cases and results in severe dementia and cortical atrophy. Higher per-fraction doses (in excess of 3.5 Gy) have been associated with greater risk of radiation-related leukoencephalopathy [16]. The capacity of neuroprotective strategies including prophylactic memantine and hippocampal avoidance during modern WBRT to prevent radiation-related leukoencephalopathy remains unclear.

The Evolving Role of Conventional WBRT

Omission of WBRT

In poor performance status patients with limited survival, there is better understanding regarding the benefit of WBRT versus modern best supportive care. The Quality of Life after Treatment for Brain Metastases (QUARTZ) trial was designed in part to address this question, randomizing 538 patients with non-small cell lung cancer (NSCLC) to either WBRT with optimal supportive care or supportive care alone. Eligible patients had brain metastases that were not amenable to stereotactic radiosurgery or resection. Using quality-adjusted life-years as the primary outcome measure, the trial found that omitting WBRT resulted in a loss of 4.7 days (in terms of QALYs). Overall survival time was also diminished by less than a week for those receiving supportive care alone when compared to those receiving WBRT [17]. While this study is commonly used to dismiss the use of WBRT in the palliative setting, it is important to avoid overgeneralizing the results. First, clinicians were encouraged to recruit patients into the trial if they had doubts regarding the benefit of

WBRT. The median survival on this study was 8–9 weeks, highlighting an extremely unfavorable cohort of patients in both groups. Symptomatic benefit from tumor regression may take 3–6 months; therefore it is not surprising that there was no difference in quality of life for patients undergoing WBRT on this study. Furthermore, subgroup analysis did demonstrate a significant survival benefit to WBRT for patients younger than 60, with a non-significant trend in favor of WBRT observed for patients of better prognosis as measured by recursive partitioning analysis (RPA) and disease-specific generalized prognostic assessment (ds-GPA) scores. Finally, relative to this study, brain metastases may be associated with a better median survival with the emergence of immunotherapy or other systemic therapies or with other types of cancer. Thus, while the QUARTZ trial demonstrated that NSCLC patients with poor prognosis might not benefit from WBRT, those with a better prognosis or a better performance status may experience survival and/or quality-of-life improvements with WBRT. To aid in decision making, Sperduto and colleagues have developed prognostic systems to provide survival time estimates for patients with brain metastases [18]. However, for patients who develop brain metastases in the setting of systemic progression and are not planned for further systemic therapy due to poor performance status and/or limited prognosis, the QUARTZ trial provides a rationale for omission of WBRT to manage the brain metastases.

Conventional WBRT Following Stereotactic Radiosurgery

Stereotactic radiosurgery (SRS) offers the ability to deliver targeted, high doses of radiation to discrete foci of metastatic disease within the brain. The hypothesis that SRS followed by adjuvant WBRT for patients with limited brain metastases could achieve superior intracranial control and survival has been tested in multiple phase-III randomized controlled trials (RCTs). Prospective studies conducted by the Japanese Radiation Oncology Study Group (JROSG 99–1) [19], MD Anderson Cancer Center [20], and the European Organization for Research and Treatment of Cancer (EORTC 22852-26,001) [21] demonstrated that adding WBRT does indeed improve intracranial disease control, resulting in a significant reduction in the absolute risk of new brain metastases by between 18% and 22% at 1 year and by 15% at 2 years. Recurrence rates at local sites were also reduced. Notably, the EORTC and MD Anderson studies found reduced quality of life and reduced Hopkins Verbal Learning Test-Revised (HVLT-R) scores, respectively, with the addition of WBRT. In addition, contrary to expectations, the MD Anderson trial identified a survival difference in patients managed with SRS alone, who experienced a median survival time of 15.2 months compared to 5.7 months in patients receiving combination therapy. The differences in survival could have in part contributed to the differences in neurocognition and quality of life observed between the arms [20]. To address these conflicting data on overall survival, Sahgal et al. (2013) analyzed individual patient data from these trials and identified patient age as a significant effect modifier. After stratifying by age, they found that SRS alone was associated with favorable survival outcomes in patients younger than 50 years old, although the majority of this difference was driven by the MD Anderson trial. For patients older than 50, there was no difference between SRS alone and SRS with WBRT. This meta-analysis also identified higher rates of salvage treatment in the SRS alone arm, highlighting the need for regular imaging follow-up with SRS alone [22].

Alliance trial N0574 assessed the impact of adjuvant WBRT after SRS on quality of life, functional independence, and radiation-related cognitive dysfunction at 3 months using a battery of standardized cognitive tests to assess learning, memory, fine motor control, verbal fluency, processing speed, and executive function. Cognitive deterioration—defined as decline greater than 1 standard deviation (SD) below baseline in any of these cognitive domains at 3 months—was more frequent with SRS and adjuvant WBRT compared with SRS alone (91.7% vs. 63.5%, $P < 0.001$). Specifically, patients receiving combined therapy were more likely to experience impairments in immediate memory, delayed

memory, and verbal fluency than those receiving SRS alone. Quality of life was significantly better with SRS alone and functional independence was the same between arms. Overall survival was not different between groups despite the improved intracranial control of combined therapy [23].

Conventional WBRT Following Surgical Resection

Upfront surgery for large or symptomatic brain metastases is associated with survival benefits. However, multiple studies have demonstrated that the rate of local recurrence following MRI-confirmed gross total resection of brain metastases without adjuvant therapy is around 50% [21, 24, 25]. Two large RCTs, a multi-center study published by Patchell et al. in 1998 and EORTC 22952-26001, have investigated the use of surgery with adjuvant WBRT versus surgery alone. Both studies demonstrated a statistically significant improvement in local control, reduction in the incidence of distant brain metastases, and reduced incidence of neurologic death with the addition of adjuvant WBRT [21, 24]. However, these studies did not find a significant difference in survival for adjuvant WBRT over observation following surgery, though they were not powered to do so.

Stereotactic radiosurgery has been shown to improve local control following surgical resection while minimizing the potential for neurocognitive toxicity. A phase III trial of postoperative SRS compared to observation (MD Anderson Cancer Center 2009-0381) demonstrated improved surgical bed control with SRS compared to observation (12-month surgical bed relapse rate: 28% with SRS vs. 57% with observation, $p = 0.015$). While there was no survival advantage to adjuvant SRS, there was a trend toward reduced neurologic death with SRS but this did not reach statistical significance ($p = 0.13$).

A phase III trial from a collaboration between Alliance and the Canadian Cancer Trials Group (N107C/CEC.3) compared surgery with adjuvant WBRT to surgery with adjuvant SRS and examined both overall survival and cognitive side effects. WBRT was again associated with improved local and distant control. Specifically, adjuvant SRS led to a 20% decrement in surgical bed control at 12 months compared to WBRT (60% compared to 80%, $P = 0.00068$). While this improved intracranial control was not associated with an increase in overall survival, this trial lacked a comparison of the rates of neurologic cause of death [15]. With respect to cognitive deterioration, adjuvant WBRT performed significantly worse than adjuvant SRS, with an overall rate of cognitive deterioration of 85% versus 52%, respectively, at 6 months ($P = 0.0003$). Within specific cognitive domains, patients in the WBRT arm had significantly higher rates of deterioration in immediate recall, delayed recall, processing speed, and executive function.

Taken together, the evidence supports the use of postoperative radiotherapy following surgical resection for brain metastasis. Both WBRT and SRS remain effective treatment options but have some limitations [26]. Neuroprotective strategies to prevent cognitive toxicity from WBRT are discussed below. The inferior surgical bed control of SRS remains an area of concern. An Alliance phase III trial of fractionated versus single-fraction radiosurgery to improve local control following surgical resection will seek to address this issue.

Prophylactic Cranial Irradiation

WBRT may be used prophylactically (i.e., before disease is radiologically detectable) in select patients with small cell lung cancer (SCLC), who demonstrate up to 80% risk of developing brain metastases 2 years after diagnosis [27]. As such, WBRT is considered the standard of care for patients with limited-stage (LS) SCLC that has responded to chemotherapy, given the potential for prolonged survival. The seminal meta-analysis by Aupérin et al. (1999) demonstrated a significant increase in overall survival (pooled relative risk of death 0.84, $P = 0.01$) and significantly reduced the incidence of brain metastases (0.46, $P < 0.001$) in patients with a complete response (CR) to chemotherapy [28]. These results were reinforced by a 2001 systematic review by Meert et al., which also showed

decreased incidence of brain metastasis (HR of 0.48, 95% CI of 0.39–0.60) and improved overall survival (HR of death 0.82, 95% CI 0.71–0.96) in patients with LS SCLC and CR [29].

Prophylactic WBRT in patients with extensive stage (ES) SCLC is more controversial. A 2007 EORTC trial seemed to demonstrate improved survival for patients with ES SCLC and any positive response to chemotherapy [30]. This study, however, did not include brain imaging as a part of its inclusion criteria, raising the possibility that some patients had asymptomatic brain metastases upon enrollment (making cranial irradiation for these patients therapeutic rather than prophylactic). A later phase III Japanese trial of 224 ES SCLC patients addressed this concern by excluding patients with brain lesions visible on MRI prior to enrollment. This study showed no benefit to overall survival (survival HR 1.27; $P = 0.094$) with prophylactic cranial irradiation (PCI) versus observation and was halted for futility [31]. In light of this most recent trial, prophylactic WBRT for ES SCLC is controversial, and a planned SWOG phase III trial MAVERICK seeks to address this question. SCLC patients in this study will be randomized to PCI with hippocampal avoidance versus MR surveillance; the primary endpoint is overall survival.

Given its success in limited stage SCLC, WBRT has also been studied extensively in non-small cell lung cancer (NSCLC). While no study has demonstrated an advantage to overall survival, two phase III trials have demonstrated significantly reduced incidence of brain metastases [32, 33]. An additional phase III study by De Ruysscher et al. in 2018 confirmed a reduced incidence of brain metastases with PCI versus observation (7% vs 27.2%, $P = 0.001$), albeit with a reduced quality of life with PCI at 3 months post-treatment and a non-significant trend toward QoL benefit to observation at 2, 3, and 4 years [34]. RTOG 0214 was a phase III trial that randomized stage III NSCLC to PCI or observation but did not complete target accrual to detect an overall survival benefit. However, unplanned analyses of longer-term results revealed an overall survival benefit of PCI in stage III NSCLC patients who did not undergo upfront surgical resection.

However, these trials of PCI in NSCLC were conducted prior to the emergence of immune checkpoint inhibitors, now considered the standard of care for most locally advanced and metastatic NSCLC patients. Thus, in the modern era of NSCLC management, the role of PCI remains uncertain. The use of neuroprotective strategies such as hippocampal avoidance during PCI to prevent cognitive toxicity also remains an area of ongoing investigation through the current NRG Oncology CC003 trial.

Modern WBRT

Preceding and concurrent with trials establishing the neurocognitive toxicity of conventional WBRT, several investigations have been pursued to identify approaches to deliver WBRT more safely. These approaches have included both pharmacologic and technologic strategies and have led to practice-changing findings that have ushered in the era of modern WBRT inclusive of prophylactic memantine and hippocampal avoidance.

NMDA Receptor Antagonists (Memantine)

N-methyl-D-aspartate (NMDA) receptors are ionotropic glutamate receptors that mediate synaptic plasticity and memory in the brain, particularly in the neurons of the hippocampus. Overstimulation of these receptors following insults to the brain by ischemia, trauma, or radiation can lead to apoptosis and necrosis via a phenomenon known as excitotoxicity. Preclinical studies have demonstrated that blockade of these receptors by the noncompetitive NMDA antagonist memantine protects against NMDA-receptor-mediated neurotoxicity [35, 36]. Animal studies have also demonstrated that giving memantine ahead of radiation can preserve long-term potentiation—a process involved in synaptic plasticity—in rodents [37, 38]. Phase II clinical studies have demonstrated the effectiveness of memantine in managing vascular dementia [39, 40]. The

apparent neuroprotective effects of memantine generated interest in its use in for managing radiation-related neurotoxicity.

A phase III trial (RTOG 0641) was designed to assess the neuroprotective effects memantine in patients treated with WBRT. Patients were randomized to WBRT (37.5 Gy in 15 fractions) with either memantine or placebo. The dose of memantine was escalated over the course of treatment beginning with 5 mg QD in week 1 of treatment and rising to 10 mg BID for weeks 4 through 24. The full regimen is detailed in Table 20.1. Because memantine is primarily cleared renally, exceptions were made for patients for patients with low creatinine clearance. Those with clearance below 30 mL/min received 5 mg BID and those with clearance less than 5 mL/min were taken off the drug. The primary endpoint was whether memantine preserved memory, as assessed by the HVLT-R Delayed Recall at 24 weeks. Although patients treated with memantine were found to experience less cognitive decline than control patients, this difference was not statistically significant (0 compared to −0.9, $P = 0.059$), possibly due to the high rate of attrition in the trial. Among the positive findings in the trial were a significantly longer time to cognitive deterioration in the memantine arm (HR 0.78, $P = 0.01$) and significantly less deterioration in delayed recognition (measured by the HVLT-R Delayed Recognition) and processing speed (Trail-Making Test A) at 24 weeks [41]. However, when cognitive toxicity was assessed as a composite endpoint, defined as a decline in the reliable change index on the HVLT-R, Trail-Making Test, or Controlled Oral Word Association tests, the use of memantine during WBRT led to a 22% relative reduction in risk of cognitive toxicity. These results, combined with the favorable safety profile of memantine, have made the drug appropriate for use in clinical practice to mitigate the cognitive toxicity of WBRT, particularly in conjunction with hippocampal avoidance as detailed below. It is not known at this time what the optimal dosing schedule and duration of memantine is to attenuate radiation-induced neurotoxicity, and further trials may help guide future management recommendations.

Table 20.1 Memantine dosing in RTOG 0614

	Twice daily dosing[a]		Extended release dosing[b]
Week(s)	Morning dose (mg)	Evening dose (mg)	Daily dose (mg)
1	5	–	7
2	5	5	14
3	10	5	21
4–24	10	10	21

[a]A dosage reduction to 5 mg orally twice daily is recommended in patients with severe renal impairment [creatinine clearance (CrCl), 5–29 milliliters/minute (mL/min)]. No dosage adjustment is needed in patients with mild (CrCl greater than 50–80 mL/min) or moderate (CrCl 30–49 mL/min) renal impairment

[b]A dosage reduction to 14 milligrams (mg) orally daily is recommended in patients with severe renal impairment (creatinine clearance (CrCl), 5–29 milliliters/minute (mL/min)). No dosage adjustment is needed in patients with mild (CrCl greater than 50–80 mL/min) or moderate (CrCl 30–49 mL/min) renal impairment

Hippocampal Avoidance

The hippocampus plays a critical role in the formation of episodic and spatial memory. Its ability to do so stems in part from the production of new neurons by neural progenitor cells (NPCs) within the subgranular zone (SGZ) of the hippocampal dentate gyrus. Animal studies have demonstrated that these NPCs are highly sensitive to radiation and that radioablation of these cells results in deficits in hippocampus-dependent learning and memory tasks [42]. Given this interaction with radiation, it is unsurprising that memory deficits are commonly reported in WBRT patients. One recent study (NCCTG N107C/CEC.3) examining WBRT versus SRS following surgical resection found deterioration of immediate and delayed memory in 49% and 62% of patients, respectively. This was significantly more than in patients treated with focal radiotherapy via SRS [15]. Clinical studies have also demonstrated a clear dose-response relationship between hippocampal radiation exposure and memory deterioration, with a study by Gondi et al. (2013) demonstrating an association between the delivery of 7.3 Gy to 40% of the bilateral hippocampi (in the equivalent of 2 Gy fractions) and long-term deterioration in list-learning delayed verbal recall as

measured by the Weschler Memory Scale-III Word Lists test [43]. Given this association and given the relatively rare rate of metastasis to the hippocampi, a technique was devised using intensity-modulated radiotherapy (IMRT) to limit the dose delivered to the hippocampus (Fig. 20.2b) [10].

A phase II study, RTOG 0933, was designed to evaluate the benefits of this hippocampal avoidance strategy. The study found that compared with historical controls, patients treated with hippocampal avoidance (HA) WBRT experienced significantly less deterioration in delayed memory as measured by the HLVT-R Delayed Recall. Consistent with previous observations, 4.5% of patients experienced progression in the hippocampal avoidance region [44].

A phase III trial, NRG Oncology-CC001, was conducted to validate these findings in patients treated with memantine and WBRT with or without HA. The study recruited and randomized 518 adult patients with brain metastases between July 2016 and March 2018. The primary endpoint was cognitive toxicity, defined as a decline in the reliable change index on the HVLT-R, Trail-Making Test, or Controlled Oral Word Association tests. There was no difference in grade 3 or higher toxicity between the treatment arms. The median follow-up for alive patients was 7.8 months. There was no difference between arms in terms of baseline cognitive function, overall survival (HR = 1.13, 95% CI: 0.89–1.44, p = 0.31), or intracranial progression (HR 1.12, 95% CI 0.90–1.39, p = 0.33).

The addition of hippocampal avoidance to WBRT+memantine significantly prevented cognitive toxicity (Fig. 20.2b) with an adjusted hazard ratio of 0.74, or a 26% relative reduction in risk of cognitive toxicity with the addition of hippocampal avoidance to memantine [12, 26]. The difference was first seen at 4 months and maintained throughout the follow-up period, and was attributable to improvements in executive function at 4 months (p = 0.01) and learning (p = 0.049) and memory (p = 0.02) at 6 months. While age also predicted for prevention of cognitive function failure, test for interaction between treatment arm and age was non-significant (p = 0.67), indicating that the cognitive benefit of hippocampal avoidance does not differ by age.

Importantly, the addition of hippocampal avoidance to WBRT+memantine preserved patient-reported symptom burden, as assessed by the M.D. Anderson Symptom Inventory Brain Tumor Module (MDASI-BT). Patients on the HA-WBRT+memantine arm experienced less symptom interference and less cognitive symptoms at 6 months (estimate = −1.02, p = 0.008 and estimate = −0.63, p = 0.011, respectively) compared to the WBRT+memantine arm. Cognitive symptom differences were driven primarily by two items: problems with remembering things and difficulty speaking. At 6 months, patients on the HA-WBRT+memantine arm had less difficulty remembering things (mean 0.16 vs. 1.29, p = 0.013) and less difficulty speaking (mean − 0.20 vs. 0.45, p = 0.049) as compared to the WBRT+memantine arm. Greater improvement in fatigue at 6 months was reported in the HA-WBRT+memantine arm as compared to the WBRT+memantine arm (mean 0.93 vs. −0.16, p = 0.036).

Analyses with longer follow-up (median follow-up of 12.1 months) additionally demonstrated better preservation of overall symptom burden (p < 0.0001) at 6 months on the HA-WBRT+memantine arm compared to the WBRT+memantine arm, while continuing to show similar benefits in cognitive function and patient-reported quality of life with hippocampal avoidance.

The summation of these findings remains consistent with cognition-specific hypothesis of hippocampal avoidance but also underscore the palliative intent of brain metastasis management and the capacity of HA-WBRT to provide optimal intracranial control to limit neurologic symptom burden.

Future Directions

All of the trials observing higher cognitive toxicity in patients receiving WBRT were conducted in the conventional era of WBRT without the inclusion of neuroprotective strategies including

memantine and hippocampal avoidance, which have demonstrated significant cognitive toxicity prevention. In the modern era of brain metastasis management, the role of WBRT with neuroprotective strategies remains under investigation. Given the increased requirement for imaging follow-up and the higher rate of salvage therapies associated with SRS alone, modern WBRT may be appropriate for patients who do not wish to undergo extensive surveillance or subsequent salvage therapy. Generally, however, SRS with omission of WBRT can be considered standard of care for patients whose survival is anticipated to extend multiple years, as the capacity of memantine and hippocampal avoidance to prevent the rare occurrence of radiation-related leukoencephalopathy in long-term survivors of WBRT remains unclear.

It is worth noting too that SRS is being investigated for use in five or more brain metastases, with one prospective observational study demonstrating that survival in patients receiving SRS alone for 5–10 brain metastases was not inferior to that seen in patients receiving SRS alone for two to four brain metastases [45]. Currently, four RCTs are either planned or actively accruing patients to directly compare SRS versus WBRT for four or more brain metastases (up to as many as 20 in one study) [46]. Absent conclusive evidence for non-inferiority of SRS alone to WBRT for patients with more than four brain metastases, modern WBRT with hippocampal avoidance and memantine remains a standard of care for these patients.

Modern WBRT for Newly Diagnosed Brain Metastases

Radiosurgery, for as many as 15 brain metastases, has been found to be safe, notably in a series of 360 patients from Japan [45]. The feasibility and safety of multiple-brain metastasis SRS, as well as studies demonstrating inferior cognitive outcomes following upfront WBRT relative to upfront SRS for one to four brain metastases, have led several institutions to consider SRS alone for patients with more than four brain metastases. However, as mentioned above, these studies were largely conducted prior to the publication of large brain metastasis trials testing pharmacologic and technologic neuroprotective strategies during WBRT and leading to the safer delivery of WBRT. Thus, the appropriate management of patients with multiple brain metastases remains unclear.

To address this question in the newly diagnosed setting of multiple brain metastases, multiple trials have been launched. Originally, a trial comparing SRS to conventional WBRT for patients with greater than five brain metastases was initiated by the North American Gamma Knife Consortium. Although this trial was of interest, it was limited in its scope to only one of the several radiosurgical platforms and limited in its statistical power (39 patients planned to be accrued per treatment arm) and the trial closed long before reaching the total target accrual.

More recently, the Canadian Clinical Trials Group (CCTG) launched a cooperative-group phase III trial of SRS versus conventional WBRT in 5–15 brain metastases with co-primary endpoints of overall survival and neurocognitive progression-free survival. Given the practice-changing evidence from NRG CC001, this trial has subsequently been amended to compare SRS versus modern WBRT with hippocampal avoidance and memantine and has also been endorsed by NRG Oncology and Alliance. The question of whether SRS or modern WBRT with hippocampal avoidance and memantine is the optimal modality in patients with 5–15 brain metastases is significant from a societal and medical resources standpoint since the charges related to SRS and IMRT for HA-WBRT can be considerably higher than those of conventional WBRT. However, examining therapy-associated costs is particularly complex in patients with multiple brain metastases, because such patients are likely to undergo additional salvage procedures for new brain metastases. Therefore, the additional costs of salvage are also important to incorporate into economic comparisons, especially when SRS is anticipated to result in higher intracranial relapse rate and need for salvage therapies [20, 21, 23, 47].

Brain Metastasis Velocity

Brain metastasis velocity (BMV) is a useful measure for predicting outcomes in patients with brain metastases who experience distant brain relapse following their first SRS treatment. It is defined as the cumulative number of brain metastases developed since upfront SRS divided by the number of years following SRS. For example, a patient who develops two brain metastases 6 months after upfront SRS would have a BMV of 2/0.5 = 4. Developed by Farris et al. (2017), BMV was found to be significantly associated with overall survival, neurologic death, and rates of salvage WBRT in a cohort of 737 patients [48]. This remained true when the same analysis was applied to a validation set featuring an additional 2092 patients across multiple institutions [49]. Farris et al. (2017) stratified patients into low (<4), intermediate (4–13), and high (>13 BMV) categories, finding that patients with high BMV experienced a cumulative incidence of neurologic death roughly twice that of low-BMV patients. Neurologic death was defined by the authors as death with progressive neurologic decline, regardless of extracranial disease status [48]. The significant association of BMV with neurologic death, thus defined, makes it a useful marker for predicting intracranial control, as does the association between BMV at first distant brain relapse and BMV at second distant brain relapse. The prognostic value of BMV has since been validated in two additional published series [50, 51].

This predictive ability is of interest for its potential utility in triaging patients at risk for poor intracranial control to optimal intracranial control offered by SRS plus WBRT. With continued refinement, BMV could be used to identify and treat patients who would benefit from the superior intracranial control offered by WBRT. This in turn could reduce both neurologic death and, more generally, the neurological sequelae of a high burden of brain metastatic disease in this patient population. A phase III trial (NRG BN009) of salvage SRS with or without modern WBRT with hippocampal avoidance and memantine for recurrent brain metastases with brain metastasis velocity exceeding four brain metastases/year is being developed through NRG Oncology with anticipated activation in 2020. The primary objective of this trial is to determine if the addition of HA-WBRT with memantine to salvage radiosurgery effectively prevents neurologic death in this high-risk patient population.

Small Cell Lung Cancer Brain Metastases

Intracranial failure is a frequent problem in patients with small cell lung cancer (SCLC). SCLC accounts for approximately 15% of all cases of lung cancer, tends to disseminate earlier in the course of its natural history than non-small cell lung cancer and is more clinically aggressive. As a result, approximately 10–20% of SCLC patients present with brain metastases at the time of initial diagnosis, and an additional 40–50% will develop brain metastases some time during the course of their disease. In addition, brain metastases have an impact on the quality and length of survival. Prophylactic cranial irradiation (PCI) has historically been used as a strategy to reduce the incidence of brain metastases in SCLC; however, the National Comprehensive Cancer Network (NCCN) guidelines recommend caution regarding PCI delivery in older patients and PCI is omitted in up to 40–50% of patients, primarily due to concerns over cognitive toxicity [52, 53]. NRG CC003 is an ongoing phase III trial testing whether the cognitive toxicity of PCI can be prevented with hippocampal avoidance during PCI for SCLC patients.

Due to the high propensity for micrometastatic seeding of the brain, WBRT remains standard of care for patients with SCLC brain metastases. Studies demonstrating cognitive toxicity from conventional WBRT have led to questions as to whether upfront SRS followed by close imaging surveillance for patients with SCLC brain metastases is an acceptable alternative. Importantly, SCLC patients have been excluded from the landmark randomized trials testing SRS for brain metastases [20, 21, 23, 47]. Historic objections to the use of SRS in SCLC

have included the concern for diffuse interval CNS progression, which could potentially result in diminished overall survival.

However, there is growing evidence to suggest that SRS alone may be safe and appropriate for some patients with SCLC brain metastases. A multi-institutional retrospective analysis of 293 patients treated with SRS for SCLC brain metastases observed the risk of radiation necrosis to be <5% [54], comparable to outcomes following SRS for brain metastases from other histologies. Serizawa et al. (2002) [55] compared the outcomes of SCLC (N = 34) and NSCLC (N = 211) patients with brain metastases treated with SRS alone and found comparable rates of overall survival, central nerve system control, and neurologic mortality in SCLC and NSCLC patients. Yomo and Hayashi (2015) [56] reported on 70 SCLC patients treated with SRS (including 46 without prior PCI or WBRT), with a median overall survival of 7.8 months and encouraging 1-year and 2-year neurologic mortality free survival of 94% and 84%, respectively. A recent analysis of the National Cancer Database compared upfront WBRT with upfront SRS for SCLC patients with brain metastases and reported favorable overall survival with SRS both overall and after propensity-score matching [57].

Although retrospective analyses are subject to cofounding from selection bias, they do suggest that some patients may be safely and effectively managed with a strategy of SRS alone. Overall, there is growing equipoise regarding the role of SRS versus WBRT in the management of SCLC brain metastases, and prospective randomized data are urgently needed to address this knowledge gap especially given practice-changing evidence demonstrating the cognitive preservation benefits of hippocampal avoidance and memantine as neuroprotective strategies during WBRT. NRG Oncology is currently developing a phase III trial of SRS versus modern WBRT with hippocampal avoidance and memantine for 10 or fewer brain metastases from small cell lung cancer with a primary endpoint of cognitive toxicity. There is data from Switzerland that is raising questions about HA-WBRT for PCI that this proposed trial may help examine, specifically a single-institution retrospective analysis that identified more significant leukoencephalopathy in patients treated with PCI using HAWBRT than conventional WBRT [58] and a multi-institution phase II trial of early HA-PCI that saw similar neurocognitive outcomes as PCI using conventional WBRT techniques [59].

Alternating Electric Field Therapy

Alternating electric fields—commonly called tumor treating fields or TTFields—have been increasingly used as part of management for glioblastoma. The low-intensity, intermediate frequency fields are applied via an adhesive cap consisting of an array of transducers and serve to interrupt cell replication by two principal mechanisms. First, TTFields interact with the strong electric dipole moments of the microtubules forming the mitotic spindle, disrupting spindle formation and stalling mitosis. Second, the fields have been shown to destroy cells nearing the end of cytokinesis, rupturing the cell membrane and generating membrane blebs that resemble the products of apoptosis. These results were observed in vitro in both glioma and melanoma cell lines [60].

A phase III trial comparing TTFields with temozolomide to temozolomide alone in patients with glioblastoma (GBM) has demonstrated a survival advantage to adding TTFields. Patients treated with TTFields were exposed to low-intensity, 200-kHz alternating electric fields for at least 18 h per day via a portable device. These patients had an overall median survival of 20.9 months compared to 16 months in those treated with temozolomide alone (P < 0.001). Systemic adverse events occurred at about the same rate in each arm with the most common side effect of treatment being mild-moderate skin irritation of the scalp in 52% of patients in the TTFields arm [61]. Prompted by this success in the management of primary CNS malignancy and by preclinical data showing effectiveness in non-CNS malignancies, a phase III trial is currently underway to evaluate the use of TTFields in conjunction with radiosurgery for patients with 1–10 NSCLC metastases. The METIS trial (ClinicalTrials.gov identifier: NCT02831959)

will evaluate as its primary outcome the time to intracranial progression and, as a secondary outcome, track cognitive function in patients receiving this novel therapy.

Concomitant Systemic Agents

Since the 1980s, a variety of systemic therapies have been investigated for use in conjunction with WBRT for patients with brain metastases. The imidazoles such as metronidazole and misonidazole were among the first agents to be tested in this context. Neither agent added any survival benefit over WBRT alone [62]. More recently, a trial of sodium glycididazole did demonstrate improved intracranial control and longer progression-free survival, but did not find a benefit to overall survival [63]. One area of success has been with the use of motexafin gadolinium (MGd), a redox modulating agent that catalyzes the oxidation of various intracellular metabolites, increasing the toxicity of reactive oxygen species and limiting the cell's ability to repair itself. While one phase III trial of MGd in patients with brain metastases demonstrated no overall benefit in survival time or time to neurologic progression overall, a subset of patients with NSCLC did experience a benefit in time to neurologic progression [64]. The phase III trial that followed compared WBRT with or without MGd in NSCLC patients and demonstrated that patients initiating WBRT within 28 days of brain metastasis diagnosis experienced a significant improvement in time to neurologic progression with the addition of MGd. This effect was identified on geographic subgroup analysis when it was found that patients in North America (where investigators were more likely to initiate WBRT earlier) had a significantly longer time to neurologic progression than the overall cohort [65]. Based on these data, MGd was deemed an appropriate adjunct therapy in NSCLC patients, provided that WBRT is initiated promptly, but has not been widely accepted.

Temozolomide (TMZ) is a DNA alkylating chemotherapeutic agent that is notable for its high blood-brain barrier (BBB) penetrance. This property has prompted a number of trials evaluating the efficacy and toxicity of WBRT with adjuvant TMZ. A phase III study from Antonadou et al. (2002) demonstrated a significantly higher radiographic response rate with combined therapy versus WBRT alone (53.4 vs. 33.3%, $P = 0.039$). The difference in response rate was even more dramatic in patients <60 years of age and with a Karnofsky performance score of 90–100 (70.6 vs. 32.4%, $P = 0.003$ in the latter group). The study found no difference in neurological response or median survival, however [66].

A later phase III trial in NSCLC patients from Sperduto et al. (2013) investigated WBRT and SRS with or without TMZ or erlotinib. The authors again found no significant survival advantage with the addition of temozolomide. They also found no difference in time to progression [67]. A 2016 meta-analysis of seven trials (including those discussed above) comparing radiotherapy with TMZ to radiotherapy alone found no advantage in survival to adding TMZ, despite a significant increase in response rate on combination therapy. Patients treated with TMZ were more likely to experience grade 3 to 4 nausea and grade 3 to 4 thrombocytopenia [68]. As TMZ has not shown a survival benefit and is accompanied by an increase in toxicity, it is not recommended for use in clinical practice for patients with brain metastases.

Inhibitors of the epidermal growth factor receptor (EGFR) tyrosine kinase are under investigation for adjuvant use with WBRT. Erlotinib is one such (EGFR) inhibitor with known radiosensitizing properties. Recent trials of this agent highlight the importance of patient selection with respect to pathway-specific mutations. While a preliminary trial from Welsh et al. (2013) suggested a benefit for adjuvant erlotinib with WBRT in lung cancer patients, subsequent trials have contradicted this [69]. The above-mentioned study from Sperduto et al. (2013) showed that adding erlotinib provided no benefit to overall survival or time to progression [67]. Another study from Lee et al. (2014) again found that adding erlotinib had no effect on neurological progression-free survival or overall survival [70]. Notably, however, over 50% of the patients in Welsh et al. with known tumor EGFR mutation status possessed EGFR mutations. Patients in that study with EGFR-mutated tumors had a median

survival time of 19.1 months compared to 9.3 months in those with wild-type EGFR tumors. With a total sample of only 17 patients, however, this difference was not significant ($P = 0.534$). In contrast, Sperduto et al. did not assess EGFR mutation status and in the study from Lee et al. only 1 of the 35 patients with known tumor EGFR mutation status possessed a mutation. The SATURN trial investigating the use of erlotinib in patients with advanced NSCLC demonstrated that although erlotinib provided a benefit to NSCLC patients generally, those with EGFR mutations derived the greatest benefit from it [71]. It seems likely then that erlotinib is most effective in intracranial metastases in which a mutated EGFR drives cancer growth and proliferation. As such, further study is warranted in this patient subpopulation. Other EGFR inhibitors such as gefitinib and icotinib have also been investigated as adjuvant therapy with WBRT with similarly mixed results. A study of icotinib versus WBRT with chemotherapy in patients with EGFR-mutant NSCLC demonstrated superior intracranial progression-free survival in the icotinib arm (10 vs 4.8 months, $P = 0.014$) [72]. It is worth noting, however, that a phase II study of NSCLC patients has shown a survival advantage to icotinib with WBRT compared to WBRT alone, with a particular advantage for patients with EGFR-mutated tumors [73]. This suggests a possible benefit to combination therapy rather than icotinib alone.

RTOG 1119 is an ongoing study assessing the treatment of HER2-positive breast cancer patients with WBRT plus adjuvant trastuzumab and lapatinib. Lapatinib is a dual EGFR and HER2 inhibitor that, unlike trastuzumab, can cross the BBB and has shown preclinical promise. Until more persuasive clinical evidence emerges, however, the benefit of combining WBRT and targeted therapies for the purpose of improving intracranial control remains unclear.

A retrospective analysis of NSCLC patients in whom radiation therapy was deferred provides further reason for clinicians to exercise caution before omitting radiation treatment. The study found that patients who received upfront SRS for brain metastases had a significantly longer median survival time than those receiving upfront erlotinib. There was also trend toward a survival advantage to WBRT over erlotinib, though this was not significant [74]. Given the intracranial activity of osimertinib as a newer generation EGFR-targeting agent [75, 76], and its establishment as first-line therapy for EGFR-mutated non-small cell lung cancer, treatment with osimertinib and omission of upfront radiotherapy for small asymptomatic brain metastases is increasingly being utilized, although further study is needed.

The use of immune checkpoint inhibitors in conjunction with brain radiotherapy is a matter of active and ongoing study. A retrospective analysis of patients with melanoma brain metastases receiving ipilimumab (an anti-CTLA-4 monoclonal antibody) with either SRS or WBRT did not demonstrate a survival advantage for combined WBRT-ipilimumab therapy compared with historical controls treated with WBRT and bortezomib. The authors did find an advantage to SRS and ipilimumab versus SRS alone [77]. There are, however, currently no published RCTs investigating the use of WBRT with immunotherapy compared to WBRT alone or immunotherapy alone. Future trials of immune checkpoint inhibitors and other targeted agents should consider not just efficacy, but toxicity as well. In particular, with significantly improved survivorship with the use of immune checkpoint inhibitors for melanoma and non-small cell lung cancer brain metastases, cognitive side effects become a significant component of both brain metastatic disease and associated therapies, and new treatments should be evaluated for impact on these symptoms.

Optimal Patient Selection: Summary

Recent research has helped identify which patients may stand to benefit the most from WBRT versus or in conjunction with other definitive treatment modalities for brain metastases. WBRT should be considered as primary treatment for patients with good performance status and with systemic therapy options for managing extracranial disease when metastatic lesions within the brain are not amenable to surgical resection or SRS. This can occur when a metasta-

sis is too large for SRS and is located in an unresectable region, when the burden of metastatic disease is too extensive for other techniques (≥ 5 metastases), in the case where there is diffuse disease (extensive dural, pachymeningeal, or leptomeningeal metastases), or in cases where there is a possibility for microscopic metastatic disease (particularly for limited-stage SCLC responsive to chemotherapy or high brain metastasis velocity after upfront SRS). These patients, at high risk for developing or experiencing progression of multiple brain metastases that may cause neurologic and cognitive impairment, may benefit the most from modern WBRT which can alleviate these symptoms and improve survival. Neurocognitive protective strategies of hippocampal avoidance and memantine can effectively prevent WBRT-associated cognitive toxicity.

Summary

WBRT remains a valuable asset in the management of brain metastases. Several trials of SRS versus conventional WBRT demonstrated inferior cognitive outcomes of WBRT in the setting of one to four brain metastases. These findings have led to a declining use of WBRT and rapidly rising use of SRS alone. However, practice-changing evidence demonstrating preservation of cognitive function with hippocampal avoidance and memantine has ushered in the modern era of WBRT. Importantly, prior trials demonstrating inferior cognitive outcomes with conventional WBRT did not include these neuroprotective strategies and thus have limited relevance in the modern management of brain metastases.

Several phase III trials are currently accruing or under development to better define the role of modern WBRT either in lieu of SRS for newly diagnosed 5–15 brain metastases or small cell lung cancer brain metastases or adjunctive to SRS for recurrent brain metastases with high brain metastasis velocity. In addition, as improvements in systemic therapy continue to prolong survival in brain metastasis patients, the impact of optimizing brain metastasis control and minimizing associated neurologic and quality-of-life sequelae will become even more apparent, and the appropriate usage of modern WBRT will be further refined.

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Stereotactic Radiosurgery Technology

21

Diana A. R. Julie and Jonathan P.S. Knisely

Introduction

Stereotactic radiosurgery (SRS) aims to non-invasively deliver ablative radiation doses to intracranial lesions, with minimal dose to nearby healthy tissues, traditionally in a single treatment. The fundamental principles of SRS include: (1) stereotactic target localization; (2) high dose, precise radiation delivery; (3) steep dose fall off, minimizing dose to surrounding tissues; and (4) acquisition of volumetric imaging for treatment planning [1–11]. Hypofractionated SRS, in which the radiation dose is delivered in two to five fractions, has also been employed [9, 11]. Hypofractionation confers several benefits, including decreased toxicity risk, ability to treat larger lesions, and potential for safer re-irradiation [2, 7, 8, 11, 12]. Since its development, SRS has become a key treatment option for a variety of benign and malignant intracranial lesions, as an alternative or adjunct to surgery [1, 2, 4, 5, 7, 10–13]. Lesions appropriate for SRS include benign and malignant tumors, arteriovenous malformations (AVMs), and some functional disorders [1, 3, 5, 7, 10–13]. The use of SRS and its applications continue to expand.

SRS was devised by the Swedish neurosurgeon Lars Leksell in the 1950s as a treatment for inoperable intracranial lesions [1, 3–6, 11, 14–16]. Leksell and his team experimented with dental x-ray tubes, as well as with proton therapy, before ultimately settling upon Cobalt-60 (Co-60) sources for administering SRS. The first Gamma Knife (GK) unit employed 179 Co-60 sources convergently focused upon a stereotactically targeted lesion. The first GK treatment occurred in 1967 for the management of a craniopharyngioma [13–16].

For many decades, the Leksell GK was the gold standard in SRS. However, since the 1950s, in parallel with advances in imaging and computing, SRS technology has rapidly evolved, and today, numerous platforms are available for intracranial SRS [1, 3–5, 7, 9, 11, 15]. The major systems to be reviewed in this chapter include the GK, manufactured by Elekta (Elekta AB, Stockholm, Sweden), linear accelerator (linac) SRS systems, and the CyberKnife (CK), manufactured by Accuray (Accuray Inc., Sunnyvale, CA) [3, 8, 9, 12]. Proton therapy is also emerging as an SRS treatment option [1, 17–19].

General SRS Concepts

Beam Shaping

Collimators are devices used to shape the radiation beam so that its edges are sharply defined. Conical collimators are typically composed of lead or tungsten and come in a variety of aperture

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diameters. They are divergently milled to minimize the penumbra, providing a sharp beam edge and rapid dose fall off beyond the target [16, 20]. Their use can yield small, sharply focused beams, as small as 0.4–0.5 cm. Multi-leaf collimators (MLCs) are composed of many (up to160) paired tungsten leaves, each with a width of 0.5–1 cm; micro-MLCs (mMLCs), with width 0.2–0.5 cm, can also be used. A computer controls the position of each independent leaf at every point in time. Compared to circular collimators, MLCs and mMLCs improve conformity to irregularly shaped target volumes and homogeneity of dose distribution throughout the target volume [1, 3, 6–8, 13, 16, 20–22]. The CyberKnife may be equipped with MLCs that function much like those on other linacs or may be equipped with an 'iris' collimator that employs two banks of six tungsten blocks that provide a dodecagonal beam whose size can be changed at will. Circular conical collimators in a range of sizes may also be employed.

For proton beam therapy, the generation of focused beams requires custom apertures and range compensators. Passively scattered beams and scanned pencil beam treatments have slightly different equipment requirements to generate a spread-out Bragg peak beam at the depth of the target tissue. Only two to four beams are used for proton radiosurgery because of the dosimetric characteristics of protons.

Treatment Planning

All modern SRS platforms are capable of both forward and inverse radiation planning. With forward planning, the planner completes a repetitive trial-and-error process, sequentially changing delivery parameters, such as beam shape, angle, or weight, to improve the plan. This process continues until an acceptable plan is generated. In contrast, inverse planning is a more automated approach. First, the target and organs at risk (OARs) are outlined, and treatment goals are set with regard to these structures. Next, an optimization algorithm generates a plan that best meets the predefined goals [13, 20, 21, 23]. The planner can iteratively adjust input specifications for the algorithm and also manually tweak the final plan [13]. Inverse planning carries some advantages over forward planning. Since trial-and-error is not required, plans can be generated more efficiently. Additionally, plans of better quality should be generated, as the optimization algorithm can evaluate and compare thousands of plans [20].

Immobilization and Image Guidance

Given the high doses per fraction delivered with intracranial SRS and the close proximity to sensitive OARs, accurate patient positioning is vital to ensuring efficacy and safety. End-to-end submillimeter accuracy and precision are desired. The methods used to position and immobilize patients for SRS can be broadly categorized into two groups: frame-based and frameless systems [4, 8, 12, 15, 21–26].

When SRS was first introduced, rigid headframes applied to the patient's skull and subsequently attached to the treatment table were always employed, and SRS continues to be delivered with headframes for both GK and linac platforms, depending upon facility capabilities and expertise. Invasive frames consist of a rigid headframe, attached to the outer table of the skull using three to four metal pins, and serve two purposes, immobilizing the patient and providing stereotactic coordinates for target localization [4, 5, 7, 12, 15, 21, 24, 27, 28]. Studies of headframe systems have demonstrated submillimeter intrafractional translational and rotational motion [12, 28]. There are several shortcomings of the invasive headframe, including patient inconvenience and discomfort, risks associated with a (minimally) invasive procedure, and regimented workflow where all treatment-related activities must be completed in 1 day. Errors can occur with frame-based SRS secondary to frame slippage or deformation, and can also be introduced from inaccuracy in imaging or image co-registration [7, 12, 21, 27, 28].

To overcome these drawbacks of invasive headframes, non-invasive immobilization systems have been developed. Today, both GK and

linac can deliver frameless SRS, while the CK is a dedicated frameless platform. Frameless SRS improves patient comfort and convenience, avoids the potential complications of frame fixation, and facilitates hypofractionated treatment. Frameless SRS is also more convenient for providers, as planning can occur over several days. This additional time can be especially important for optimizing complex plans. Given these advantages, there has recently been a transition to predominantly frameless systems [4, 7, 10, 12, 16, 21, 27, 28].

Many non-invasive SRS immobilization systems have been introduced. Some systems use a headframe attached to the treatment table, combined with a mouthpiece with a vacuum-fixed bite-block. The individualized bite-block is suctioned to the patient's hard palate and maxillary teeth, and loss of vacuum is a surrogate for motion. Vacuum bite-block systems require patient compliance and adequate dentition. Perhaps the simplest frameless system in use is the thermoplastic mask. With this setup a custom thermoplastic mask is created, with a mouthpiece and supplemental reinforcing strips across the forehead, below the nose and across the chin. Frameless SRS is not without shortcomings, including most importantly inaccuracies in patient positioning and target localization. Since frameless systems do not rigidly immobilize, there may be errors due to patient motion as well as setup errors with subsequent immobilizations; machine characteristics may also fluctuate slightly from day to day [12, 21, 27, 28].

In order to replicate the reliability of frame-based SRS with frameless systems, sophisticated image guidance is crucial for initial patient positioning, as well as real-time or near real-time monitoring of intrafraction motion. Image-guidance systems commonly employed for SRS include onboard CBCT (cone beam computed tomography) and ceiling- and floor-mounted x-rays [3, 9, 12, 21, 27, 28]. The term CBCT derives from the conical x-ray beam employed, unlike the fan beam used in diagnostic CT (computed tomography) [3]. CBCT is now integrated into nearly all modern SRS systems and generates high-quality 3D images, which can be used to confirm patient positioning and target location relative to the treatment plan. An alternate image-guidance system integrates stereoscopic x-rays in the treatment room, such that two orthogonal kilovoltage (kV) x-rays are taken. Digitally reconstructed radiographs (DRRs) are generated, which are x-ray images synthesized from the planning CT. Bony anatomy is compared between the x-rays and DRRs, and patient position can be verified or corrected [3, 4, 7, 12, 21, 23, 27]. This method can also be used to acquire images during treatment delivery, monitoring for patient motion. For intrafraction monitoring, optical tracking can also be used. Reflective markers can be placed on the mask, detected by wall-mounted infrared cameras, and compared to fixed reflectors on the couch head cradle. A threshold level is set for allowable patient deviation from the initial position, and treatment delivery is automatically stopped if this is exceeded [12, 21, 27]. It is common for proton facilities performing cranial treatments to implant several tiny stainless steel BBs into the outer table of the skull under local anesthesia to serve as a rigid fiducial system that can be employed to confirm accuracy of patient positioning at the time of treatment.

Invasive headframes were long considered the most accurate immobilization and localization systems. However, with experienced users, modern frameless systems combined with image guidance can achieve submillimeter accuracy, and setup accuracies routinely approach those achieved with frame-based treatments [4, 7, 12, 16, 21, 27, 29–34].

Workflow

The general workflow required to administer SRS is similar regardless of the system used. Figure 21.1 provides an overview of frame-based and frameless SRS treatment workflow. When delivering frame-based SRS, the first step on the day of treatment is attachment of the headframe. The rigid lightweight frame is affixed with metal screws penetrating the skin and outer table of the skull at three or four points. Next, volumetric imaging is acquired to ascertain target and patient

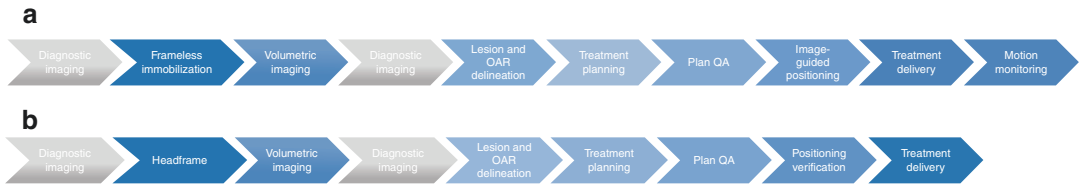

Fig. 21.1 General workflow for (**a**) frame-based SRS and (**b**) frameless SRS

position relative to the stereotactic frame. A stereotactic MRI brain, or other required diagnostic imaging, is obtained, as necessary. This can be performed prior to the treatment day, or with the frame in place, but the frame limits the imaging that can be obtained. Diagnostic imaging is then rigidly co-registered with the volumetric imaging for treatment planning. Target volumes and OARs are contoured on the co-registered data sets, and the treatment planning software (TPS) is used to generate the plan [1, 10, 15, 21, 23–25]. The plan must be approved by the treating physicians, and quality assurance (QA) checks must be performed to ensure that the plan generated in virtual reality parallels what is delivered to the patient. Once the plan is ready to be delivered, the patient lies supine and the headframe is again affixed to the treatment table. Patient positioning is verified, and treatment is delivered [1, 10, 15, 21, 24, 27].

When delivering frameless SRS, the first step is creation of any of a variety of SRS-quality immobilization devices (i.e., thermoplastic mask). With the patient immobilized, a non-contrast CT scan of the head is acquired, which is necessary for target localization and treatment planning. A stereotactic MRI brain, or other required diagnostic imaging, is obtained prior to treatment planning and rigidly co-registered with the CT scan. Target and OAR delineation, treatment planning, plan approval, and QA proceed as with frame-based treatment. For treatment delivery, the patient lies supine and is immobilized. Image guidance is used to confirm patient positioning in 3D space relative to the planning CT scan. With frameless SRS, patient motion during treatment is monitored using real-time or near real-time imaging [1, 10, 13, 15, 21–25, 27].

Gamma Knife

Beam Properties, Arrangement, and Shaping

Gamma rays are a form of ionizating radiation produced from the radioactive decay of a Co-60 nucleus. Co-60 sources have a half-life of approximately 5 years and produce gamma radiation of 1.17 and 1.33 MeV (mean 1.25 MeV). The total activity of new GK Co-60 sources is approximately 6000 Ci, with a dose rate of 3.3–3.6 Gy/min. Over time, the Co-60 sources decay and treatment times increase, such that the source must be replaced approximately every 5 years [1, 2, 15, 16, 24].

A GK uses either 192 or 201 highly collimated Co-60 sources arranged hemispherically or conically around an isocenter, representing the point where the beams converge. These sources are able to deliver radiation to a specific target volume in a highly conformal manner, with sharp dose fall off within a few millimeters, and minimal dose to surrounding tissue [1, 2, 4–7, 15, 16, 24, 26]. Shaping of each Co-60 beam, or 'shot,' is accomplished by a secondary circular collimator system consisting of collimators of different diameters (4, 8, and 16 mm or 4, 18, 14, and 18 mm). These collimators can be combined or selectively blocked to allow conformal treatment of lesions of complex shape [1, 5, 7, 10, 15, 16, 24].

Treatment Planning and Delivery

With GK SRS, dose is prescribed to an isodose surface between 30% and 90%, most often 50–80%. This increases the maximum dose and plan

inhomogeneity, with a high central dose and steep fall off [2, 4, 8, 15, 20, 24]. GK treatment planning employs Leksell Gamma Plan, a dedicated TPS capable of single or multiple isocenter treatments, and forward or inverse planning. Simple spherical lesions can be treated using a single isocenter, while complex volumes are created by combining dose to multiple isocenters. A plan is generated by 'shot packing,' combining individual shots of radiation of varying sizes to create a dose distribution corresponding to the desired volume. For treatment delivery, the isocenter is stereotactically aligned with the focal point of the GK sources, and radiation is administered one isocenter at a time [1, 5, 10, 15, 16, 20, 24].

Immobilization and Image Guidance

Traditionally, GK SRS is delivered with a rigid headframe, with accuracy, documented as <0.3 mm. More recently, frameless systems have been developed for GK SRS, with target localization accomplished via an onboard CBCT, specifically integrated into the GK machine. The accuracy of the GK CBCT imaging system has been investigated, with excellent results, comparable to frame-based treatment. Intrafraction motion can be monitored with optical tracking [1, 15, 24, 27].

Cost

The initial cost of a GK unit is approximately US$3.2 million, with a total start-up cost of US$3–5 million. Shielding requirements are lower for GK relative to linac systems, and therefore, less expensive. Source replacement every 5 years costs US$0.5–1 million. The break-even patient volume for GK in the United States has been estimated at 86 patients annually, which may limit its use for smaller practices. Relatively large annual volumes of over 200 patients (with reimbursement levels at current rates in the United States) are required for GK to be cost effective relative to linac SRS [16–18, 20, 21, 23, 24].

Modern Model

The most modern GK system is the Icon (Elekta AB, Stockholm, Sweden). It consists of 192 Co-60 sources in a conical arrangement of 8 sectors, with 24 sources per sector. It also contains several collimator sizes (4, 8, and 16 mm). Each source can be placed in front of a specific collimator or can be blocked [1, 5, 7, 15, 24]. Intermediate sizes can be achieved by sequential combination of collimators. For the Icon system, all source, collimator, and couch motions are automated, representing a key improvement over prior models. The entire collimation system is embedded within the unit as a 12–cm-thick tungsten collimator array, with no secondary collimator helmet. This results in a 300% increase in the inner diameter of the unit compared to prior models, allowing for treatment of multiple or peripheral lesions, with minimal collision risk. Compared to prior models, the majority of sources are closer to the isocenter in the Icon, increasing the dose rate [5, 7, 15, 24, 27]. Increased automation and this higher dose rate combine to reduced treatment times with the Icon. The Icon can deliver treatment with improved conformity, dose fall off, sparing of adjacent OARs, and sparing of normal brain tissue compared to prior GK models [5, 7, 24, 35–38]. This machine can be used to treat intracranial lesions or vertebral lesions up to and including the C3 level. The Icon can employ frameless immobilization and is equipped with onboard CBCT and optical tracking for intrafraction motion [1, 4, 5, 15, 24]. With the Icon, studies have shown a total error of below 1 mm [1, 2, 9, 15, 24, 39].

Linac

Linacs were first developed in the 1950s and have been used since the 1960s for the overwhelming majority of patients treated with conventional radiotherapy (RT) [13, 21, 22]. Leksell and his colleagues did not pursue linac SRS because existing linacs had a variety of shortcomings that made them unreliable, including low beam energy, low output, limited range of motion of the

gantry and couch, and inaccuracies in patient positioning and dose delivery. In the 1990s, many of these limitations were overcome and linac SRS systems were developed [1, 3, 6, 7, 14, 21, 22]. Key technological developments included smaller machines, higher beam energy and output, improved collimation, flattening filter-free (FFF) beams, greater and more precise automated gantry and couch mobility, improved target localization and image guidance systems, and dedicated TPS [1, 5, 7, 21, 22].

Beam Properties, Arrangement, and Shaping

In a linac, an electron beam is accelerated toward a heavy metal alloy, and the interaction of the electron beam with the metal produces x-rays, which can be focused upon a target. For linac SRS, numerous high-energy x-ray beams are sequentially focused on the intracranial target [1, 2, 5, 13, 21, 22]. The energies commonly used for linac SRS are 6 and 10 MV, associated with constant dose rates of 3–6 Gy/min over the lifetime of the machine [16, 21, 22]. The gantry can be rotated around an isocenter located within the patient, and the couch itself can also be rotated, so that the numerous non-coplanar beams are focused upon the lesion, allowing for conformal dose around a target volume, with minimal dose to surrounding tissues [8, 13, 21, 22].

The linac radiation beam is shaped by conical collimators or by MLCs and mMLCs [1, 2, 5, 7, 13, 16, 20–22]. In conventional RT, the beam passes through a flattening filter (FF), which homogenizes the beam as low energy x-rays are filtered out. Treating without an FF significantly increases the dose rate. For the high fractional doses delivered with SRS, flattening filter-free (FFF) treatment allows for significant decreases in treatment time. In addition to increased patient comfort, the reduced treatment time potentially decreases patient intrafraction motion. All major linac SRS platforms now offer a FFF treatment mode [1, 12, 21].

Treatment Planning and Delivery

In linac SRS, the treatment is often prescribed to the 80–90% isodose surface. There are dedicated TPS for linac SRS, which can create single and multiple isocenter plans, with planar and non-coplanar fields, and forward or inverse planning. In the earliest linac SRS plans, a single isocenter was used, creating a roughly spherical dose distribution. Non-spherical targets were treated with the smallest sphere of dose encompassing the entire target. With multiple isocenter plans, by combining dose distributions, more complex treatment volumes can be delivered [8, 20–22].

There are several different methods available for treatment planning and delivery with linac SRS, including static fields, dynamic conformal arcs, intensity-modulated radiotherapy (IMRT), and volumetric modulated arc therapy (VMAT). In static field planning, fields of fixed position are used, and shaped with collimators, equivalent to 3D conformal technique in conventional RT. With dynamic conformal arcs, the field rotates in an arc around the target, and MLCs or mMLCs alter field shape to match the shape of the target at each position [16, 20–22]. With IMRT planning, the time that the beam spends in any location and the leaf configuration can be modulated during radiation delivery, along with the photon fluence [1, 3, 12, 13, 16, 20–22]. IMRT allows for increased dose to areas of tumor and decreased dose to normal tissues, in a more complex and precise manner. VMAT allows for delivery of intensity-modulated radiation along an arc around the isocenter, rather than from a series of static positions, and can be delivered from non-coplanar arcs, improving the dose fall off outside the target. As the gantry rotates along its arc, dose rate, MLC shape, intensity, and gantry speed can all be independently controlled by the TPS running the linac. IMRT and VMAT planning allows for highly conformal complex dose distribution plans, with sharp dose fall off, as well as shortened treatment time [12, 20–22].

With advances in diagnostic techniques and oncologic therapies, patients with intracranial

metastatic disease are living longer. This, combined with improved SRS capabilities, has resulted in patients with increasing numbers of brain metastases receiving SRS. Consequently, vendors have been developing TPS specifically for planning treatment of multiple brain metastases. Elements (Brainlab) and HyperArc (Varian) are examples of such TPS [21].

Immobilization and Image Guidance

Initially linac SRS used a rigid headframe, but in modern systems, frameless treatment can be delivered, in combination with image guidance [12, 16, 21, 22, 27]. Linac image guidance can be accomplished with a CBCT mounted perpendicularly on the linac gantry, using orthogonal kV x-rays, optical tracking, or a combination of these tools [3, 5, 12, 21, 22, 27]. Modern linac couches have 6 degrees of freedom (6DOF), allowing for motion along the three primary Cartesian axes, as well as three rotational directions (pitch, roll, yaw). Such flexibility of couch motion was crucial in the development of frameless SRS, as it allowed for the most precise patient positioning based on image guidance [7, 12, 21–23, 27]. Overall, modern linacs are able to deliver SRS with the same accuracy and precision as GK [39].

Cost

Dedicated linac SRS platforms are less expensive than GK SRS, and modifying an existing linac to perform SRS is the most cost-effective means of establishing an SRS program. In the early 2000s, the cost of implementing a new linac SRS system was approximately US$2.5–3.2 million. Updated estimates of cost are difficult to obtain, as this information is not made public by vendors but is likely US$3–4 million. A TPS may cost an additional several hundred thousand dollars. It has been estimated that 122 SRS patients must be treated annually to break even with a dedicated linac SRS system, though the system can also be used for conventional RT. Because linacs are more complex than other SRS platforms, they require more intensive maintenance and QA [10, 16, 22].

Modern Model

An example of a modern linac for SRS treatment is the Novalis TX (Brainlab AG), a linac able to deliver radiation at 2 energies, with beams shaped by an mMLC consisting of 120 2.5 mm leaves. The Novalis TX system can be used for intra- or extracranial treatments, and for SRS, SBRT or conventional RT. It can deliver SRS treatment via static fields, dynamic arcs, IMRT, or VMAT. Novalis TX can perform frame-based and frameless SRS, as necessary. For image guidance, the Novalis TX machine includes dedicated stereotactic kV x-ray imaging equipment mounted in the floor and above the linac and a CBCT mounted on the linac gantry [1, 7, 21, 22]. Treatment of multiple metastases simultaneously with a non-coplanar VMAT or 3D forward planned approach on a linac permits brain metastasis radiosurgical treatment session times to be reduced below a half an hour, though considerable time is required to perform the necessary planning steps, of course.

CyberKnife

The CK (Accuray Inc., Sunnyvale, CA), developed by neurosurgeon John Adler in the late 1990s, is a lightweight 6 MV linac mounted on a robotic arm. The goal in designing the CK was to create an SRS tool, which could deliver high doses of RT conformally to target lesions, with sharp dose fall off, without requiring an invasive headframe or being limited to intracranial sites [2–7, 10, 13, 21, 23, 25]. It was first used to treat patients in 1994 at Stanford University, and at that time was called the Neurotron 1000. The CK system gained FDA approval for intracranial use in 1999 and for full-body use in 2001 [5, 6, 13, 23].

Beam Properties, Arrangement, and Shaping

The CK produces an unflattened 6 MV beam from a lightweight linac with dose rates of 3–6 Gy/min, constant over the lifetime of the machine [4, 6, 12, 21, 23, 25]. A major innovation of the CK system is the robotic arm, which moves the linac about the patient with 6 DOF, compared to conventional linac gantries, which can rotate only in one plane. It directs the radiation from numerous angles and positions above (but not below) the patient, such that hundreds of small, circular non-coplanar beams converge upon the target [1, 2, 5–7, 10, 13, 21, 23, 25]. Each beam of treatment is defined by a 'node,' consisting of a robotic arm location, a beam direction, and a field size. Usually, 23–133 unique beams are employed in a single CK treatment, but there are over 1000 possible beam directions. This flexibility is a distinct advantage of CK, allowing for treatment planning with excellent homogeneity and conformity, even with large and complex targets [6, 9, 12, 21, 23, 25].

The CK system can use fixed circular collimators, creating a beam diameter of 5–60 mm. The more advanced IRIS variable collimator employs 12 secondary tungsten-copper alloy circular collimators and automatically changes aperture size, decreasing treatment time [6, 7, 12, 21, 23, 25]. The newest CK collimation system, the InCise, consists of 2 banks of 26 leaves, and brings MLC beam shaping to CK treatment. The InCise MLC is able to further reduce treatment time and improve conformity, especially for complex targets [23]. The InCise system can also be employed for multitarget radiosurgical treatments to decrease treatment delivery time [40].

Treatment Planning and Delivery

CK treatments are prescribed to the 50–80% isodose surface [21, 23, 25]. Given their unique features, CK systems use a dedicated TPS, Multiplan, or the more recent Precision, capable of isocentric and non-isocentric treatment, with forward or inverse planning [1, 6, 7, 9, 21, 23, 25]. Non-isocentric plans are particularly useful for conformally and homogeneously treating complex target volumes. Since treatment time is a significant concern with CK SRS, an attempt is made to reduce the number of nodes, while maintaining plan quality. Based upon the treatment plan, the robotic arm travels along a predetermined path from node to node, delivering radiation in a step-and-shoot manner [9, 21, 23, 25].

Immobilization and Image Guidance

The CK is an exclusively frameless SRS system that employs real-time image guidance to assure accuracy. In CK, image guidance for initial patient setup, prior to treatment delivery from each node, and for movement correction during treatment consists of the orthogonal kV x-ray method described [1, 4, 6–10, 12–14, 21, 23, 25]. For CK, this system is referred to as 6D skull tracking. If any patient motion or target misalignment occurs, radiation delivery is automatically halted, the robot readjusts, and treatment resumes [6, 7, 14, 21, 23, 25]. Different publications recommend different frequencies of image guidance during treatment, ranging from every 1–5 minutes [12].

Cost

CK systems require a substantial initial investment, in addition to considerable maintenance expenditures. The cost of a new CK system is approximately US$3.5 million [16, 25]. Since radiation beams can be directed from such a variety of locations and directions, all walls, including the ceiling, must be primary radiation barriers reinforced with concrete, so a dedicated or upgraded vault is required. Alternatively, if CK is to be used in a conventional linac room, the beam angles employed must be limited [5]. Hardware and software for the CK system are estimated to cost US$225,000–450,000 per year. Approximately 109 treatments annually are necessary to break even with the CK system,

but these numbers can be reached with the addition of extracranial treatments to intracranial SRS treatments [16, 25].

Modern Model

The modern CK system, the CK M6, can deliver dose rates of up to 1000 MU/min, in as many as 1600 beam directions. CK M6 includes a couch with 6DOF, such that patients can be set up efficiently and reliably. The CK M6 also includes fixed collimators, the IRIS variable collimator system, and the InCise MLC system. With these updated features, the CK M6 can deliver intracranial treatments in 15–60 minutes, depending upon the complexity of the case; average treatment times are approximately 30 min. With the CK M6, employing initial and near real-time imaging, treatment accuracy has been reported as submillimeter, comparable to that delivered with headframe systems [9, 23].

Protons

Beam Properties, Arrangement, and Shaping

Proton therapy confers several advantages over photon RT. Uniquely, protons stop their propagation through tissue at the point of maximum energy deposition in the tissue. There is a slow increase in dose deposition with depth, followed by a steep increase toward the end of the range, at the Bragg peak. There are minimal ionizations beyond the Bragg peak, sparing tissue beyond the target. This confers dosimetric advantages to proton therapy, especially in the context of SRS, where sparing of normal tissue is paramount [1, 14, 17–19]. With reduced angle of scatter, proton therapy also attains a steep lateral dose fall off, minimizing dose spill laterally [1, 14, 19, 41]. Protons in the energy range used therapeutically have radiobiological effectiveness (RBE) of 1.1. Therefore, the ability of protons to induce cellular damage is comparable to that of photons, but perhaps 10% higher. These dosimetric features make proton therapy an attractive candidate for SRS [17–19]. For therapeutic use, protons are accelerated using a cyclotron or synchrotron and directed to the gantry, maintaining their energy via bending magnets. Proton beam energies used for RT are usually 150–250 MeV. Apertures or collimators can be used to shape the beam, and a range of compensators can be used to finely control the distal edge of the field [17–19].

Treatment Planning

Since the Bragg peak is very narrow, a single proton beam is not practical therapeutically. For treatment of targets wider than the Bragg peak, two planning methods have been established: passive scattering and scanning beam. Passive scattering involves scattering and flattening the beam, combining beams of different energies such that the target is covered. Passive scattering technique is comparable to conventional 3D conformal radiation planning, making highly conformal complex plans challenging to generate [1, 17–19]. However, studies have demonstrated that with experienced users, passive scattering proton plans can be generated, which are dosimetrically superior to photon SRS plans. Scanning beam planning involves using changes in beam energy to vary depth of dose deposition, as the beam scans across the width of the target. As the proton nears the gantry, an electromagnetic field is used to modulate the direction and energy of the beam such that the proton deposits energy in a specific plane or voxel. Scanning beam technique can be employed such that each field covers the target, single-field uniform doses, or multiple fields with intensity modulation and inverse planning can be used. Since this planning technique is similar to photon IMRT, it is sometimes called intensity-modulated proton therapy (IMPT). IMPT is useful for conferring increased conformity with irregularly shaped targets or those near critical structures. One shortcoming of this planning approach is that, secondary to its great conformity, it is very sensitive to motion or setup error [17–19].

Proton SRS planning carries unique dosimetric challenges. There is some uncertainty in the con-

version of CT Hounsfield units to proton stopping power, in the range of each beam, and in the depth of the Bragg peak [17–19]. Additionally, most proton TPS apply a constant RBE of 1.1 for converting proton dose to equivalent photon dose, but the RBE likely changes along the proton range. The RBE may also change based upon histology, dose, and fractionation, factors not accounted for in proton TPS [17–19, 42, 43]. One approach for overcoming these uncertainties is to add a margin to the lesion when creating the treatment volume. While this will increase the likelihood of target coverage, it mitigates some of the benefits of proton therapy in sparing surrounding tissues. Another method is known as the "smearing technique," in which compensator dimensions are changed within the range of uncertainty to ensure that the target lesion is covered adequately [18, 19].

With regard to treatment efficiency, any change in proton energy requires approximately 2 seconds. In IMPT plans, energy could be changed as many as 50 or 60 times, as layers of treatment are delivered. In a three- or four-beam IMPT proton plan, 5 or 6 minutes would be required simply for energy change, in addition to actual radiation delivery time [19].

Immobilization and Image Guidance

Given the highly conformal nature of proton therapy, the sharp dose fall off, and the sensitivity of protons to changes in tissue shape or density, immobilization and localization are even more critical than in conventional SRS. The immobilization and patient positioning methods used for other SRS modalities can be used for proton SRS. Dedicated frame-based and frameless immobilization systems have also been developed specifically for intracranial proton RT, similar to those for other platforms. As with other SRS modalities, a variety of models and techniques exist. Patients sometimes undergo additional steps to ensure appropriate target localization, such as placement of fiducial markers within the outer table of the skull. On-board imaging systems compatible with proton machines, such as x-ray, fluoroscopy, or CBCT, are also well-developed [17–19].

Cost

Because protons have substantially higher mass than electrons, cyclotrons or synchrotrons capable of accelerating protons are of considerable size and require high energy input. The cost of establishing a proton facility is at least an order of magnitude higher than for any photon SRS platform. Historically, building a proton therapy medical facility could cost as much as US$120–200 million. With more modern technology and increasingly compact systems, it may be possible to establish a single room proton facility for approximately US$30 million. A multi-room facility could cost over US$100 million. Additionally, dedicated maintenance, QA, and trained staff such as physicists and engineers confer high operational costs [14, 18, 19].

Efficacy and Appropriate Indications

Delivery of therapeutic radiation doses to CNS lesions is often challenging, secondary to dose constraints of adjacent OARs. Given the dosimetric advantages of proton therapy, treatment of CNS lesions may be an appropriate application for proton therapy. Evidence regarding feasibility, efficacy, and toxicity of proton SRS is limited and is largely derived from retrospective single institution series. Given limited availability and high cost of proton SRS, coupled with a lack of robust, prospective, randomized efficacy and toxicity data, guidelines regarding which patients are appropriate for such treatment are lacking [17–19]. There continues to be great controversy regarding appropriate use of proton therapy [17–19, 44, 45]. In general, proton SRS may be considered for patients who are young, have benign intracranial lesions, have malignant lesions with long expected survival, have lesions adjacent to sensitive OARs, require re-irradiation, and finally for those participating in clinical trials. The feasibility, efficacy, and safety of proton SRS have been demonstrated for several intracranial lesions, including vestibular schwannoma, AVM, pituitary adenoma, and meningioma [17–19]. There is great need for more compelling evidence from randomized controlled trials regarding the benefits of proton SRS.

Table 21.1 Key features of different SRS platforms

	GK Icon	LINAC	CK M6	Proton SRS
Beam source	Gamma ray	X-ray	X-ray	Proton
Beam energy	1.25 MeV Co-60	6 or 10 MV photons	6 MV photons	150–250 MeV
Beam arrangement	192 fixed converging beams	Planar and non-coplanar beams	Non-coplanar beams	Planar and non-coplanar beams
		Arcs		
Beam shaping	Circular collimators	Circular collimators	Circular collimators	Collimators
		MLCs	MLCs	Apertures
				Compensators
Treatment planning	Shot-packing	Static fields	Shot-packing	Passive scattering
		IMRT		Scanning beam
		Dynamic arcs		(IMPT)
		VMAT		
Dosimetry	High conformity	High conformity	High conformity	High conformity
	Low homogeneity	High homogeneity	High homogeneity	High homogeneity
	Decreased low-dose spillage	Greater low-dose spillage	Greater low-dose spillage	Least low-dose spillage
Immobilization	Invasive Headframe	Invasive Headframe	Frameless	Invasive Headframe
	Frameless	Frameless		Frameless
Image guidance	CBCT	Planar x-rays	Planar x-rays	Planar x-rays
	Optical monitoring	CBCT		CBCT
		Optical monitoring		
Machine availability	Dedicated intracranial SRS unit	SRS, SBRT, and conventional RT, intracranial and extracranial sites	SRS and SBRT only, intracranial and extracranial sites	Limited availability

Table 21.1 provides a summary of the key features of the different SRS platforms.

Comparisons

Much debate has been generated regarding the benefits and shortcomings of the various SRS modalities and, unfortunately, existing literature comparing different SRS systems is largely retrospective with low sample sizes [7, 12, 16]. These studies are often multi-institutional, with a different machine at each facility, as it would be impractical and costly for one center to have two SRS platforms. There may be significant differences in patient populations, staff expertise, and treatment planning across institutions [3]. SRS planning is very complex, and different studies have evaluated different machine models, dose prescriptions, target volumes, target locations, target numbers, beam arrangements, planning techniques, outcomes, etc. [7]. This further complicates comparisons of SRS technologies, and adds to the controversy.

While each SRS system has distinct advantages and disadvantages, it is important to stress that the overall clinical efficacy of all modern platforms is felt to be equivalent. Each system should be able to generate and deliver acceptably accurate and precise high-quality SRS plans [4, 14, 16, 21, 46]. As technological advances lead to improved plan quality, the dosimetric differences between platforms are likely to decrease further. It warrants emphasis that user expertise is likely the most vital determinant of plan quality [8, 12, 16]. Large, multi-institutional, prospective trials would likely be required to definitively determine whether any SRS platform confers dosimetric or clinical advantages.

Clinical Outcomes

Since GK SRS has been in use the longest, the published literature regarding clinical outcomes is most robust for GK. Despite significant differences in the SRS platforms with regard to how radiation is prescribed and planned, and the resultant dose distributions, studies to date have not found significant differences in clinical outcomes for patients with brain metastases depending upon treatment modality [10, 47–49]. The use of SRS for patients with a limited number of intracranial metastases (1–4) has been well established [46, 48–50]. As oncologic treatments improve and patients with metastatic disease live longer, SRS is increasingly being used in the management of multiple brain metastases [41, 46, 48]. More recently, Yamamoto et al. demonstrated that SRS management of patients with 5–10 brain metastases resulted in non-inferior overall survival relative to those with 1–4 metastases [51]. Currently, there are no published clinical trial data establishing the role of SRS in patients with multiple (>4) brain metastases, though there are ongoing phase III trials exploring the role of SRS in this patient population [48]. That said, it may well be that volume of disease treated in the brain is more important than the number of metastases. Numerous prospective and retrospective studies have been published regarding disease outcomes with SRS for multiple brain metastases [2, 7, 9, 47, 48]. In these studies, a wide range of local control (LC) rates is found, likely due to heterogeneity in patient diagnosis, performance status, and burden of systemic or intracranial disease [48]. However, in general, excellent outcomes are conferred by SRS, with LC rates at 1 year ranging from 69.5% to 97% [2, 7, 9, 47–49]. Given their reduced life expectancy, patients with brain metastases have not been managed extensively with proton SRS. In fact, to our knowledge, there is only one publication regarding proton SRS for brain metastases. Atkins et al. retrospectively evaluated 370 patients with 815 brain metastases. They reported 1 year LC of 91.5% [41].

Dosimetry

Treatment of single brain metastases is relatively straightforward, and a high-quality plan can be generated regardless of modality used. As physicians are treating patients with increasing numbers of sometimes complex targets, this places additional dosimetric demands on the SRS system. Several studies have compared dosimetric features of the different SRS platforms in the management of multiple brain metastases [7, 39, 46, 47, 52–54]. With regard to conformity in multiple brain metastasis plans, the data generally indicate superiority of GK compared to linac SRS. Further, linac may perform better than CK [39, 46, 54]. GK treatments are often prescribed to the 50–80% isodose surface, leading to increased maximum dose, dose inhomogeneity, and dose fall off [8, 15, 20, 24, 46, 47, 55]. Prescription to a higher isodose surface, such as with linac and CK, allows more homogeneous dose distributions [16, 20–22, 46, 55]. The strongest determinants of dose fall off are target volume and number, but treatment planning techniques can also influence dose fall off. Comparative studies either demonstrate the sharpest dose fall off with GK or report similar dose fall off across the platforms [7, 39, 46, 52–55].

Since a goal of SRS is to reduce radiation exposure to surrounding tissues, dose to normal brain is an important factor to consider. In addition, V10 or V12, the volume of normal brain receiving 10 or 12 Gy, are important validated predictors of symptomatic radionecrosis for single-fraction SRS [4, 7, 8, 46, 47, 55]. In management of multiple brain metastases, there is literature to support improved V12 with GK relative to linac and CK [46, 50, 52, 53, 55, 56]. However, these findings have not been universally observed, and some studies have not demonstrated any difference in normal brain V12 across the SRS platforms [54]. The greatest concern with treating multiple intracranial lesions is the integral dose to normal brain tissues [53]. It is noteworthy that there are no published data establishing any neurocognitive consequences of this low-dose spillage and any

benefits of normal tissue sparing are theoretical [41, 46, 53]. The published literature most commonly demonstrates sparing of normal brain tissue from low-dose radiation, measured as V3–6, with GK, compared to the other platforms [46–48, 53, 54, 56]. At least one study has further demonstrated improved V4 with linac compared to CK [46]. Of interest, in the sole brain metastasis proton SRS study published to date, the authors generated linac plans for 10 representative patients and reported improved V4 and V10 with proton SRS [41]. Other dosimetric studies have confirmed decreased integral brain dose with proton SRS compared to photons [41, 57–59].

Extracranial radiation doses for various photon radiosurgery platforms have been measured and compared, and the lowest radiation doses outside the brain are seen with the Gamma Knife platform. Successively higher doses are delivered with linac radiosurgery and CyberKnife radiosurgery, which may confer higher risks of secondary malignancies in patients treated for conditions for which long survivals are expected (Paddick I, Personal communication, 2019).

Treatment of multiple brain metastases via linac confers significantly reduced treatment time compared to GK and CK [39, 46, 48, 50, 54]. Single isocenter VMAT plans, especially, can increase treatment efficiency, potentially at the cost of increased low-dose spillage [46]. Reduced treatment time increases patient comfort and reduces the likelihood of intrafraction motion and the need for real-time imaging [48]. Treatment time with GK can be as much as three to five times longer than with VMAT linac SRS in multiple lesion plans [39]. In patients with multiple brain metastases in whom minimizing treatment time is an important consideration, linac SRS may be the modality of choice.

Table 21.2 provides a summary of the major advantages and disadvantages of the different SRS modalities.

Table 21.2 Advantages and disadvantages of different SRS platforms

	Advantages	Disadvantages
GK Icon	Most robust, long-term efficacy, and safety data Sharp dose fall off, minimal low-dose spillage Simple system, minimal maintenance and QA Least shielding required Best suited for very small lesions near critical OARs	Dedicated intracranial or high cervical SRS machine Co-60 decay causing variable dose rate over time and necessitating eventual source replacement Longer treatment time
LINAC	Widespread machine availability Easiest and cheapest to establish SRS program Machine versatility (conventional RT, SBRT, SRS) Extracranial treatments Most efficient treatment delivery Best suited for large lesions and efficient treatments	More maintenance and QA Higher low-dose spillage
CK M6	Flexibility in beam arrangement Extracranial targets	More maintenance and QA Most shielding required SRS and SBRT only Higher low-dose spillage Longer treatment time
Protons	Best dose fall off distal to target and laterally Least low-dose spill, best normal tissue sparing	Limited machine availability High cost Least efficacy and safety data Uncertainties in dosimetry

Conclusion

The critical features of several modern SRS platforms, GK, linac-based, CK, and proton have been reviewed and critically compared with regard to clinical efficacy and plan quality. Overall, the choice of ideal SRS platform for each individual case is a complex one, and myriad machine, patient, and target factors can be considered, including patient performance status and prognosis, radiation source, dose rate, collimator type, beam arrangement, method of immobilization, image guidance, TPS, treatment time, lesion size and shape, and distances to OARs.

Of course, the experience of the entire treatment team, including radiation oncologist, neurosurgeon, dosimetrists, physicists, and therapists, must also be considered. It may be the case that patients with more complex and challenging treatments should be evaluated at regional centers of excellence, given that treatments can be provided in one or only a few treatments, minimizing inconvenience and potentially optimizing long-term outcomes.

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22

Stereotactic Radiosurgery: Indications and Outcomes in Central Nervous System and Skull Base Metastases

Henry Jeison Ruiz-Garcia, Daniel M. Trifiletti, and Jason P. Sheehan

Abbreviations

ASTRO	American Society for Radiation Oncology
CDFS	Cognitive Deterioration Free Survival
CP	Cognitive preservation
CSF	Cerebrospinal fluid
CT	Computed tomography
CTV	Clinical target volume
DS-GPA	Diagnosis-specific Graded Prognostic Assessment
EORTC	European Organization for Research and Treatment of Cancer
FI	Functional independence
GPA	Graded Prognostic Assessment
GTV	Gross tumor volume
HSRS	Hypofractionated stereotactic radiosurgery
KPS	Karnofsky Performance Status
LC	Local control
LINAC	Linear accelerator
LMD	Leptomeningeal disease
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NSCLC	Non-small cell lung cancer
OS	Overall survival
PTV	Planning target volume
QoL	Quality of life
RCT	Randomized controlled clinical trial
RN	Radiation necrosis
RPA	Recursive partitioning analysis
RTOG	Radiation Therapy Oncology Group
SRS	Stereotactic radiosurgery
UPMC	University of Pittsburgh Medical Center
WBRT	Whole-brain radiotherapy

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Introduction

Brain metastases account for the majority of intracranial brain tumors, most frequently originating from cutaneous melanoma and carcinomas of the lung, kidney, and breast. Brain metastases appear in 20–40% of cancer patients, even in the setting of controlled extracranial disease, leading to 200,000 newly diagnosed cases per year in the United States [1].

The prognosis of patients with brain metastases has evolved over time, with survivals historically ranging from 1 to 2 months for untreated patients to up to 27 months and beyond with multi-modal therapy. Whole-brain radiotherapy (WBRT) has been

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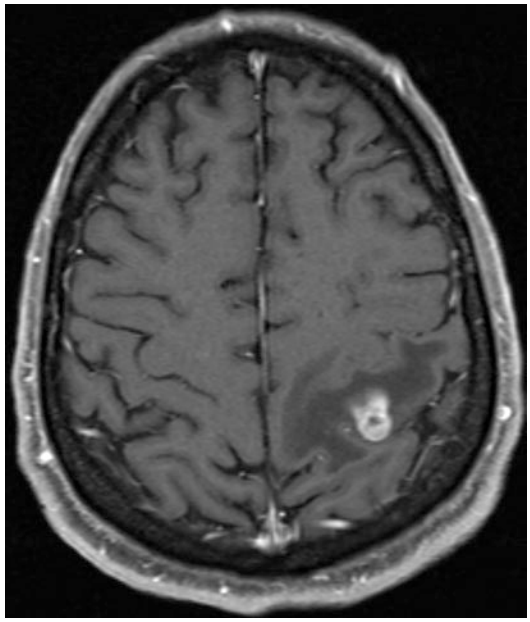

Fig. 22.1 Typical appearance of a T1-weighted post-contrast axial MRI image from a patient with a metastatic brain lesion from primary lung cancer located on the left postcentral gyrus with associated edema

utilized for more than 60 years and has shown a benefit in the treatment of neurologic symptoms and intracranial tumor control. However, in more recent years, WBRT has been shown to increase the risk of iatrogenic neurocognitive deficits and worsen quality of life (QoL) relative to stereotactic radiosurgery (SRS) [2]. Advancements in imaging technology have allowed for early (presymptomatic) identification of brain metastatic lesions in cancer patients (Fig. 22.1). As a result, SRS has become a dominant therapeutic option in the management of selected patients with one to four metastases and even in patients harboring 10 or more lesions [3].

Contemporary management of patients with brain metastases typically involves a multimodality regimen, including some combination of surgery, WBRT, SRS, glucocorticoids, and/or systemic therapy. Each patient should be evaluated in a personalized manner, and ideally, every patient eligible for treatment should also be considered for radiosurgery, weighing the risks and benefits [4, 5].

In this chapter, we will discuss the rationale for patient selection in SRS, SRS in the postoperative and preoperative setting, SRS for previously irradiated patients, and SRS near critical intracranial structures.

Stereotactic Radiosurgery

During SRS, a large dose of highly conformal radiation is delivered in one to five fractions at the targeted lesion. This is possible due to the creation of a sharp dose fall-off at the margin of the tumor that allows for the sparing of surrounding normal tissue. Since the Swedish neurosurgeon Lars Leksell described the stereotactic utilization of therapeutic irradiation in 1951 in the paper entitled "The Stereotaxic Method and Radiosurgery of the Brain" [6], newer systems have been launched allowing improved sparing of normal brain tissue. Currently, linear accelerator (LINAC)-based SRS, Cyberknife®, and Gamma Knife® technologies allow treating patients with "frameless" SRS with safety and reliability afforded by real-time patient tracking during irradiation.

SRS has emerged as one of the most effective treatments for the management of brain metastases. SRS has similar survival outcomes and is associated with less neurocognitive side effects, as compared to WBRT [2, 7]. Furthermore, it is often delivered in a single ambulatory session and does not interrupt or delay systemic therapies.

Prognostic Scoring Systems and Patient Selection

Patients with brain metastases were generally classified as a single group until 1997, when a paradigm shift occurred after the publication of the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) [8]. The RPA identified patient clinical factors

that influence survival and prognosis, allowing for improved clinical decision making. Later, specific biological tumor features were included in the Graded Prognostic Assessment (GPA) and diagnosis-specific GPA (DS-GPA) scoring systems [9, 10], incorporating more disease-specific parameters and even molecular profiles into the prognostic systems. Consequently, clinicians have more tools than ever to provide patients with optimized and personalized therapy.

Stereotactic Radiosurgery for the Management of Patients with One to Four Brain Metastases

Role of Surgical Resection

Phase III randomized clinical trials (RCT) have established that surgery improves the survival of oligometastatic intracranial disease [11–13]. Patchell et al. described the benefit of adding surgery to WBRT in patients with solitary brain metastasis, by randomizing patients into "surgery + WBRT" versus "biopsy only + WBRT"; surgery improved local control, preservation of functional status, and most importantly, overall survival (OS) [12]. To determine if surgery alone without WBRT was sufficient for patients presenting with solitary brain metastasis, Patchell et al. conducted a subsequent phase III RCT and found that surgery with WBRT was superior to surgery alone in terms of intracranial tumor control (local and distal failure) and decreasing neurologic death; however, there was no significant difference with regard to OS [14]. Very similar findings in oligometastatic patients presenting with one to three lesions were reported more than a decade later by Kocher et al. as part of the EORTC 22952-26001 study (Table 22.1) [15]. Thus, patients with oligometastatic disease should routinely receive neurosurgical evaluation for potential resection. This is especially important in patients with large tumors (generally >3 cm), particularly if it is causing edema and/or if neurologic symptoms refractory to steroid management, as surgical decompression is the fastest manner to improve neurological function [20, 21].

Postoperative Irradiation: SRS or WBRT?

Even as the studies from Patchell et al. [14] and Kocher et al. [15] positioned postoperative WBRT as the standard of care in oligometastatic patients, concerns were raised over the detrimental effects of WBRT on quality of life (QoL) domains such as fatigue and cognitive impairment [2, 19, 22, 23].

As a result of the most recent advances in SRS, radiosurgery has challenged the historical use of WBRT. Postoperative SRS to the surgical cavity following the resection of brain metastases has established itself as a reasonable standard of care, owing to data from phase III RCT [24]. The parallel development of hypofractionated postoperative SRS and preoperative SRS could potentially both minimize symptomatic radiation-induced injury and improve local tumor control [25–27].

Postoperative Resection Cavity SRS

Apart from the neurotoxicity associated with WBRT, postoperative WBRT can delay systemic therapy, especially if the patient needs to recover from acute side effects.

Although numerous retrospective studies reported local control rates from 70% to 90% with SRS to the postoperative resection cavity [28], Brennan et al. from Memorial Sloan Kettering Cancer Center published the first prospective trial and detailed local control, distant failure, and overall survival for patients with limited number of metastases. Delivering a median margin dose of 18 Gy (15–22 Gy), approximately 85% local control was reported during a median follow-up of 12 months [29].

Two recent phase III RCTs further validated the role of adjuvant postoperative SRS after

Table 22.1 Randomized controlled clinical trials evaluating different treatment combinations for patients carrying limited brain metastases

Phase III randomized controlled trials evaluating the role of surgery, SRS, and WBRT through the time									
Study	Randomization		Criteria	Primary end point	Tumor control		Survival	Functional outcomes	Radiation necrosis
					Local control	Distal control			
Evaluating the addition of surgery to WBRT									
Patchell et al. (1990) [12]	WBRT + Surgery	($n = 25$)	1 lesion	NR	52%	20%	40 w	Sx > Bx	NR
	WBRT + Biopsy	($n = 23$)	No RT		20% ($p < 0.02$)	13% ($p = 0.52$)	15 w ($p < 0.01$)	($p < 0.005$)	
Vetch et al. (1993) [11]	WBRT + Surgery	($n = 32$)	1 lesion	Overall survival	NR	NR	10 m	Sx + WBRT>	NR
	WBRT	($n = 31$)					6 m ($p < 0.04$)*	WBRT ($p < 0.06$)	
Mintz et al. (1996) [13]	WBRT + Surgery	($n = 41$)	1 lesion	Overall survival	NR	NR	6.3 m	NS	NR
	WBRT	($n = 43$)					5.6 m ($p = 0.24$)		
Evaluating the addition of WBRT to surgery									
Patchell et al. (1998) [14]	Surgery + WBRT	($n = 49$)	1 lesion	Local control	90%	86%	NS	NS	NR
	Surgery	($n = 46$)			54% ($p < 0.01$)	37% ($p < 0.01$			
Kocher et al. (2011)[a] [15]	Surgery + WBRT	($n = 81$)	1–3 lesions	OS with FI	59%	42%	10.7	NS	NR
	Surgery	($n = 79$)			27% ($p < 0.001$)	23% ($p < 0.008$)	10.9 ($p = 0.89$)		
Evaluating the addition of SRS to WBRT									
Kondziolka et al. (1999) [16]	WBRT + SRS	($n = 13$)	2–4 lesions	Local control	92%	34 m**	11 m	NR	0%
	WBRT	($n = 14$)	<2.5 cm		0% ($p < 0.001$)	5 m ($p < 0.002$)	7.5 m ($p < 0.22$)		0%
Andrews et al. (2004) [17]	WBRT + SRS	($n = 164$)	1–3 lesions	Overall survival	82%	NR	6.5 m	WBRT + SRS >	
	WBRT	($n = 167$)	<4 cm		71% ($p = 0.01$)	NR	4.9 m ($p = 0.04$)***	WBRT ($p = 0.03$)	

Evaluating the addition of WBRT to SRS									
Aoyama et al. (2006) [18]	SRS + WBRT	(n = 65)	1–4 lesions	Overall survival	96.9%	67.6%	7.5 m	33.9%	4.6%
	SRS	(n = 67)	each <3 cm		91.0% (p = 0.02)	49.2% (p < 0.003)	8 m (p = 0.42)	26.9% (p = 0.53)	1.5%
Kocher et al. (2011)[b] [15]	SRS + WBRT	(n = 99)	1–3 lesions	OS with FI	81%	67%	10.7	NS	13%
	SRS	(n = 100)			69% (p = 0.04)	52% (p < 0.02)	10.9 (p = 0.89)		8%
Chang et al. (2009) [19]	SRS + WBRT	(n = 28)	1–3 lesions	Cognitive outcomes	100%	73%	63%	52%****	
	SRS	(n = 30)			67% (p = 0.012)	45% (p = 0.02)	21% (p < 0.003)	24%	
Brown et al. (2016) [2]	SRS + WBRT	(n = 102)	1–3 lesions	Cognitive outcomes	90%	92.3%	7.4 m	SRS > WBRT+SRS	2.9%
	SRS	(n = 111)	<3 cm		73% (p < 0.003)	69.9% (p < 0.001)	10.4 m (p = 0.92)	For CP and QoL	4.5% (p = 0.72)

Abbreviations: *WBRT* whole-brain radiation therapy, *SRS* stereotactic radiosurgery, *Sx* surgery, *NR* not reported, *NS* not significant, *LC* local control, *OS* overall survival, *FI* functional independence, *CP* cognitive preservation

∗No differences for patients with active extracranial disease. ∗∗Time to any brain failure. ∗∗∗Survival time for patients with single metastasis (months). ∗∗∗∗HVLT-R total recall mean probability to decline

a & b are part of the same RCT (EORTC 22952-26001)

surgical resection of a limited number of metastases. Mahajan et al. [30] randomized 132 patients with one to three lesions to receive surgery and SRS or surgery alone, with respective local tumor control rates of 72% and 42%, supporting the use of SRS in the postoperative setting. Brown et al. reported results of NCCTG (N107C/CEC3) [31], a cooperative group phase III RCT comparing surgery + SRS versus surgery + WBRT in 194 patients with resected single metastatic brain lesions. Cognitive deterioration at 6 months was less frequent with SRS than with WBRT. As no differences were found in overall survival during a median 11.1 months follow-up, SRS was recommended over WBRT as a less toxic alternative in these patients (Table 22.2).

Larger tumor size/volume has been reported as an unfavorable risk factor for local control [32–34]. Brennan et al. had reported that tumor diameter >3 cm as well as superficial dural/pial invasion were associated with increased local failure [29]. On the other hand, lesions <3 cm, deep lesions, and non-small cell lung cancer (NSCLC) histology were associated with improved local control in the same study. In general, tumor recurrence at the surgical site was associated with increased volume of the surgical cavity or the lack of a 1–3 mm margin.

The Radiation Therapy Oncology Group 95-08 trial established the initial SRS margin dose recommendations in recurrent brain metastases and gliomas based on tumor diameter. However, it is now clear that dose prescription for SRS to a resection bed will depend on the postoperative resection cavity volume on postoperative imaging, as well as tumor location, previous irradiation, and prescription isodose.

The role of the margin expansion in target delineation was initially studied by the Stanford group. Soltys et al. [35] found improved local control in treatment plans with a lower conformality index—a measure of the compactness of the high-dose radiation given during SRS relative to the target volume. Choi et al. [36] later prospectively studied the role of target margin on tumor control of resection cavities treated by SRS, finding that the addition of 2 mm margins contributed to a statistically significant reduction in local failure at 12 months (16% vs 3%), with no significant increase in toxicity. The use of margin expansions is heavily dependent on radiosurgical platform and technique; extrapolation between centers should be done with caution.

Soliman et al. [37] published the *Contouring Consensus Guidelines for Postoperative Completely Resected Cavity Stereotactic Radiosurgery for Brain Metastases* in 2017, where SRS experts contoured 10 postoperative resection cavities of brain metastasis patients with lesions located in either supratentorial or infratentorial regions. Overall, the absolute kappa agreement for clinical target volume (CTV) was high in each of the cases (mean sensitivity 0.75, mean specificity 0.98). The findings led to the following recommendations on CTV contouring: (1) CTV should include the entire contrast-enhancing surgical cavity using the T1-weighted gadolinium-enhanced axial MRI scan, excluding any vasogenic edema determined by MRI; (2) CTV should include the entire surgical tract seen on postoperative CT or MRI; (3) if the tumor was in contact with the dura preoperatively, CTV should include a 5- to 10-mm margin along the bone flap beyond the initial region of preoperative tumor contact; (4) if the tumor was not in contact with the dura, CTV should include a margin of 1–5 mm along the bone flap; and (5) if the tumor was in contact with a venous sinus preoperatively, CTV should include a margin of 1–5 mm along the sinus. Clinical judgment is still required on a case-by-case basis until these recommendations are fully validated by clinical outcomes and patterns of recurrence [37].

Another important factor for postoperative SRS is the resection cavity volume dynamic [24]. Iorio-Morin et al. [38] recommended 3 weeks after resection as ideal timing to deliver SRS, after they found longer surgery-to-SRS delay to be associated with local recurrence on a multivariate analysis. This agrees with Patel et al. [39] who recommend against delaying SRS after surgery. After prospectively reviewing 79 cases, the authors found that there was a 28% increase in the postoperative cavity volume with a median time of surgery-to-SRS of 20 days and that, the

Table 22.2 Randomized clinical trials evaluating postoperative stereotactic radiosurgery to resection cavities in patients with brain metastases

Postoperative stereotactic radiosurgery to resection cavity in brain metastasis									
Study	Randomization		Criteria	Primary end point	Tumor control		Survival	Functional outcomes	Radiation necrosis
					Local control	Distal control			
Brennan et al. (2014)	Surgery + SRS	(n = 49)	1–2 lesions	LC at	85%	44%	14.7 m	NR	17.50%
Phase II [29] (MSKCC)			> 18 yo	12 m	50% (p = 0.08)[a]				
			PTV = cavity + 2 mm						
Mahajan et al. (2017)	Surgery + SRS	(n = 64)	1–3 lesions	LC	72%	42%	17 m	NR	0%
Phase III [30]	Surgery + Obs	(n = 68)	>3 yo		43% (p = 0.015)	33% (p = 0.35)	18 m (p = 0.24)		
			PTV = cavity + 1 mm						
Brown et al. (2017)	Surgery + SRS	(n = 98)	1 lesion, >18 yo	OS and	61%	64.70%	12.2	CDFS: 3.7 m	1%
Phase III [31]	Surgery + WBRT	(n = 96)	<5 cm	CDFS	81% (p < 0.0007)	89.2% (p < 0.0005)	11.6 (p = 0.7)	3 m (p < 0.001)	0%
			PTV = cavity + 2 mm						

Abbreviations: *WBRT* whole-brain radiation therapy, *SRS* stereotactic radiosurgery, *NR* not reported, *LC* local control, *OS* overall survival, *CDFS* cognitive deterioration free survival, *PTV* planning target volume, *Obs* observation

[a]Based on competing risk analysis including patients who completed postsurgical SRS and those who did not receive SRS (n = 40 and n = 10, respectively)

smaller the cavity, the higher the probability of postoperative cavity volume enlargement. The ideal interval between surgical resection and delivery of SRS was conjectured to be 2–3 weeks, as it allows for recovery after surgery and limits risk of local recurrence. Ultimately, though, it is clear that resection cavity sizes fluctuate after surgery. As such, it is imperative that planning MRIs be performed as close as possible to the actual time of radiation delivery. Platforms that involve MRI acquisition on the day of radiation treatment may thus have an inherent advantage in accuracy.

Hypofractionation and Postoperative Resection Cavity SRS

Single fraction SRS may have increased risk of toxicity in patients who have been previously irradiated, have lesions larger than 3 cm in diameter, produce more than 1 cm of midline shift, and/or abut critical organs-at-risk [40, 41]. According to the RTOG 90-05, recurrent previously irradiated lesions of 3.1–4.0 cm receiving 15 Gy, as the maximum tolerated dose, present a risk of unacceptable neurological toxicity up to 16 times that of lesions <2 cm [42].

Hypofractionated SRS is being increasingly used as it allows for dose escalation while limiting the risk profile, taking advantage of the improved repair of normal brain tissue. Eaton et al. reported on local control and the incidence and severity of radiation necrosis (RN) among patients treated with single fraction SRS or hypofractionated SRS (HSRS) for postoperative resection cavities ≥3 cm in diameter. Seventy-six patients with a median follow-up of 11 months were included. No significant differences in local control were found, but single-fraction SRS was associated with higher risk of radiation necrosis on multivariate analysis (HR: 3.81; 95% CI 1.04–13.93, $p = 0.043$).

Although several other retrospective studies support the utilization of hypofractionated SRS in the postsurgical setting for brain metastases [25, 26], there is still a lack of RCT data supporting the superiority of hypofractionated SRS over single-fraction SRS with regard to efficacy and toxicity.

Preoperative SRS

A novel potential strategy to approach some of the drawbacks associated with postoperative SRS is the use of preoperative SRS. Advantages include lack of need for margin addition to the gross tumor volume (GTV; GTV = PTV or planning target volume), no delay in treatment delivery, and the decreased risk of potential seeding of viable malignant cells into the CSF during surgery. Given that preoperative SRS treats a non-violated brain metastatic lesion, the borders will be well defined for target delineation; this could explain the decreased risk of radiation necrosis reported with this technique [25, 43].

Asher et al. [44] published the first study regarding local efficacy and safety of preoperative SRS for patients with one to three metastases where at least one of them was scheduled for surgical resection. A dose reduction strategy was used under the principle that intact brain metastases would maintain their blood supply and oxygenation and consequently a lower dose would be necessary to reach the same biological effect; 80% of the standard dose according to RTOG 95-08 was delivered 48 hours before surgery and no margins were applied for delineation (GTV = PTV). Overall survival at 6 and 12 months was 77.8% and 60% and local control at 6, 12, and 24 months was 97.8%, 85.6%, and 71.8%, respectively. There were no reports of leptomeningeal disease (LMD) during the 12-month follow-up.

A subsequent study from the same group compared postoperative WBRT with preoperative SRS. There were no differences in OS or LC, and interestingly no advantage with regard to LMD with WBRT [45].

Two potential drawbacks could arise with the use of preoperative SRS. The first is the possibility of incomplete resection of the metastatic lesion after a lower and less ideal preoperative radiosurgical dose. The second and major drawback is the lack of pathological confirmation of the lesion. Although there are no robust data, the

reported rate of false positive lesions ranges from 2% to 11%.

Radiosurgery as Definitive Treatment

SRS Versus Surgery

Currently, there are no clinical trials available comparing SRS and surgery. In 1996, Bindal et al. [46] from MD Anderson reported on this comparison. They prospectively followed 31 patients with lesions <3 cm who underwent SRS between 1991 and 1994 and matched them to 62 patients from a pool of retrospective cases that had only received surgery. Median SRS dose was 20 Gy (12–22 Gy) and WBRT was given equally in both groups. They found improved overall survival and local control with surgery. The authors suggested that SRS should be limited to surgically inaccessible lesions or patients with significant medical comorbidities.

Muacevic et al. [47] reported the results from a phase III RCT that was stopped prematurely given poor accrual. In the final analysis based on 64 patients with a single lesion <3 cm and randomized into surgery + WBRT or SRS alone, the authors found similar OS (median, 9.5 vs. 10.8 months, $p = 0.8$), LC (82% vs. 96%, $p = 0.06$), and neurological death rates (29% vs. 11%, $p = 0.3$). Although higher rates of distal recurrence were observed with SRS, this difference was not seen after salvage therapy.

A phase III RCT comparing surgery and SRS (both with adjuvant WBRT) was reported by Ross et al. [48]. Although there was a trend favoring SRS regarding OS (6.2 vs 2.8 months) and median failure free survival (3.1 vs. 1.7 months), the number of patients ($n = 21$) was too small to obtain any robust conclusions.

In general, either treatment should not exclude the other. We have already discussed the benefit of postoperative resection cavity SRS, and there is a growing body of knowledge on ways to balance the risks and benefits of these two approaches. Recent retrospective series showing the benefit of adding surgery to SRS support this premise [20, 21]. Regardless, it is clear that surgical resection, unlike SRS, can provide immediate intracranial decompression and pathologic confirmation.

The National Comprehensive Cancer Network (NCCN) recommends that surgery is followed by either WBRT or SRS for patients with one to three lesions and limited systemic disease. The choice between surgery and SRS depends on several factors such as size and location; a small, deep lesion should be treated with SRS at an experienced institution [49]. Surgery also can lead to almost immediate symptom relief as well as rapid discontinuation of glucocorticoid therapy.

SRS with or Without WBRT

Two RCT comparing WBRT with WBRT + SRS reported suboptimal local control with WBRT alone in patients with limited metastases [16, 17]. Four recent randomized studies evaluated SRS versus WBRT + SRS in patients with up to three to four metastases [2, 15, 18, 19] and reported the following conclusions: (1) adjuvant WBRT improves local and distal control; (2) adjuvant WBRT increases the risk of neurotoxicity, with consequent neurocognitive and quality-of-life decline; and (3) adjuvant WBRT does not improve survival over SRS alone (Table 22.1). This last conclusion has been challenged by retrospective studies. Wang et al. [50] who analyzed 15 years of experience from Columbia University Medical Center and a new secondary analysis of the JROSG 99-1RCT published by Aoyama et al. [51] have suggested that WBRT + SRS may improve OS in select patients with favorable prognoses. A secondary analysis of EORTC 22952-26001 did not find any survival advantage for WBRT relative to SRS in patients with limited systemic disease or favorable GPA scores [52]. The National Comprehensive Cancer Network (NCCN) recommends SRS plus WBRT (Level 1 evidence) or SRS alone (Level 2B evidence) for patients with a single brain metastasis, limited systemic disease, and good performance status.

The American Society for Radiation Oncology (ASTRO) [53] released a list of definitive recommendations as part of the *Choosing Wisely* campaign and recommended against routinely adding adjuvant WBRT to SRS for patients with limited brain metastases. The impact of WBRT on QoL and cognition should be taken into consideration, especially as salvage SRS or WBRT is always an option for dealing with future recurrences without worsening toxicity.

Stereotactic Radiosurgery for the Management of Patients with More Than Four Brain Metastases

Patients with a higher number of brain metastases should be managed with WBRT or SRS as primary treatment, unless at least one of the indications for surgery is present. While select patients with poor prognosis are offered WBRT [15], SRS is indicated for patients with good performance status and low overall tumor volume [49].

The group from University of Pittsburgh Medical Center (UPMC) [54] published outcomes of SRS for patients with four or more metastatic brain lesions. They found that cumulative tumor treatment volume was the most important prognostic factor for survival, supporting the use of the total volume of brain metastases rather than the number of lesions for treatment decision making. In their analysis, patients with a total treatment volume <7 cc and <7 brain metastases benefited the most from single SRS [55].

Yamamoto et al. [3] published the results of a non-inferiority trial in 2014 finding no differences in survival or treatment-related adverse events between the group of patients treated with SRS for 5–10 brain metastases and the group with 2–4 lesions (largest tumor <10 mL in volume and <3 cm in longest diameter, total cumulative volume ≤15 mL, KPS ≥70, SRS only treatment). This study supports the use of SRS for patients with five or more lesions; however, further prospective data are needed to validate other aspects of this treatment; recursive partitioning analyses could be useful to identify the groups of patients that can benefit the most from SRS. Several such studies are currently underway.

Stereotactic Radiosurgery in the Reirradiation Setting

Radiation necrosis is a known potential complication of SRS and can be difficult to distinguish clinically and/or radiographically from tumor recurrence. For intact brain metastases treated with SRS, rates of radiographic radiation necrosis (RN) could reach up to 24%, while in the postoperative resection cavity setting RN rates range from 1.5% to 18% [24]. If there is a high index of suspicion for recurrence, resection or stereotactic biopsy should be considered.

If recurrence is pathologically confirmed, SRS could be delivered as a salvage treatment in this context after previous WBRT. In the setting of resection for tumor recurrence after previous SRS, adjuvant therapy should be individualized, although observation after gross total resection is a reasonable approach. Repeat SRS can be offered, and other options include resection with intraoperative brachytherapy, detailed elsewhere in this book, and laser interstitial thermal therapy (LITT) to cauterize the tissue.

For patients who have previously been treated with SRS, the NCCN guidelines [49] recommend repeat SRS if there was a durable response longer than 6 months as long as imaging supports active tumoral lesion and not necrosis (2B recommendation). That said, imaging in the recurrent, post-treatment setting is often a mixed picture, and thus clinician best judgment must prevail. Because of the possibility of pseudoprogression in patients with metastatic disease, it is often prudent to monitor suspicious post-radiosurgical abnormalities unless they become symptomatic.

SRS for Brain Metastases Involving Eloquent or Critical Structures

Radiating eloquent regions of the brain requires a careful analysis of risk and benefit in order to prevent damage to adjacent tissues that serve important neurologic functions (Fig. 22.2). Sensorimotor, language, visual cortex, hypothalamus, thalamus, brainstem, cerebellar nuclei, optic pathways, and regions immediately adjacent to these structures are generally considered organs at risk of symptomatic radiation injury.

Two retrospective series evaluating SRS for metastases located in eloquent areas (primary motor, somatosensory, speech, and visual cortex; basal ganglia; thalamus; and brainstem) indicated that it is safe and effective [56, 57]. Hsu et al. reported no differences in the overall survival when compared to the cohort harboring non-eloquent lesions receiving a higher median prescription dose. New neurological deficits were transient and rates of radiation necrosis were as expected for SRS.

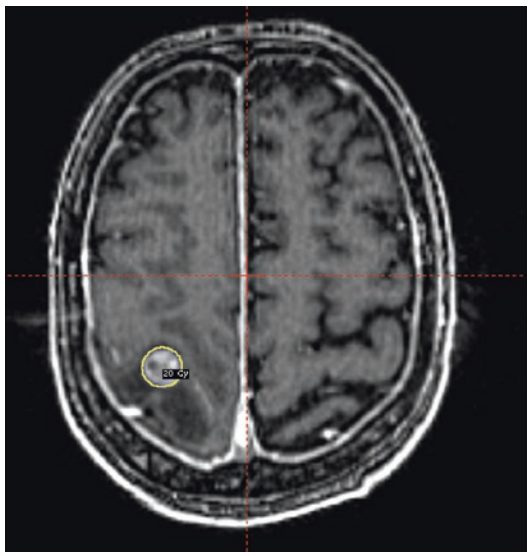

Fig. 22.2 T1-weighted post-contrast axial MRI image from a patient presenting a metastatic brain lesion from a soft tissue sarcoma primary located on the right postcentral gyrus. Given the tumor volume, SRS was delivered to a dose of 20 Gy. There have been no complications, and local control was maintained in the last follow-up at 12 months

In a study of radiosurgery in 161 patients harboring 189 metastases in the brainstem, 52% of had received whole brain radiotherapy (WBRT) prior to SRS. These results suggest that SRS can be safely administered after WBRT, even in eloquent or critical brain locations [58]. However, after this report, we conducted an international cooperative study to define response and toxicity in brainstem metastases and found an increased risk of injury when SRS is administered shortly after WBRT [40]. This could be due to sublethal damage from WBRT decreasing with time, allowing for recovery and lower radiation-induced injury risk with subsequent SRS. It is evident that previous intracranial therapies, specifically radiation, should be considered during treatment decision making.

Taken together, it is possible for an experienced team to perform stereotactic radiosurgery to brain metastases located within or near critical structures. In the presence of an intact tumor capsule, the target would consist solely of tumor cells (i.e., non-neural tissue), and therefore accurate delineation and accurate conformal delivery should rarely result in clinical toxicity. Furthermore, given the dismal prognosis of patients carrying metastatic brain lesions, it is possible that the survival is not long enough for late complications such as radiation necrosis to present.

Hypofractionation in SRS is advantageous for larger lesions, allowing maintenance of therapeutic dose while decreasing the risk of radionecrosis. Hypofractionated SRS delivery for lesions located in critical structures is a topic of ongoing prospective clinical research.

Conclusion

Stereotactic radiosurgery has proven safety and efficacy for the management of brain metastatic lesions in the definitive and adjuvant setting. The total volume of brain metastases, rather than the number of lesions, seems to be more important to clinical decision making. With the appropriate clinical and biological factors taken

into consideration, SRS is a powerful therapeutic tool that can improve the quality of life of our patients. Prospective data are needed to further validate the superiority of novel SRS approaches.

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23

Hypofractionated Stereotactic Radiosurgery (HF-SRS) in the Treatment of Brain Metastases

Jordan A. Torok, Scott R. Floyd, Peter E. Fecci, and John P. Kirkpatrick

Introduction

Single-fraction stereotactic radiosurgery (SF-SRS) is recognized as a primary treatment for brain metastases based on its ability to deliver a high dose of radiation to a target, killing all viable tumor cells, while minimizing damage to surrounding normal tissue. Initially, delivery of high dose of radiation with sufficient accuracy and precision necessitated that a stereotactic headframe be fixed to the patient's skull. Thus, radiosurgical treatments were most often delivered in a single fraction, as it was difficult and uncomfortable to remove and reattach the headframe on successive days. While single-dose treatment of small lesions is effective at killing small brain metastases and sparing normal tissue injury, the ability to safely deliver a sterilizing dose in a single fraction to larger tumors is lost because normal brain tissue cannot be adequately spared. In Radiation Therapy Oncology Group (RTOG) 9005, a dose escalation study of SF-SRS delivered to either recurrent brain metastases following whole-brain radiotherapy (WBRT) or recurrent gliomas after partial brain irradiation, dose limits of 24, 18, and 15 Gy were established for lesions <2, 2–3, and 3–4 cm in maximum dimension, respectively. Paradoxically, as tumor diameter and volume increase, the number of tumor cells increases dramatically, so administering lower doses to a much greater number of tumor cells limits the success of SRS for larger tumors. This limitation has definite clinical consequences; a study from the Cleveland Clinic found that the dose limit imposed by increasing size resulted in much lower rates of local control for brain metastases larger than 2 cm diameter [1].

The location of a brain metastasis often imposes an additional constraint on SF-SRS. In SF-SRS, a limiting maximum dose of 8–10 Gy is typically employed as single fractions of 12 Gy or more to the anterior visual pathways carry a risk of radiation-induced optic neuropathy [2, 3]. Indeed, patients with metastases within 5 mm of the optic nerves and chiasm were not even eligible for several RTOG trials involving SF-SRS [4, 5]. Similarly, metastases either abutting or within the brainstem impose a substantial limitation on the use of SF-SRS, as it is desirable not to exceed the 13–14 Gy maximum dose to this organ in a single fraction [6, 7]. The "implicit bias" imposed by volume and critical organ dose constraints is less well appreciated. In particular, when con-

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touring the dural attachments of intact or resected metastases, it is important to include the entire involved dural surface in the target volume [8]. However, this often results in an irregularly shaped target where the maximum diameter is much larger than that of the intraparenchymal tumor or resection cavity. Consequently, when intending to employ a single-fraction technique, there is a tendency to draw a structure that does not exceed the geometric limits that would permit single-fraction SRS.

In contrast to SF-SRS, "conventional" radiation therapy minimizes damage by utilizing multiple small fractions, typically administered to large target volumes consisting of the tumor and the surrounding tissue at risk for tumor involvement. Normal tissue repair between fractions permits one to administer high total doses of radiation and still obtain acceptable toxicity in the surrounding normal tissue. In conventionally fractionated regimens, a course of radiation therapy delivered to a brain tumor typically spans weeks. In addition, older linear accelerator-based technology employed relocatable immobilization devices that resulted in larger day-to-day variations of patient positioning than the fixed headframes. Over the past decade, the implementation of high-resolution image guidance, integrated into the radiosurgery system and coupled to a robotically controlled couch, permitted correction of translational and rotational errors in patient position at the time of treatment. These technological advances allow for tighter, or smaller, volume expansion to account for set-up error or patient motion during the administration of radiation therapy.

The introduction of image-guided radiosurgery systems offers highly accurate, precise, and reproducible patient positioning and target localization, facilitating multi-fraction treatments with radiosurgical quality. The use of a hypofractionated (nominally two to five sessions) stereotactic radiosurgery (HF-SRS) may provide an improved balance of tumor control and normal tissue toxicity over single-fraction radiosurgery (SRS), particularly in larger tumors and those located next to or within critical structures. This chapter discusses the radiobiologic rationale underlying HF-SRS and presents clinical data on HF-SRS in the treatment of brain metastases.

Modeling Tumor Kill and Normal Tissue Damage in Radiosurgery [9]

The relationship between radiation dose and tumor cell survival may be represented by the linear quadratic model, at least below 10 Gy per fraction [9]. In the linear-quadratic model, a plot of surviving cell fraction versus single radiation doses shows that the log of the surviving cell fraction (SCF) can be represented by a two-parameter model, where the first parameter, α, is the initial, linear portion of the plot—for example, where the SCF is linearly proportional to dose (D, units Gy) on a log-linear graph with a slope of $-\alpha$, that is, SCF = $\exp[-\alpha D]$. The second parameter, β, describes the portion of the curve, where SCF is proportional to the square of dose. A radiation survival curve thus "bends" at moderate doses, and SCF depends on both dose and the square of dose, that is, SCF = $\exp[-\alpha D - \beta D^2]$. In this linear-quadratic (LQ) model, the response to radiation is often characterized by the α/β ratio, which tends to be on the order of 2–3 Gy for brain tissue and 10 Gy for rapidly proliferating tumors, such as brain metastases. Admittedly, this is a somewhat simplistic view and the response to radiation is also influenced by many other factors including the microenvironment (e.g., oxygen concentration); the capacity of cells to repair, repopulate, and redistribute in the cell cycle; and the immunologic milieu.

The concept of using multiple small daily fractions of radiation to minimize normal tissue toxicity is well-supported by preclinical data and clinical experience [9]. Using the linear-quadratic model, one can calculate a biologically effective dose (BED) for a particular α/β ratio (units Gy), total dose (D), and dose/fraction (d, Gy):

$$\mathrm{BED}_{\alpha/\beta} = D\left[1 + d\left(\alpha / \beta\right)\right]$$

For a low α/β tissue, BED will increase much more rapidly with increasing dose per fraction than the BED for a high α/β tissue. Consequently,

one could potentially exploit the difference in α/β ratio between tumor and normal tissue, by fractionating the dose and, thereby, improving the therapeutic ratio. For example, consider the case of a tumor in a normal tissue with α/β ratios of 10 and 2 Gy, respectively. For 16 Gy delivered in a single fraction, the BED will be 41.6 Gy_{10} and 144 Gy_2 for tumor and normal tissue, respectively. However, for a course of eight fractions delivered at 5.08 Gy/fraction, BED for the normal tissue remains at 144 Gy_2 but the BED for the tumor is 61.3 Gy_{10}, an increase of 47%. Alternatively, treating in five fractions at 5.4 Gy/fraction yields the same BED for the tumor (41.6 Gy_{10}), though the BED for the normal tissue is reduced by 31% (99.9 Gy_2 versus 144Gy_2). On-line BED calculators can be used to guide radiation dose prescriptions. Representative BED isoeffect plots are presented in Fig. 23.1.

The calculated BED_2 (associated with normal tissue toxicity) and BED_{10} (modeling control of rapidly proliferating tumors) for typical single-fraction SRS and HF-SRS regimens encountered in the treatment of brain metastases are shown in Fig. 23.2. Note the improved balance of lower BED_2 and higher BED_{10}, which should yield decreased toxicity and improved tumor control for the hypofractionated versus single-fraction schemes. In particular, consider the case of a single fraction of 15 Gy—the maximum "safe" dose for a 3–4 cm diameter lesion established in RTOG 9005. In this case, BED_2 and BED_{10} are 127.5 Gy_2 and 37.5 Gy_{10}, respectively. When utilizing three 8 Gy fractions, BED2 decreases to 120 Gy_2 while BED10 increases to 43.2 Gy_{10}. While this clearly favors the HF-SRS regimen over SF-SRS, other patient, tumor, and treatment factors must be considered when selecting the appropriate dose regimen for an individual patient, including performance status, medical comorbidities, psychosocial issues, logistics, histology, and the timing and nature of surgery, and systemic treatments.

The shape of the dose-response curve above 10 Gy is controversial [11–13]. Some argue that the linear-quadratic model provides an adequate representation of the dose-response relationship at high doses, and that observed clinical outcomes are entirely consistent with the predictions

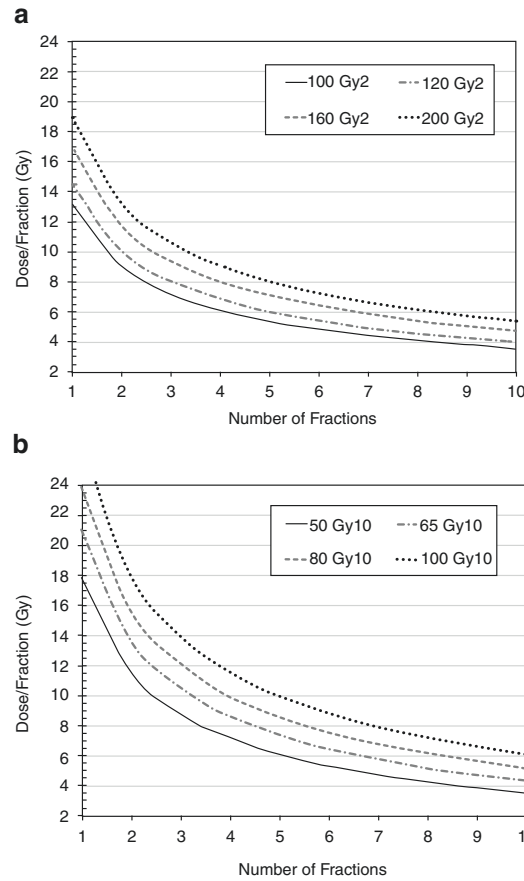

Fig. 23.1 Biologically effective dose (BED) isoeffect plots for dose/fraction and number of fractions administered for (**a**) α/β = 2 Gy and (**b**) α/β = 10 Gy calculated using the linear-quadratic (LQ) mode [9]. (From Kirkpatrick et al. [10]. Reprinted with permission from Duke University Press)

of this model [14–16]. Others assert that radiobiologic mechanisms, such as profound vascular damage [17, 18] and antigen expression, apart from classic DNA damage, are evoked above a threshold dose of 8–12 Gy, and that the high levels of tumor control observed in radiosurgery reflect this "new radiobiology" and enhanced dose-response [16, 19–21] (Fig. 23.3). If one assumes that there is an exaggerated tumor response above some threshold dose, it would seem appropriate to design treatment plans and select dose regimens such that the dose encompassing the metastasis always exceeds this threshold dose [10]. Conversely, the plan should

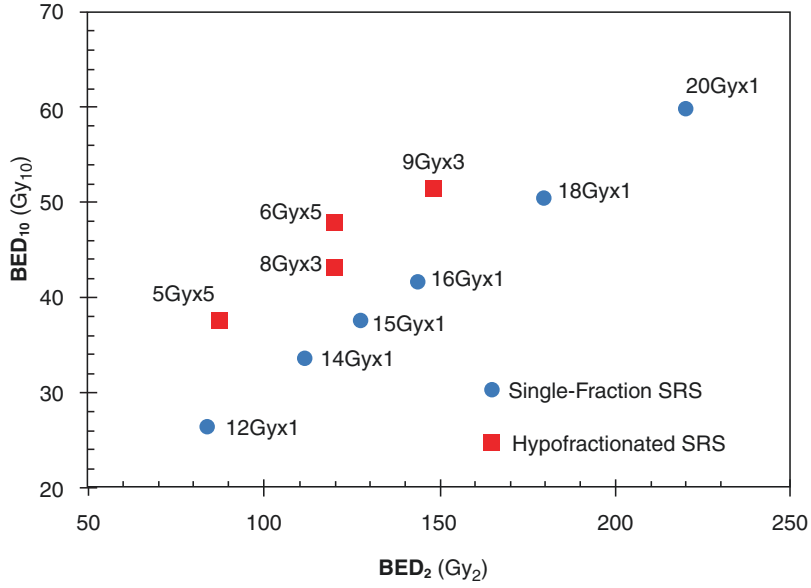

Fig. 23.2 BED_2 and BED_{10} (biologically effective doses calculated for α/β ratios of 2 and 10 Gy, respectively) for clinically employed single-fraction SRS and hypofractionated SRS. Note that BED_2 is associated with response of normal tissue to radiation, and increasing BED_2 results in more damage to normal tissue. The response of rapidly proliferating tissue, such as brain metastases, to radiation is better represented by BED_{10} with a higher BED_{10} suggesting improved local control. (From Kirkpatrick et al. [10]. Reprinted with permission from Duke University Press)

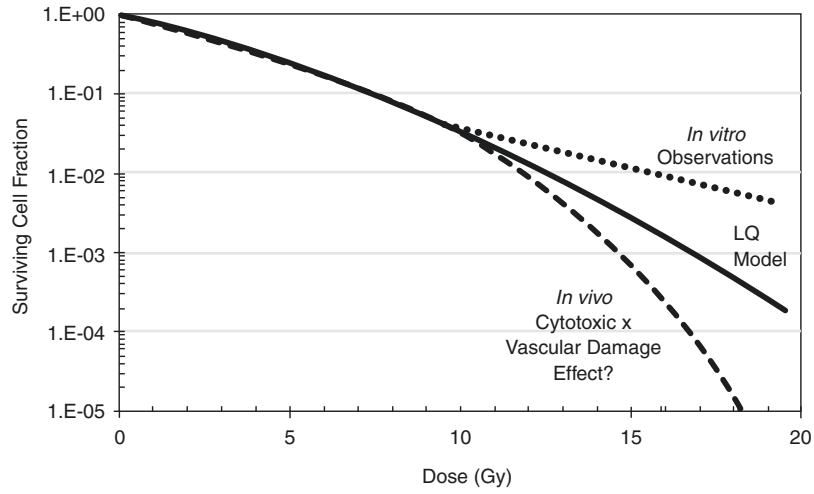

Fig. 23.3 Speculative surviving cell fraction (SCF) versus single-dose irradiation response curves for the linear-quadratic (LQ) model, in vitro cell cultures and in vivo tumors with SCF determined by the product of direct cell kill and indirect vascular damage. (From Kirkpatrick et al. [10]. Reprinted with permission from Duke University Press)

be designed such that the dose in the surrounding normal tissue rarely goes above the threshold. It is also important to recall that there is no fundamental reason that the threshold for a dose effect should be the same for a brain metastasis as the surrounding normal brain parenchyma. In any case, an improved understanding of the in vivo dose-response curves and underlying mechanisms for metastases and normal tissues (which may differ) would not only aid rational plan design but could open new avenues for increasing the therapeutic ratio.

The above issue of dose-response does not include the other critical element in assessing toxicity—the volume of normal tissue irradiated. As discussed by Marks et al. in the Quantitative

Analyses of Normal Tissue Effects in the Clinic (QUANTEC) series of papers [22–24], normal tissue complications increase as the volume of tissue receiving some minimum dose increases, and this behavior is observed in a wide variety of tissues. For example, the volume of brain tissue receiving 12 Gy or more (V_{12Gy}) in radiosurgery appears to be correlated with the risk of radionecrosis, particularly when this volume exceeds 10–15 ml. Note, however, that this limitation appears overly restrictive, as nearly all single-fraction radiosurgery plans would exceed this limit when even moderately sized lesions were treated to accepted doses [6]. While the linear-quadratic model is useful in comparing BED delivered via different dose fractionation regimens, the most relevant method for doing so remains unclear [25]. Recognizing these limitations, the fundamental principles of stereotactic radiosurgery—highly conformal treatment plans, small margins around the target, accurate target localization, minimal position deviation, exquisite attention to detail, and unwavering quality assurance—should aid in minimizing the irradiated volume and should always be employed.

To identify and select the optimal dose regimen that maximizes tumor kill and minimizes normal tissue damage, one should also consider time. Decreasing the time between fractions and the total length of the treatment course should decrease tumor cell repopulation and, thus, enhance the efficacy of the regimen. In particular, this should be more beneficial in the more rapidly growing malignant tumors (e.g., metastases) than in the indolent tumors (e.g., benign schwannomas and meningiomas). If insufficient recovery time between treatments is allowed, the normal brain parenchyma would experience incomplete repair and would exhibit more pronounced late effects. While an interval of at least 8 h between fractions has generally been considered sufficient to permit repair of normal tissues, the QUANTEC analysis of daily versus twice-daily brain treatments called this into question. The analysis by Lawrence et al. [23] suggested that *hyper*fractionated treatment was associated with an increased risk of radionecrosis compared to once daily treatment at equivalent BED. In hypofractionated SRS, treatment may be delivered once daily on consecutive days or as infrequently as twice/week. In this case, the issue still remains on the optimum timing that permits adequate repair of normal tissues while minimizing the adverse impact of tumor cell repopulation.

Finally, intriguing evidence is emerging that irradiation of tumors may also release epitopes that stimulate the immune system, improve local control, and, perhaps more importantly, decrease the appearance of new, distant disease in the brain and body [26]. While the high dose per fraction observed in single-fraction SRS may be quite effective at damaging the vasculature and enhancing local control, the resulting impaired perfusion could limit transport of antigens and immune cells, inhibiting the global immunomodulatory effect of radiation [27]. Thus, it has been suggested that a hypofractionated regimen could still generate antigens without impairing transport, and that this treatment strategy would produce a more robust immune response [26, 28]. Such an approach might have even greater impact when combined with one or more of the immunomodulating drugs (discussed elsewhere in this book) that are profoundly changing clinical practice, though a great deal remains to be understood about this complex relationship.

Clinical Outcomes

Brain metastases occur in approximately 20–40% of patients with advanced cancer and have become more prevalent over the past decade, given improved systemic therapies for certain cancers, such as trastuzumab for Her2-amplified breast cancer, targeted tyrosine kinase inhibitors for EGFR-mutated and ALK-rearranged non-small cell lung cancer, and immunotherapy for melanoma. Given these systemic therapy advances, patients not only live longer with more time to develop brain metastases, but these patients with treated brain metastases also live longer, thus leading to the rising prevalence of brain metastases. Given the longer survival of many cancer patients with brain metastases, the local control of each treated lesion and potential long-term toxicity are increasingly important clinical con-

siderations that may influence not only survival, but neurocognitive function and quality of life.

There have been numerous retrospective studies published about the outcomes of intact and resected larger brain metastases following HF-SRS [29–71]. To date, there is no prospective randomized evidence demonstrating either superior efficacy or reduced toxicity between SF-SRS and HF-SRS. However, multiple retrospective series lend support for this approach and will be reviewed further in this section. Single institution experience from Seoul National University compared their results with SF-SRS (n = 58) to HF-SRS (n = 40), where the latter typically utilized a regimen of 6 Gy × 6. In both groups, 1-year local progression-free survival was approximately 70%, while toxicity was significantly less for HF-SRS [48]. Minniti et al. first reported their experience of HF-SRS (9–12 Gy × 3) in patients with one to three brain metastases, describing 1-year local control and radionecrosis rates of 88% and 7%, respectively [54]. These authors subsequently compared their institutional experience of SF-SRS versus HF-SRS (9 Gy × 3) for brain metastases measuring >2 cm. With 289 patients, the 1-year cumulative local control for SF-SRS and HF-SRS were 77% and 91%, respectively, while the rate of radionecrosis with HF-SRS and SF-SRS were 20% and 8%, respectively [57]. These differences remained significant after propensity score adjustment.

At Dana Farber/Harvard Cancer Center, HF-SRS (~90% received 5 Gy × 5) was generally utilized for tumors of size >3 cm, cases with a high V_{12Gy}, or for those in close proximity to a critical structure. In 70 patients treated with HF-SRS, the authors reported a 1-year LC of 56% with symptomatic radiation-induced treatment changes occurring in only 4% [63]. In one of the few prospective studies investigating HF-SRS, Murai et al. performed a dose escalation study utilizing three- and five-fraction regimens. Patients with tumors ≥2.5 cm were included—tumors in the 2.5–4 cm range were treated with three fractions while those with tumors ≥4 cm were treated with five fractions. A total of 54 patients with 61 large brain metastases were included, with the dose safely being escalated to the highest dose levels of 27–30 Gy in three fractions and 31–35 Gy in five fractions [59]. One-year local control was 69%, and no grade 3 toxicities were reported.

Many of the above studies included patients with intact brain metastases. In patients who undergo initial surgical resection, the need to adequately cover the surgical cavity often results in large and irregular target volumes. For SF-SRS, this necessitates a lower dose to limit significant toxicity. Two recent prospective studies of postoperative SF-SRS lend insight into the challenges of this situation. Investigators at the MD Anderson Cancer Center randomized patients after surgical resection for brain metastases to either observation or SF-SRS (with a maximum allowed resection cavity diameter of 4 cm). SRS dose was based on the SRS target volume: 16 Gy for ≤10 cc, 14 Gy for 10.1–15 cc, and 12 Gy for >15 cc. The addition of SRS significantly reduced local recurrence, with a 1-year freedom from local recurrence of 72% with SF-SRS [52]. Tumor size even after resection was an independent predictor for local recurrence; however, suggesting lower dose SF-SRS provided suboptimal local control. In our experience, resection of intact brain metastases usually results in a planning target volume for postoperative SRS greater than 3 cm in maximum diameter and, consequently, our practice is to hypofractionate such patients.

NCCTG N107C/CEC.3 was a multi-institutional randomized phase III trial comparing the efficacy and toxicity of postoperative WBRT versus SF-SRS (with a maximum allowed resection cavity diameter of 5 cm). SF-SRS dose was based on cavity size in a similar manner to the above study. The 1-year surgical bed local control was 60% with SF-SRS, which was inferior to that of WBRT at 81% [30]. While cognitive endpoints were improved with SF-SRS and survival was similar to the WBRT arm, the disappointing surgical bed control warrants further study to improve efficacy.

In evaluating the optimal surgical cavity target volume, investigators at Stanford reviewed their experience with HF-SRS with a 2 mm margin to a cohort primarily treated with SF-SRS with no expansion. Compared to the SF-SRS cohort, the 12-month cumulative incidence of local failure

for the HF-SRS group was only 3% (compared to 16%), while toxicity rates trended in favor of HF-SRS [31]. Minniti et al. reported their experience of HF-SRS after resection for melanoma brain metastases and found a 1-year local failure rate of 12% [72]. This compared favorably to a cohort that did not receive surgery, where 1-year local failure was 28% with HF-SRS alone.

Collectively, these studies suggest reduced toxicity rates and potentially increased local control with the use of HF-SRS in situations where high-dose SF-SRS is not feasible. Further validation with prospective controlled trials will be

Table 23.1 Summary of studies of single-fraction, staged, and hypofractionated SRS in the treatment of intact and resected brain metastases

Study	Year	*n*	Median follow-up, months	SRS approach	Median marginal dose/ Fx × Fx #	Median lesion diameter[a] (range), cm	Local control 1-year post SRS	Rate of RN
SRS to intact brain metastases								
Angelov et al. [29]	2017	54	NR	Staged	15Gy × 2	2.7 (1.7–3.9)	NR	11.1%
Dohm et al. [32]	2017	54	7.7	Staged	14.5Gy × 2	2.8 (1.2–4.9)	88.7%	10.3%
Feuvret et al. [37]	2014	24 vs 12	20 vs 11	SF-SRS vs HF-SRS	20Gy × 1 vs 11Gy × 3	4.5 (3.2–6.0) vs 3.8 (3.3–4.7)	60.4% vs 100%	0% vs 0%
Han et al. [40]	2012	80	13.8	SF-SRS	13.8Gy × 1	4.0 (mean)	84.6%	38.8%
Hasegawa et al. [42]	2017	56	6.0	HF-SRS	13Gy × 2	3.4	80.0%	NR
Higuchi et al. [43]	2009	43	10	Staged	10Gy × 3	3.2 (mean)	75.9%	2.0%
Inoue et al. [44]	2014	78	6.2	HF-SRS	6.2Gy × 5	2.9	98.4%	2.0%
Jeong et al. [46]	2015	37	10	HF-SRS	11.7Gy × 3	3.2 (2.6–4.6)	86.7%	15.8%
Kim et al. [47]	2016	36	13.4	HF-SRS	8Gy × 3	3.3 (mean)	NR	2.7%
Minniti et al. [57]	2016	151 vs 138	NR	SF-SRS vs HF-SRS	18Gy × 1 vs 9Gy × 3	All >2 cm	77% vs 90%	27.7% vs 14.4%
Minniti et al. [72]	2017	60	13	HF-SRS	9Gy × 3	2.5 (1.6–4.3)	72%	8%
Mucaevic et al. [58]	2008	31	21	SF-SRS	21Gy × 1	2	96.8%	NR
Murai et al. [59]	2014	51	NR	SF-SRS vs HF-SRS	8-14Gy × 1 vs 5-11Gy × 3	>2.5	76% vs 59%	NR
Navarria et al. [60]	2016	51	NR	HF-SRS	9Gy × 3 vs 8Gy × 4	2.9 (2.1–5)	100% vs 91%	5.9% vs 5.9%
Prabhu et al. [62]	2017	60	10.3	SF-SRS	18Gy × 1	2.2	63.3%	17.2%
Wegner et al. [67]	2015	36	NR	HF-SRS	24Gy in 2–5Fx	3.1 (2.7–5.4)	63.0%	NR
Yomo et al. [69]	2014	58	14	HF-SRS	5.5Gy × 5	3.2 (2.7–4.7)	98.4%	2.0%
Zimmerman et al. [71]	2015	52	NR	SF-SRS	15Gy × 1	3.5 (3.0–5.8)	80.2%	7.0%

(continued)

Table 23.1 (continued)

Study	Year	*n*	Median follow-up, months	SRS approach	Median marginal dose/ Fx × Fx #	Median lesion diameter[a] (range), cm	Local control 1-year post SRS	Rate of RN
SRS to resection cavity								
Brown et al. [30]	2017	39	NR	SF-SRS	15Gy × 1	60% <3 cm, 40% >3 cm	34%	10.3%
Choi et al. [31]	2012	97	10	HF-SRS	8Gy × 3	2.5 (0.5–5.0)	90.7%	5%
Doré et al. [73]	2017	95	17	HF-SRS	7.7Gy × 3	2.8 (1.2–5.0)	84%	20.6%
Ling et al. [51]	2015	99	12.2	HF-SRS	7.3Gy × 3	>3.0	71.8%	NR
Mahajan et al. [52]	2017	17	11.1	SF-SRS	12Gy × 1	2.6 (1.2–3.8)	72%	0%
Minniti et al. [56]	2013	101	16	HF-SRS	9Gy × 3	3.2 (2.9–4.1)	93%	9.0%
Minniti et al. [72]	2017	60	13	HS-SRS	9Gy × 3	2.8 (1.7–4.8)	88%	13%
Pessina et al. [61]	2016	69	12.5	HF-SRS	10Gy × 3	3.8 (2.0–7.3)	100%	0%
Prabhu et al. [62]	2017	93	10.3	SF-SRS	15Gy × 1	2.6	80.8%	33.5%
Vogel et al. [65]	2015	30	9.5	HF-SRS	7.8Gy × 5	3.8 (2.8–6.7)	68.5%	10%
Zimmerman et al. [71]	2015	33	NR	SF-SRS	15Gy × 1	4.0 (3.0–6.8)	79%	3.0%

[a]When only tumor or resection cavity volume reported, diameter calculated from $(1.91 \times \text{volume})^{1/3}$
Abbreviations: *Fx* fraction(s), *Gy* Gray, *n* total number of patients, *NR* not reported, *RN* radionecrosis

critical to further optimize the HF-SRS platform (Table 23.1).

Ongoing Clinical Trials

Clinical trials of hypofractionated SRS for brain metastases registered at ClinicalTrials.gov are presented in Table 23.2. To illustrate the opportunities to better define the role of HF-SRS in the treatment of brain lesions, it is worthwhile to discuss several of these trials. For example, the Stanford study (NCT00928226) asks the question, "What is the maximum tolerated dose (MTD) of HF-SRS for large brain metastases treated using a 3 fraction regimen?" Eligible patients have one to four brain metastases, one of which is 4.2–33.5 cm^3 (equivalent to a uniform sphere 2–4 cm in diameter), intact and unresectable. The primary outcome is MTD with secondary measures of acute and late toxicity, quality of life, local control, appearance of distant metastases in the brain, and overall survival. Patients are treated on 3 consecutive days to doses of 24, 27, 30, or 33 Gy (8–11 Gy/fraction) using a 3 + 3 dose escalation scheme. Preliminary results have been presented in abstract form.

A retrospective study of patients with four or more brain metastases treated with single-isocenter, multi-target (SIMT) SRS showed that patients with higher V_{12Gy} exhibited poorer overall survival than those with lower V_{12Gy} [74]; an increased number of brain metastases was not associated with diminished survival. As these patients were primarily treated with single-fraction SIMT SRS, the authors speculated that hypofractionated SRS might have reduced radiation-related toxicity and improved outcome. This notion informed the subsequent prospective trial at Duke University of SIMT SRS in patients with 4–10 brain metastases (NCT02886572). In that study, patients are initially planned for sin-

Table 23.2 Clinical trials of hypofractionated stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) in patients with brain metastases

Study	Institution	Principal investigator	ClinicalTrials.gov identifier	Primary outcome
Phase I/II study of fractionated stereotactic radiosurgery to treat large brain metastases	Stanford University	S. Soltys	NCT00928226	Determine MTD of SRS given in 3 fractions for brain metastases 4.2–14.1 cm^3 and 14.2–33.5 cm^3
SRS to brain metastases resection cavity vs. post-op WBRT (ESTRON)	Heidelberg University	J. Debus	NCT03285932	Evaluate safety/efficacy of post-op SRS compared to WBRT
SRS or hypofractionated stereotactic radiotherapy (HF-SRT) to brain metastases resection cavity	Oncology Inst. of Southern Switzerland	G. Pesce	NCT03561896	Rate of local recurrence in post-op SRS or HF-SRT
Fractionated stereotactic radiotherapy (FSRT) in treatment of brain metastases	Moffitt Cancer Center	S. Sahebjam	NCT02187822	Determine MTD of TPI 287 given concurrently with FSRT to treat brain metastases
Hypofractionated stereotactic radiosurgery in treating patients with large brain metastasis	Emory University	B. Eaton	NCT01705548	Determine MTD of 5-fraction SRS for brain metastases, 3–6 cm diameter
Hypofractionated stereotactic VMAT to the resection cavity from a single, large brain metastasis	Istituto Clinico Humanitas	M. Tedeschi	NCT02576522	Rate of local recurrence in post-op HF-SRS for a single large brain metastasis
Perfexion brain metastasis (HF-SRT)	Princess Margaret Hospital	C. Chung	NCT00805103	Determine MTD of HF-SRS for recurrent brain metastases (at least 1 > 2 cm diameter) post WBRT
Single-isocenter multi-target SRS for patients with 4–10 brain metastases	Duke Cancer Institute	G. Kim	NCT02886572	Overall survival (SF-SRS vs HF-SRS for V_{12Gy} < vs. > 20 ml)
Fractionated stereotactic radiosurgery with concurrent bevacizumab for brain metastases: a phase I dose escalation trial	National Taiwan University Hospital	C.-C. Wang	NCT02672995	Determine MTD of 3-fraction SRS + bevacizumab for brain metastases, 1.5–3.5 cm diameter
Frameless fractionated stereotactic radiation therapy (FSRT) for brain mets	MD Anderson	A. Garg	NCT02798029	Local control based on imaging for each lesion (up to 5 cm diameter) after 3–5 fraction SRS
Fractionated stereotactic radiosurgery for large brain metastases	University of Pittsburgh	D. Heron	NCT02054689	MTD for 3-fraction SRS for brain metastases, 3–5 cm diameter
Hypofractionated stereotactic radiation therapy of brain metastases: evaluation of WBRT	Institut de Cancérologie de Lorraine	P. Royer	NCT02913534	Overall survival of patients with 1–3 brain metastases treated with HF-FSRT

gle-fraction SIMT SRS using the dose-volume constraints imposed by RTOG 9005, that is, 24 Gy marginal dose for targets <2 cm maximum dimension and 18 Gy for targets 2–3 cm maximum diameter. However, if either the planned V_{12Gy} to normal brain parenchyma exceeds 20 ml or any lesion involves the brainstem, the patient is replanned and treated with a marginal prescribed dose of 25 Gy administered in five 5-Gy fractions over consecutive days. Accrual to this protocol was completed in August 2019 and the results will be reported in 2020.

Given the need to optimize treatment strategies and to identify appropriate patient popula-

tions for HF-SRS in the treatment of large brain lesions, all eligible patients should consider enrollment on a clinical trial.

Conclusion

Compared to single-fraction SRS, hypofractionated SRS appears to offer a superior balance of efficacy and toxicity in patients with large brain metastases and resection cavities, as well as in lesions located close to critical normal organs. This potential benefit comes at the expense of an increased number of treatment fractions. Fundamental studies and clinical trials are required to identify the most appropriate applications for HF-SRS based on tumor and patient characteristics. It would be worthwhile to establish the optimal scheme for total dose and dose/fraction in HF-SRS as a function of tumor histology, diameter, and location. Moreover, given the rapid progress in targeted and immunomodulating treatments for primary and metastatic malignancies, these outcomes with HF-SRS need to be evaluated in the setting of concurrent and adjuvant systemic therapies. Establishing the benefits and toxicities of combined HF-SRS and immunomodulating therapy is particularly important, given the imputed role of HF-SRS in stimulating the immune response. Because of the known toxicity of high-dose, single-fraction SRS when treating large lesions, it would be difficult to perform a randomized trial of single-fraction SRS versus HF-SRS with equipoise. Consequently, optimizing HF-SRS demands well-constructed and well-analyzed clinical trials with sufficient size and length of follow-up to determine the safety and efficacy of HF-SRS for the treatment of large and/or critically located lesions, either intact or surgically resected.

Conflict of Interest The authors report no conflicts of interest.

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Challenges and Controversies in Stereotactic Radiosurgery

24

Jugal K. Shah and Douglas Kondziolka

Introduction

Patients diagnosed with cancer have a 20–40% incidence of brain metastases, and 70% of those patients have multiple brain metastases [1]. For a decade, treatment has evolved to include more focal approaches, such as radiosurgery and resection, and less use of whole-brain radiation therapy (WBRT) [2]. Clinicians strive to reduce undesirable effects, including induced cognitive deficits, hair loss, nausea, and fatigue, and to improve functional survival. Stereotactic radiosurgery (SRS) was developed to deliver powerful and precise energy to targeted tumors [3]. While the treatment of one to four brain metastases with SRS alone without WBRT has reached the level of Class 1 evidence, controversy persists in the case of larger, multiple, and radioresistant tumors. Management of radiation effects can be challenging both in terms of diagnosis and therapy. Here we present five cases of uses of SRS in challenging and controversial ways.

Case 1: Large Metastases

We first present the case of a 62-year-old woman with locally advanced colorectal cancer diagnosed 7 years previously who presented with 2 weeks of headache, 2 days of worsening ataxia, and two episodes of nausea and vomiting. She presented to the emergency department and neurological exam was notable for no focal deficits. Brain magnetic resonance imaging (MRI) revealed bilateral cerebellar hemisphere tumors: a right superior cerebellar tumor measuring 2 cm with mild surrounding edema and a left mid lateral cerebellar tumor measuring 3 cm with surrounding edema and mild 4th ventricular effacement, but no hydrocephalus (Fig. 24.1a).

Current Treatment Paradigm

The specific challenges in this case are both the size and location of the lesions. Larger brain metastasis (≥3 cm in diameter) present a treatment challenge for stereotactic radiosurgery, as the doses required may increase the risk of acute and late side effects and dose to the surrounding tissue, and risk of radiation necrosis [4]. A dose too low may be ineffective. Metastasis to the cerebellum has been reported as a negative prognostic factor for survival [5, 6]. In addition, the risk of acute decompensation from obstructive hydrocephalus with compression of the 4th ventricle must be weighed when managing posterior fossa masses [7, 8]. Treatment options include (1) resection followed by postoperative stereotactic radiosurgery/radiotherapy, (2) stereotactic radiosurgery only, or (3) stereotactic radiosurgery followed by resection.

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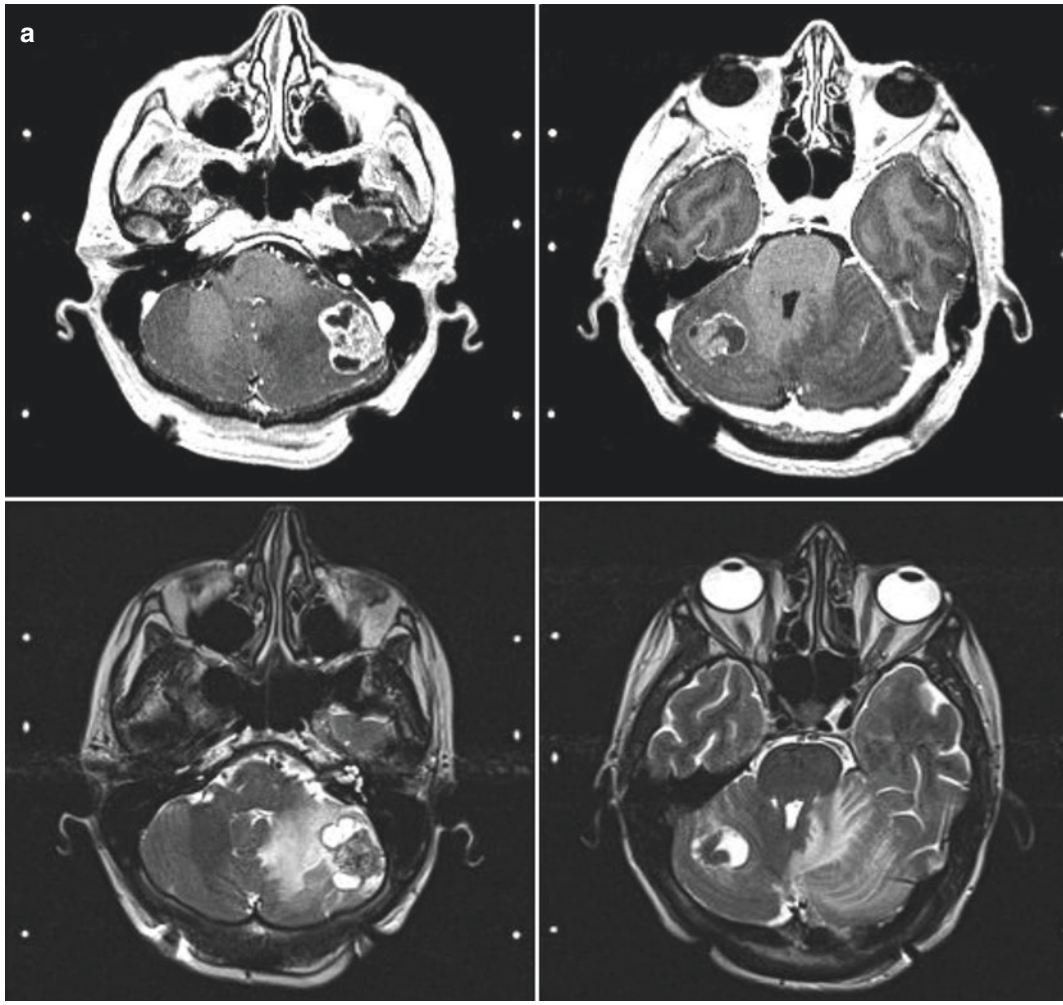

Fig. 24.1 Large bilateral cerebellar hemisphere colorectal cancer metastases treated with stereotactic radiosurgery monotherapy. (**a**) Pre-treatment post-contrast (above) and T2 (below) MRI, demonstrating 4th ventricular effacement and surrounding edema. (**b**) One-month follow-up post-contrast MRI demonstrating major regression of both lesions. (**c**) Five-month post-contrast MRI demonstrating further regression

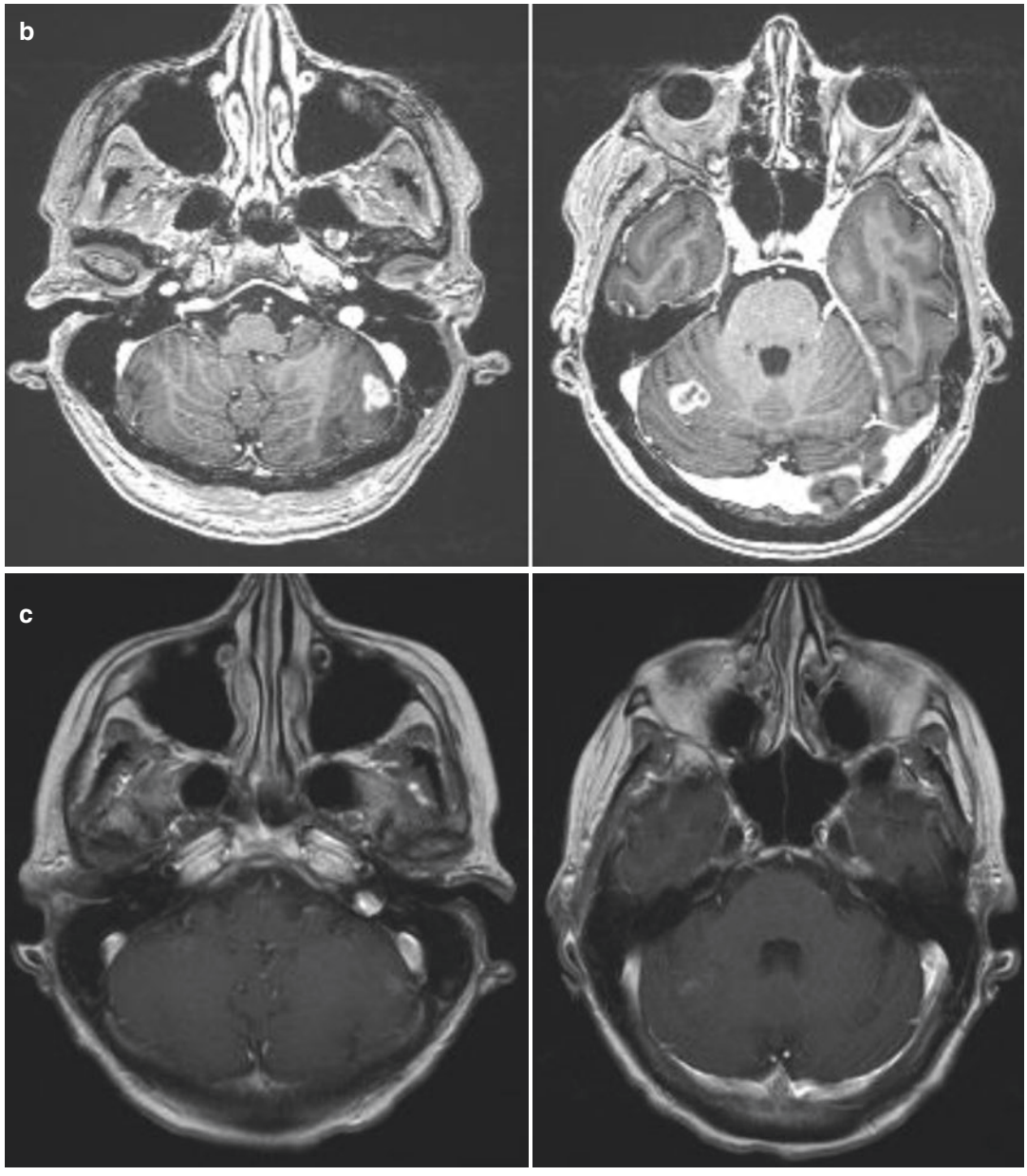

Fig. 24.1 (continued)

Resection followed by radiotherapy has been a mainstay of treatment for single brain metastasis [9]. For colorectal cancer specifically, Wronski et al. studied a series of 73 patients who underwent brain metastasis resection and found that resection may increase survival of these patients [5]. In addition, for metastasis to the cerebellum, Rajendra et al. concluded that surgical treatment appeared beneficial, provided the absence of postoperative complications [8, 10].

More recently, evidence for stereotactic radiosurgery monotherapy for cerebellar metastases is increasing. Hill et al. studied 100 patients with 155 cerebellar metastases and found that SRS is generally safe and effective [11]. In this study, only 10% of patients had undergone pre-SRS resection, with resection prior to SRS associated with increased long-term risk for subsequent hydrocephalus.

Alternatively, a new treatment paradigm for the management of cerebral metastases has emerged. Preoperative neoadjuvant SRS (NaSRS) has been described in two studies, the rationale for which is clearer target delineation and the theoretical reduction of intraoperative dissemination of tumor cells. Asher et al. reported on 47 consecutive patients treated with NaSRS with a median dose of 14 Gy to 80% isodose followed by surgical resection a median of 1 day later and found local control of 97.8%, 85.6%, and 71.8% at 6, 12, and 24 months, respectively [12]. Patel et al. reported 12 patients treated with 16 Gy followed by resection a median of 1 day later, with posterior fossa tumors comprising 75% of their cohort [13]. Local control rates at 6 and 12 months were 81.8% and 49.1%, respectively.

Case Outcome

After reviewing her options, the patient wished to avoid open surgery and elected for treatment with primary SRS. The tumor margin dose was 17 Gy at the 50% isodose line to the larger left cerebellar tumor and 18 Gy to the 50% isodose line for the right cerebellar tumor. Her dexamethasone dose was tapered over the course of 1 month. One-month follow-up demonstrated major regression of tumors (Fig. 24.1b). Her balance improved. Five-month follow-up demonstrated further regression of the tumors (Fig. 24.1c). At her most recent follow-up, 22 months after radiosurgery showed no regrowth and no new tumors.

Case 2: Melanoma

We present the case of a 68-year-old man who originally presented with abdominal pain and was found to have lung, adrenal, and gastric masses found to be S100 positive and HMB45 positive melanoma metastases on biopsy. Staging MRI demonstrated six intracranial metastases—right and left cerebellar, right temporal, right occipital, and right frontal (Fig. 24.2a). He had no focal deficits on examination.

Current Treatment Paradigm

Half of melanoma patients will develop brain metastases during their treatment course, with prior reports noting a poor median overall survival of 4–5 months, but recent data is more encouraging [14]. For this patient, the diagnosis-specific Graded Prognostic Assessment (DS-GPA) predicted a survival of 4.7 months [15]. Traditionally, treatment options included SRS, resection, or a combination thereof. Although resection followed by SRS or SRS alone has been a mainstay of management of brain metastases, this treatment strategy is optimized for local control of few metastases. Addition of WBRT for prevention of distant intracranial metastasis results in cognitive deficits that are unacceptable to many patients and may not be effective in melanoma.

An alternative treatment option that has been emerging is the use of targeted (*BRAF* mutation) therapy or immunotherapy. Immune checkpoint inhibitors have generated promising results in some patients, with food and drug administration (FDA) approval of ipilimumab followed by pembrolizumab and nivolumab in 2014. However, immune-related adverse events are a known side effect due to the mechanism of releasing inhibition on T cell proliferation and activity. The

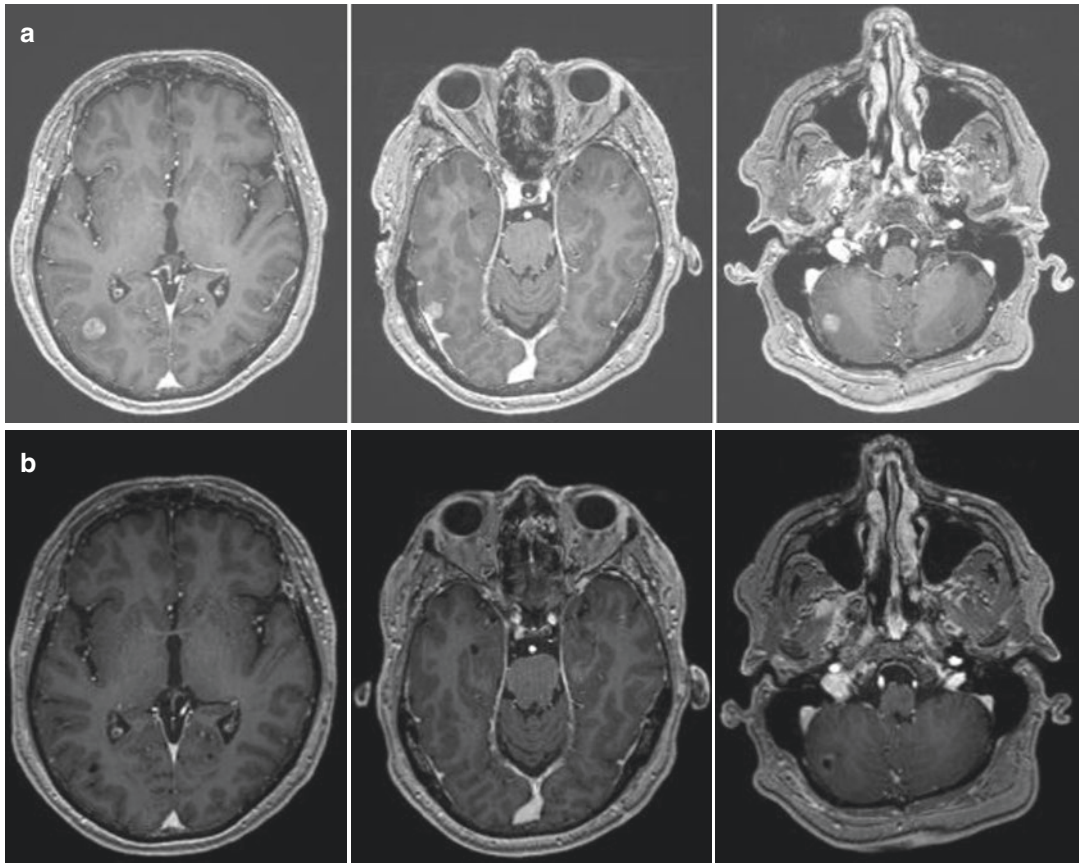

Fig. 24.2 Multiple melanoma brain metastases treated with first-line stereotactic radiosurgery and systemic immunotherapy. (**a**) Pre-treatment post-contrast T1 MRI demonstrating the three most significant lesions: right occipital, right temporal, and right cerebellar (left to right). (**b**) Sixteen months post-treatment post-contrast T1 MRI demonstrating regressed appearance of tumors

value may be in patients with very small tumors, but even in these we see treatment failures. Specifically in the case of ipilimumab, incidence of immune hypophysitis has been reported to be as high as 17%, with frequent hormonal deficiencies at diagnosis [16]. Increased doses of immune checkpoint inhibitors are also associated with an increased risk of hypophysitis, further limiting the clinical potential of immune checkpoint inhibitor monotherapy [17].

Case Outcome and Discussion

After staging, the patient underwent Gamma Knife radiosurgery (GKRS) for his six intracranial metastases. Afterwards, he was started on combination immunotherapy with ipilimumab and nivolumab. He developed hypopituitarism and started hormone replacement therapy. Four months after his initial GKRS, the treated tumors regressed, but a new punctate metastasis in the right postcentral gyrus was found on imaging. He underwent GKRS to that lesion. New intracranial metastases were subsequently found and treated with GKRS an additional two times, for a total of four procedures, in addition to a specific dosing regimen of ipilimumab and nivolumab. Twenty-one months after initial Gamma Knife radiosurgery, the patient remains without neurological deficits. Recent imaging shows a regressed appearance of all tumors (Fig. 24.2b).

A recent unpublished study at our institution revealed among 123 multiple melanoma patients

combining first-line SRS with immunotherapy had a median OS of 17.5 mo (31% 3-year OS). Furthermore, among BRAF mutated patients, median OS was 31.0 mo (47% 3-year OS) in the setting of combined immune checkpoint inhibition and *BRAF* targeted therapy. Combination SRS with immunotherapy is part of a trend of improving survival in patients with multiple brain metastases.

Case 3: Multiple Metastases

We present a 50-year-old woman with ER/PR/Her2+ metastatic breast cancer diagnosed 4 years prior to first brain metastasis. She underwent lumpectomy, mastectomies, radiation, and chemotherapy with tamoxifen, letrozole, trastuzumab, and vinorelbine. Her initial brain MRI demonstrated miliary metastases, and she underwent whole-brain radiation therapy with an excellent early response on serial scans for 6 months, at which time recurrence of 26 tumors was noted (Fig. 24.3). Her only neurologic deficit was a left facial weakness, which was the result of a left parotid metastasis resection. She remained normal in cognition and continued to work and drive.

Current Treatment Paradigm

Whole-brain radiation therapy (WBRT) has been the primary treatment for multiple intracranial metastases for decades [18], with the rationale of preventing local and distal intracranial relapse in addition to treating undetected lesions, the presence of which increases in probability with increasing number of detected lesions. WBRT has significant side effects, including hair loss, fatigue, nausea, and most significantly, neurocognitive decline [3]. Nevertheless, it remains an important therapy for some patients.

The maximum number of lesions suitable for SRS alone has been controversial but increasing steadily. Early studies focused on comparing the addition of SRS to WBRT compared to WBRT alone, which demonstrated improved local disease control in the WBRT plus SRS group compared with the WBRT alone group (92% vs 0% at 1 year) and non-statistically significant trends toward improved survival in WBRT plus SRS group (11 months vs 7.5 months), ($p = 0.22$) [19].

A subsequent randomized control trial compared SRS alone to WBRT plus SRS in patients with one to four brain metastases and found no difference in overall survival [20]. However, the SRS alone group had increased rates of distal metastases. Comparable overall survival in SRS alone versus SRS plus WBRT was recapitulated in two more studies by different groups [21, 22]. Since then, SRS, while withholding WBRT in patients with one to four metastases with controlled systemic and primary disease, has become the preferred treatment [18].

The efficacy of GKRS in up to 10 metastases was studied in a prospective multi-institutional trial, Japanese Leksell Gamma Knife (JLGK) 0901 [23]. Included were 1194 patients with

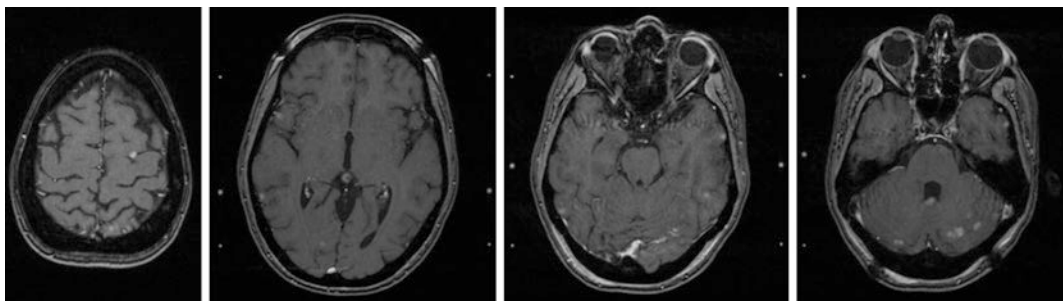

Fig. 24.3 Multiple breast cancer metastasis treated with multiple rounds of stereotactic radiosurgery. Pre-treatment post-contrast T1 MRI demonstrating multiple small lesions throughout different axial slices

newly diagnosed 1–10 brain metastases, KPS >70, and absence of cerebrospinal fluid (CSF)dissemination, with the primary endpoint of overall median survival. The purpose was to study noninferiority of treatment of 5–10 brain metastases compared to 2–4 metastases as measured by survival. In this study, overall median survival after SRS was 12 months for all patients included. The median survival was 13.9 months in patients with a single lesion, and a similar 10.8 months in those with 2–4 lesions and 10.8 months in those with 5–10 lesions. Local recurrence rates were similar throughout; however, risk of new lesion occurrence was significantly lower in single lesion group compared with other groups (2–4 and 5–10 lesions) ($p < 0.0001$).

A follow-up study to the JLGK trial found total tumor volume to correlate with overall survival, with longer survival time in patients with ≤15 cm^3 total tumor volume than those with volume >15 cm^3 ($p < 0.0001$). Other significant prognostic factors for poor survival were MRI evidence of CSF dissemination and KPS <70 [24]. Thus, a new paradigm of prognostication by overall tumor volume rather than number of brain metastases has emerged.

Use of SRS in greater than 10 metastases was specifically studied in a retrospective trial by Kim et al. [25]. This small study included 26 patients with 10 or more intracranial metastases who underwent GKRS. All patients had KPS >70, mean age was 55, and mean cumulative tumor volume was 10.3 cm^3. Overall median survival was 34 weeks, with 79.5% local control rate, and control of all lesions at 54% 6 months post-GKRS. Synchronous onset in non-small cell lung cancer, high KPS (≥80), and controlled primary disease were found to be favorable prognostic factors in their analysis.

However, data for SRS alone for multiple metastases has not been completely favorable. Grandhi et al. retrospectively reviewed patients with 10 or more metastases managed with Gamma Knife surgery and found that factors associated with poor survival included greater than 14 metastases (which decreased median survival from 6 months to 3 months) [26]. Other factors correlating with poor survival were melanoma primary, active systemic disease, and higher RPA class.

In summary, no randomized controlled trials exist for greater than four metastases, and current outcome data indicates that SRS may be used in patients with >10 brain metastases, specifically those with controlled primary cancer, absence of systemic disease, and good KPS. It can be important as initial targeted brain tumor care prior to systemic cancer therapy for which longer survivals may be expected.

Case Outcome

The patient first underwent GKRS for 10 tumors. A conformal radiosurgery plan was created to give these tumors a margin dose of 16 Gy, keeping the surrounding brain at a low dose. One week later, 16 more tumors underwent GKRS. All tumors regressed initially; however, 10 months later 16 new small tumors were detected on imaging. She underwent GKRS for these tumors, followed by two more sessions for multiple new small tumors. Over the next 3 years, she continued to have multiple new tumors which were treated with GKRS. She entered a clinical trial and stabilized for 18 months, but then additional radiosurgery was required. Over 100 tumors were targeted over 6 years following WBRT.

Case 4: Radiation Injury

We present the case of a 75-year-old woman diagnosed with endometrial adenocarcinoma, who underwent total abdominal hysterectomy/bilateral salpingo-oophorectomy and lymph node dissection. She underwent four cycles of carboplatin and 5040 Gy of adjuvant local radiation. Two months later, she presented with imbalance, widened gait, nausea/vomiting, malaise, and hyponatremia. Imaging revealed a 2 cm left medial frontal tumor (Fig. 24.4a). Given the surrounding edema, the lesion was considered to be a metastasis, and the patient elected to proceed with SRS and declined surgery or a biopsy. She

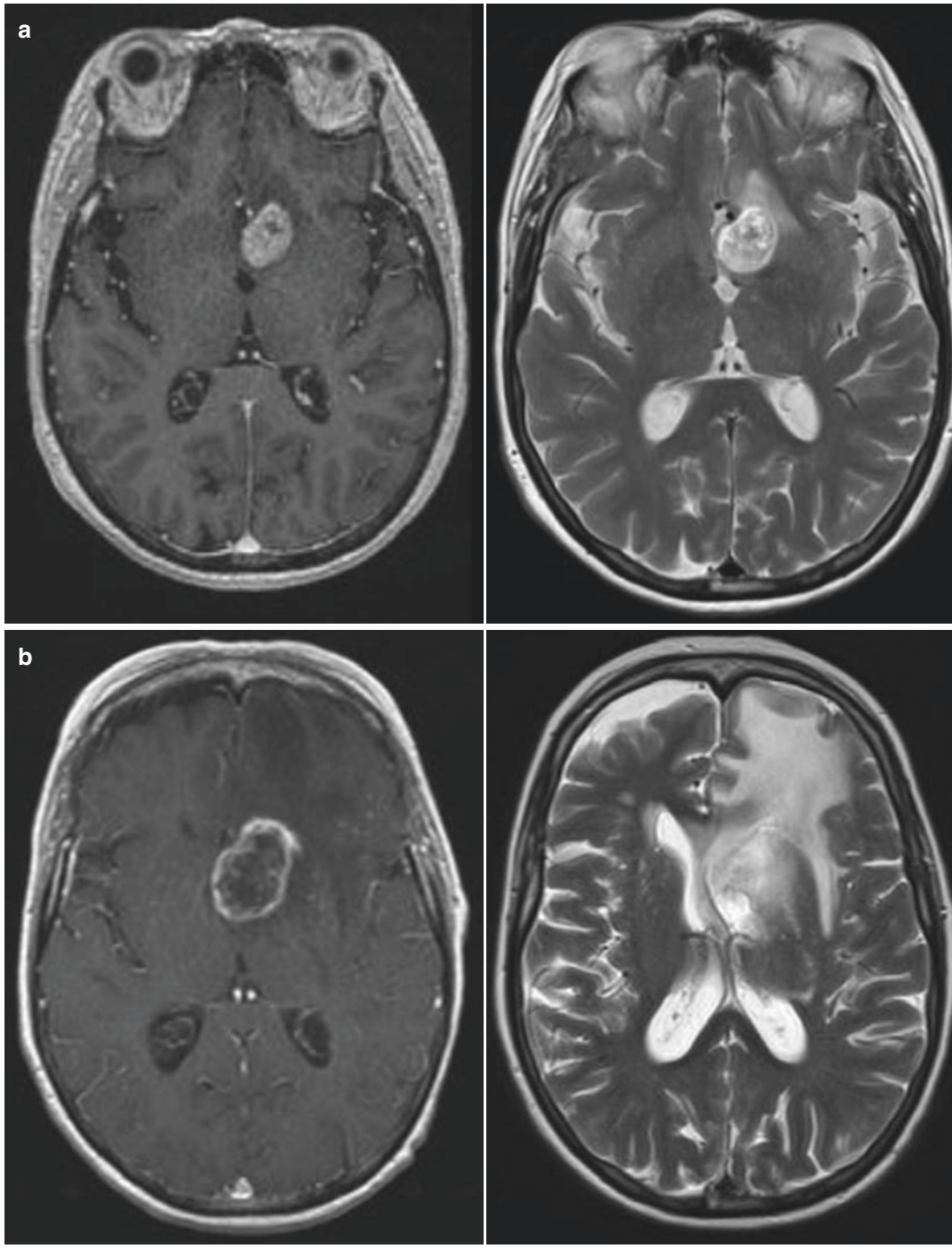

Fig. 24.4 Left medial frontal endometrial cancer metastasis treated with first-line SRS. (**a**) Pre-treatment post-contrast T1 (left) and T2 (right) MRI demonstrating lesion with surrounding edema. (**b**) Three-month follow-up MRI demonstrating further peripheral increased enhancement of the tumor and more edema. (**c**) Ten-month follow-up MRI demonstrating regression of lesion. (**d**) Sixteen-month follow-up demonstrating further regression on post-contrast T1 (left) and minimal edema on FLAIR (right)

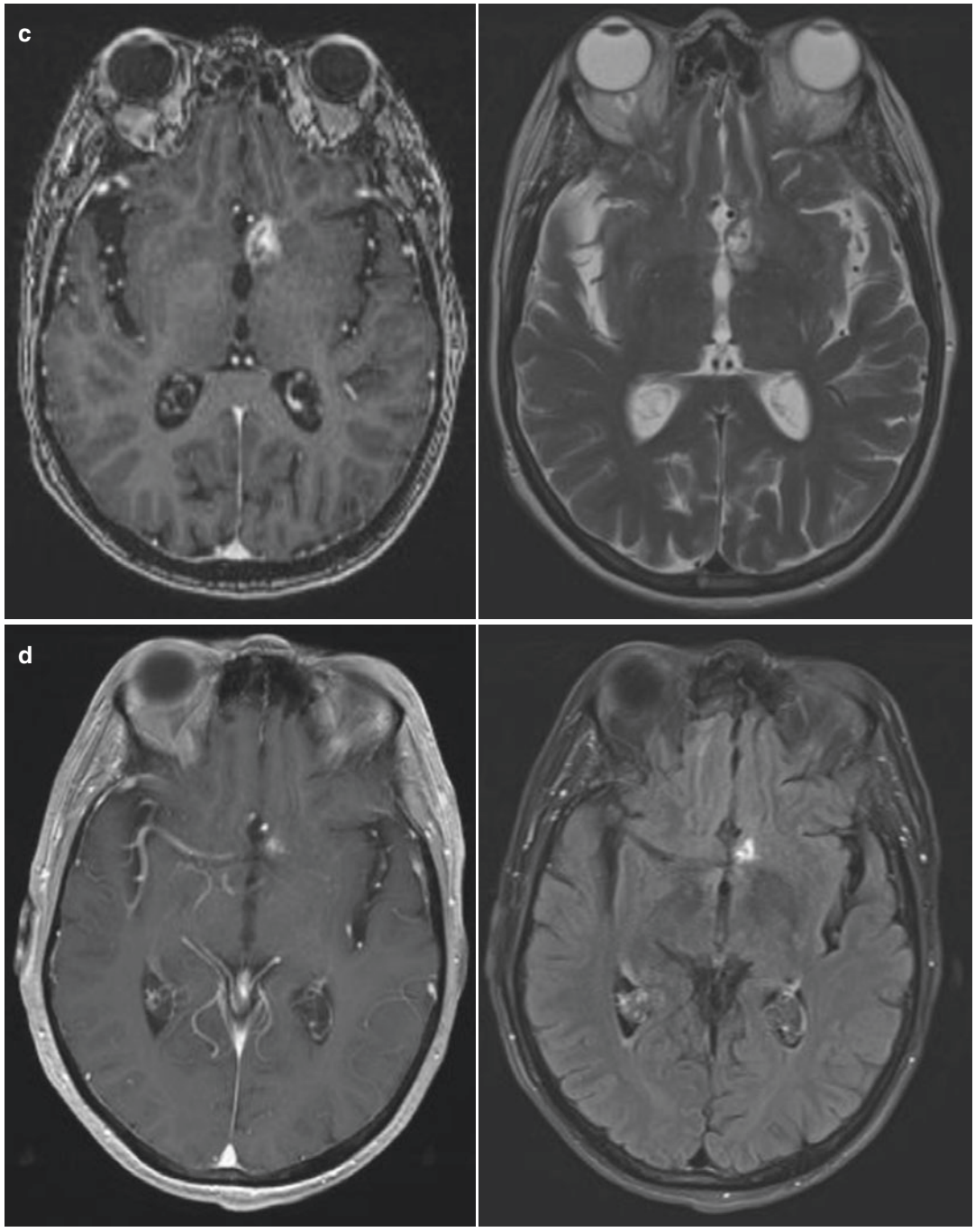

Fig. 24.4 (continued)

underwent GKRS. The dose plan consisted of 10 isocenters using 8- and 4-mm collimators. The tumor margin dose was 17.5 Gy at the 50% isodose line. She was placed on a 3-week dexamethasone taper starting at 4 mg TID.

Three-month follow-up imaging after GKRS demonstrated further peripheral increased enhancement of the tumor and more edema (Fig. 24.4b). No other new tumors were seen. The maximum tumor measurements increased from 20, to 30, to 35 mm on serial scans. Although radiation-associated expansion was likely, these imaging findings raised the concern for tumor growth, or reconsideration of the diagnosis which presumed was metastatic, given its appearance and the active cancer history. A separate pathology such as a malignant glioma was also possible.

Current Treatment Paradigm

Treatment options at this point included bevacizumab therapy, biopsy, biopsy and laser interstitial tumor therapy, and continued observation with use of corticosteroids. Surgical resection was felt to be hazardous in this location.

Case Outcome

She was initially observed and there was neurological improvement with respect to cognition. One-month follow-up MRI demonstrated slight improvement without intervention. She continued to be observed and continued to experience improvement clinically and radiographically, with a salvage plan of high-dose steroids or bevacizumab therapy should her imaging or clinical status worsen. Ten-month follow-up imaging after initial GKRS demonstrated significant decrease in the size and surrounding edema of the lesion (Fig. 24.4c). At last follow-up, 20 months after GKRS, the imaging remained stable (Fig. 24.4d).

Case 5: Tumor Bed Radiosurgery

A 47-year-old man was diagnosed with melanoma and treated with 1 month of interferon. A serial positron emission tomography (PET) revealed a lesion in the brain and subsequent MRI demonstrated it to be a 21 × 17 × 22 mm left parietal cortex with surrounding edema (Fig. 24.5a). The patient elected to proceed with resection and

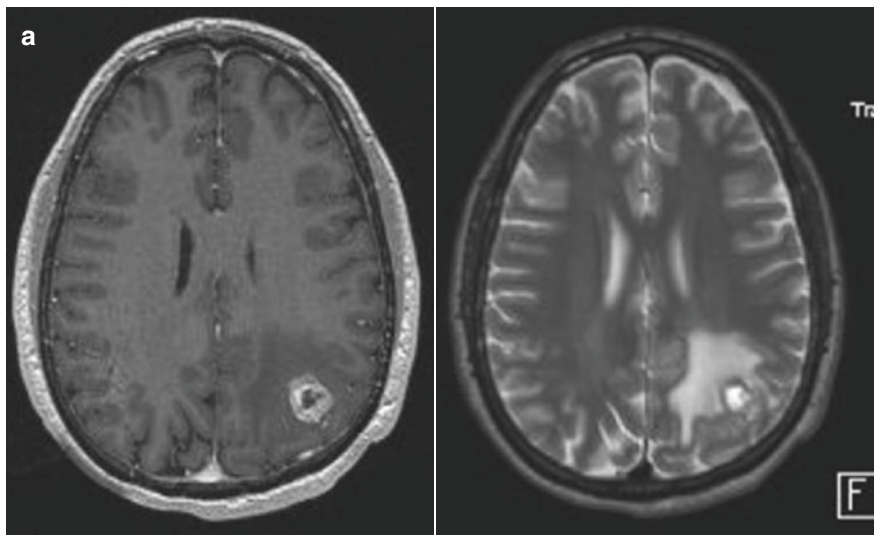

Fig. 24.5 Left occipital melanoma metastasis treated with resection followed by GKRS. (**a**) Pre-treatment post-contrast T1 (left) and T2 (right) MRI demonstrating lesion and surrounding edema. (**b**) Postoperative imaging demonstrating gross total resection. (**c**) Last follow-up 59 months after initial imaging, demonstrating no residual tumor on T1 post-contrast (left) and minimal evidence of parenchymal alteration on T2 (right)

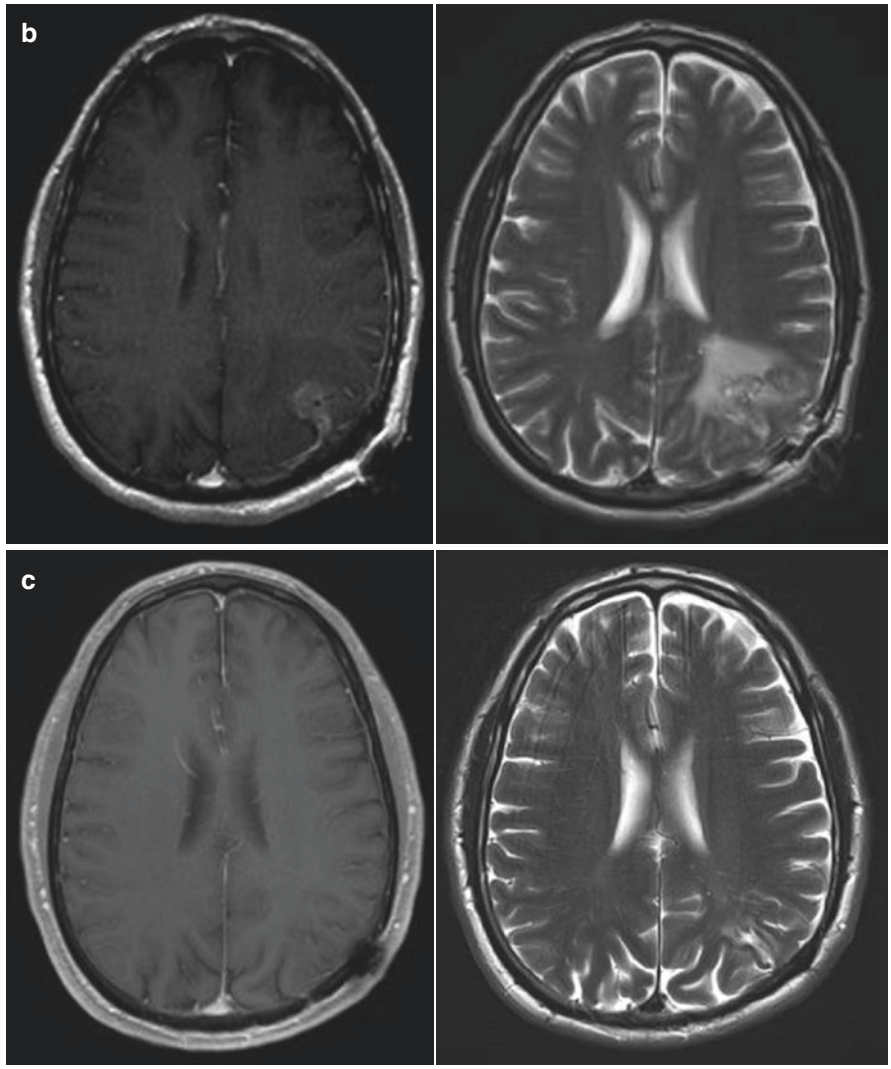

Fig. 24.5 (continued)

he underwent an uncomplicated gross total resection (Fig. 24.5b). Two weeks later, he underwent GKRS with a tumor bed margin dose of 16 Gy. Subsequent serial imaging every 3 months initially demonstrated a regressed appearance of the tumor and he did not require systemic melanoma treatment. At last follow-up, 59 months after initial adjuvant GKRS, no recurrence and no new tumors were visible (Fig. 24.5c). The patient has no neurological complaints. Local tumor management and avoidance of whole-brain radiation therapy have fostered continued normal neurological function and full-time employment.

Current Treatment Paradigm and Outcome

As in Case 2 above, mean survival after diagnosis of melanoma brain metastases is 4–5 months. This patient exceeded this outcome and follow-up imaging continues to demonstrate no residual.

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Synergy of Immunotherapy and Radiosurgery

25

Andrew G. Brandmaier, Rohan Ramakrishna, and Silvia C. Formenti

T Cells in Immunity

The immune system encompasses a broad spectrum of cells from the hematopoietic lineage. Each cell type contributes specialized functions which together perform key steps in host immunity: sensing danger stimuli, secreting cytokines that recruit and activate effector cells, displaying peptide fragments, detecting antigens, and engulfing and lysing targets. A guiding hallmark of immune activity was defined by immunologists Burnet and Medawar, who proposed the Self-Nonself Model (SNS), which posited that immune cells cooperate to recognize and attack foreign (non-self) antigens [1]. This framework rationalized how microbes and infected or transformed cells harbor aberrant "Nonself" protein antigens, which are recognized and subjected to immune attack, whereas regular normal "Self" host tissues are spared from immune targeting. SNS helps explain how B and T cell repertoires emerge in the host to respond against certain antigens and ignore others [2]. During development, each T cell clone is individually educated to recognize a peptide: major histocompatibility complex (MHC), but emerging clones that respond to self-antigens are directed to undergo apoptosis. Despite its broad applicability, SNS does not completely explain key phenomena such as tumor immunity. The "Danger Model" is a newer theory developed by Matzinger, and it proposes that immune activation is controlled by the context of innate immune signals in the tissue environment that are generated by perturbation of homeostasis. Viewing immune responses through the lens of "danger" has provided a logical way to interpret fundamental principles of tumor immunology [3]. These include the requirement of co-stimulation signaling to activate naïve T cells and the regulatory role of checkpoint molecules, which attenuate T cell activation and proliferation. In the tumor microenvironment, homeostatic regulatory processes and suppressive signals maintain a balance that suppresses T cell function. These mechanisms create a high threshold for the immune system to activate effective anti-tumor responses.

αβ T cells play a central role in the adaptive immune system and are also the key constituent of anti-tumor immunity. Individual T cell clones express a unique T cell receptor (TCR) dimer on the plasma membrane. The receptors contain an immunoglobulin-like subunit with a unique

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variable sequence at the surface, which scans MHC:peptide complexes expressed on adjacent antigen-presenting cells (APCs). MHC class I molecules are expressed on nearly all cell types, and these complexes are recognized by $CD8^+$ T cells. MHC class II molecules are primarily presented by professional APCs, which include dendritic cells (DCs) and macrophages, and they are recognized by $CD4^+$ T helper cells. When a TCR is engaged by an MHC:peptide complex with sufficient affinity to bind, activation signals are transmitted from the TCR through downstream signaling cascades that activate T cell effector functions and clonal proliferation. Class I antigens stimulate $CD8^+$ T cells to produce TNF-α and IFN-γ and to secrete cytotoxic granules that release perforin and granzyme, which cause lysis of the targeted cell [4]. Class II antigens stimulate $CD4^+$ T cells, which mediate helper activities including release of supportive cytokines and expression of CD40 ligand, which binds CD40 on adjacent APCs and promotes their activation. Type I helper cells (T_h1) can promote anti-tumor activity when activated to secrete IFN-γ, which is a strong paracrine signal that promotes surrounding cells to present class I and class II MHC complexes. For tumor cells, this increases recognition by cytotoxic $CD8^+$ T cells [5]. Additionally, T_h1 cells release IL-2, which is a growth factor that promotes survival and proliferation of surrounding T cells. Collectively, $CD8^+$ and $CD4^+$ T cells directly attack tumor cells and produce immunostimulatory signals that promote anti-tumor activity of other immune populations. In the following sections, we will describe some of the mechanisms cancers utilize to escape immune recognition and rejection.

APC Activation of T Cells

T cell clones emerging from the thymus are in a naïve phenotypic state prior to antigen encounter. The context of a T cell's initial recognition of cognate antigen is critical for its long-term fate in the immune system. When a naïve T cell's TCR binds MHC:peptide antigen without co-stimulation, the cell is induced to undergo anergy and enters a state of reduced proliferation and diminished IL-2 secretion [6]. The Danger Model predicts that immune cells are activated by alarm signals from pathogens or distressed cells. Toll-like receptors (TLRs) represent a prominent family of innate danger sensors expressed by APCs, and activation through these receptors induces their maturation. When mature, professional APCs, such as dendritic cells, increase surface expression of B7-1 and B7-2; these molecules co-stimulate naïve T cells by binding CD28 [7]. TCR stimulation coupled with CD28 co-stimulation activates a naïve T cell to adopt its mature, effector status; its TCR subunits reorganize at the plasma membrane to respond to future antigen encounters at a lower threshold. The cell also expresses CD25 to enable rapid proliferation in response to IL-2. With these changes, the activated T cell can clonally expand and effectively attack antigenic targets in the periphery. It also spawns effector and memory daughter cells to expand the reach and longevity of cells recognizing the antigen in question.

Mature DCs perform key functions necessary for T cell priming. They phagocytose distressed or dead cells, process and present antigens for T cell recognition, and release stimulatory cytokines [8]. In tumors, DCs are activated if they encounter danger-associated molecular patterns (DAMPS) which bind their TLRs. In particular, a subpopulation of BATF-3-dependent $CD103^+$ DCs have been found to efficiently engulf and process tumor cells and vesicles and transport this cargo to tumor draining lymph nodes [9]. Upon arrival, the DCs present MHC class I and II peptide antigens from the tumor and prime anti-tumor T cells. The presence of sufficient DAMPs in the tumor microenvironment is critical for this initial step in generating an anti-tumor response.

Multiple innate regulatory signals are utilized by the immune system to prevent overactive or redundant T cell responses and maintain homeostasis. This includes checkpoint signals, which are transmitted through an array of receptors to control the duration and amplitude of T cell activity. The two most prominent checkpoint targets with a proven efficacy in immunotherapy are CTLA-4 and PD-1. T cells upregulate surface

expression of CTLA-4 following stimulation of their TCR. This provides a negative signaling axis, wherein the B7-1 and B7-2 costimulatory molecules can transmit regulatory signals by binding CTLA-4. In mouse models, a germline knockout of CTLA-4 leads to fatal autoimmunity associated with generalized T cell activation, illustrating the regulatory power of this checkpoint molecule in suppressing T cells [10]. A second checkpoint pathway is mediated by the receptor, PD-1. T cells upregulate PD-1 expression following activation, and ligand binding regulates tissue inflammation, which protects against autoimmunity. Its ligands, PD-L1 and PD-L2, are expressed on tumor cells and regulatory immune cells. When PD-1 is bound, the T cell downregulates kinases involved in activation and acquires an "exhausted" phenotype with limited function and potentially apoptosis [11]. Mice with a genetic knockout of PD-1 demonstrate tissue-specific autoimmunity, though less severe than CTLA-4 [12]. Overall, the immune checkpoint molecules maintain homeostasis by dampening immune activation. They also are utilized in the tumor microenvironment to create a barrier to anti-tumor immunity.

Immunity in the Brain

The central nervous system (CNS) has a unique landscape compared to other tissue types with its own resident immune cells, a distinct lymph drainage pathway, and restricted vascular permeability maintained by the blood-brain barrier. Microglia reside exclusively within the CNS, and they perform similar functions to macrophages, including processing and presentation of antigens and expression of MHC class II complexes. At baseline, microglial cells maintain immune homeostasis; they also stimulate and remove various neighboring cells for maintenance of the microenvironment. Innate immune signals can activate microglia and turn on their antigen-presenting and immune-priming functions. Their persistent activation has been associated with destructive inflammation and neurodegenerative diseases [13]. In metastatic and primary brain tumors, microglia function can be subverted to a tolerogenic phenotype, similar to M2 macrophages. Peripheral macrophages and monocytes are often recruited to brain tumors and can function together with altered microglia to release tumor-promoting cytokines and growth factors. In doing so, they help vascularize the tumor tissue and promote tumor cell growth and invasion [14].

The blood-brain barrier stringently regulates passage of substrates and cells into the brain from the vasculature. It is comprised of tight junctions between endothelial cells and support from astrocytes and pericytes. This tight barrier hinders immune cell trafficking, and therefore the brain has been sometimes characterized as an "immune privileged" site due to the limited cross-talk between its tissue epitopes and the APCs and lymphocytes of the immune system, though this interpretation has been challenged. Three sites of immune cell access into the brain have been proposed: choroid plexus, leptomeningeal vessels, and parenchymal vessels [15]. Metastatic tumors exhibit heterogenous vascular regions with selective disruption of the blood-brain barrier, which is due, in part, to their suppression of molecular signaling pathways of CNS endothelial cells [16]. Nevertheless, modeling of the "blood tumor barrier" has found that chemotherapeutic agents are significantly excluded from brain tumors relative to non-CNS tissues [17]. Tumor-directed radiation has been found to disrupt the blood-brain barrier. It is not clear how or whether more extensive alterations of the blood-brain barrier in tumors would impact the systemic anti-tumor immune response.

The origins and extent of tumor immunosurveillance in the CNS are not fully defined. Preclinical evidence has shown that APCs are present in the brain parenchyma and ultimately drain into cervical nodes of the neck, where they can present tumor antigens to circulating T cells to generate a systemic immune response. Recently, discovery of draining lymphatics along the dura has provided more insight into this pathway. Intraparenchymal cerebrospinal fluid (CSF) carrying cells and antigens from the brain tissue flow out to the subarachnoid reservoirs of CSF [18]. Enriched by these substrates,

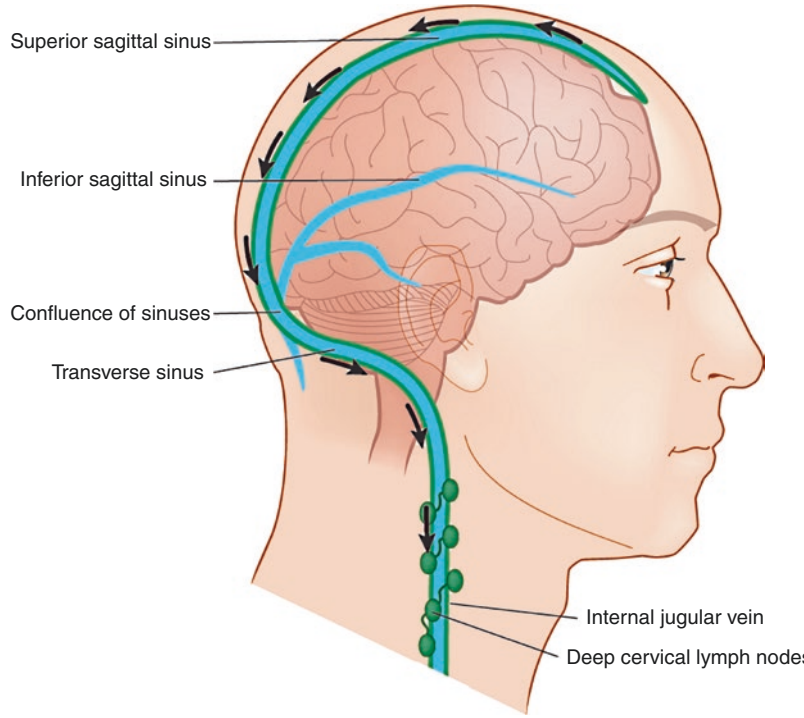

Fig. 25.1 Histologic evaluation has revealed the presence of lymphatic vessels in the meninges of the brain. They line the dural sinuses and serve as an interface with cerebrospinal fluid carrying cells and soluble particles from the brain parenchyma. The brain lymphatics are a channel for immune cells and fluids to drain to the deep cervical nodes where they can interact with the peripheral immune system

the CSF diffuses into lymphatic vessels, which run in parallel along the dura. The lymph fluid follows this path along the sagittal sinus, which ultimately reaches deep cervical lymph nodes to interface with the peripheral immune system (Fig. 25.1). Overall, the brain has a unique immune microenvironment. Its resident immune cell population, blood-brain barrier, and distinct lymph drainage channels add to the complexity of strategically targeting metastatic CNS tumors with immunotherapy.

Tumor Immunosurveillance

Tumor immunosurveillance is a model of the dynamic interaction between the immune system and emerging cancers. It postulates that most neoplastic cells are eliminated before they proliferate to form tumors. Newly transformed cells possess genetic or cellular aberrations that are presented in antigen complexes and recognized by circulating T cells. Schreiber et al. defined three main categories of tumor antigens: tumor-associated antigens, cancer germline antigens, and tumor-specific antigens [19]. Tumor-associated antigens (TAAs) are proteins associated with cell function that may be recognized by T cells when expressed at aberrant levels. In melanoma, several substrates involved with pigment synthesis are TAAs, such as MART-1 and GP100. In breast cancer, HER2/neu is a TAA. Germline antigens are proteins normally restricted to the gonads but ectopically expressed by tumor cells. MAGE-A and NY-ESO-1 are well-characterized germline antigens expressed by various cancers. Tumor-specific antigens, also known as "neoantigens," are proteins expressed from nonsynonymous gene mutations occurring in cancer cells that result in novel peptide epitopes recognized as foreign by lymphocytes. Innovations in bioinformatics are creating new applications to apply whole genome sequencing and mass spectrometry data from tumor samples to predict the presence of neoantigens and identify corresponding reactive lymphocytes from the patient [20]. Tumors that contain a high mutational load, such as in the setting of defective mismatch repair genes, have shown an increased response to immunotherapy. This may be due to an increased abundance of neoantigens susceptible

to T cell attack. The ability to analyze tumors and predict antigenic targets may lead to new opportunities in immunotherapy.

Immune Suppression by Tumors

In addition to immunoediting, tumors also activate regulatory processes that suppress host anti-tumor immunity. Histologically, the tumor microenvironment contains supporting and regulatory stromal cells dispersed among the primary cancer cells. They include fibroblasts, myeloid cells, and tumor-associated vascular endothelium. In cancer, these populations converge to create an immunosuppressive network resembling an unhealed wound [21]. They condition the microenvironment by secreting growth factors and chemokines including vascular endothelial growth factor (VEGF), chemokine ligand 2 (CCL2), and granulocyte-macrophage colony-stimulating factor (GM-CSF), which attract myeloid cells from the periphery that differentiate into myeloid-derived suppressor cells (MDSCs) and macrophages; these cells potently suppress APCs and T cells within the tumor [22]. Clinically, high levels of tumor infiltrating polymorphonuclear MDSCs have been associated with disease progression and worse prognosis in cancer patients, which illustrates how local immunosuppression favors tumor persistence and growth [23]. They produce reactive oxygen species which affect $CD8^+$ T cells by reducing levels of the TCR zeta chain and BCL-2, which increases their proclivity to undergo apoptosis [24]. MDSC metabolism also suppresses immune function, by depleting arginine in the tumor microenvironment, disrupting the function of the TCR complex and limiting proliferation of activated T cells [25]. MDSCs also express the enzyme IDO, which catabolizes tryptophan to kynurenines. Low tryptophan concentration sensitizes T cells to apoptosis, and kynurenines induce T_{reg} cell differentiation [26]. Tolerogenic DCs also synthesize IDO and metabolize tryptophan. MDSCs, tumor macrophages, and T_{regs} all produce IL-10 and transforming growth factor (TGF)-β. IL-10 attenuates DC activation and reduces macrophage expression of both MHC class II complexes and CD86 costimulatory molecules [21]. TGF-β promotes expansion of T_{regs} and induces differentiation of naïve $CD4^+$ T cells to $Foxp3^+$ T_{regs}. It also induces apoptosis of activated $CD8^+$ T cells, attenuates DC activation, and directs macrophages toward a suppressor phenotype [27]. In summary, the tumor microenvironment maintains specific populations of cells and produces a profile of cytokines that are potently immunosuppressive, establishing a significant barrier to effective anti-tumor immune responses.

Radiation Therapy in Cancer

Radiation biology dogma has traditionally attributed anti-tumor effects of radiotherapy to cytocidal DNA damage. Measurements of tumor cell sensitivity to radiation, such as survival curves generated from clonogenic assays, have traditionally provided a means to model therapeutic efficacy of various dose and fractionation approaches [28]. This approach interprets radiotherapy through the lens of cell kill. However, more modern data has revealed that radiation also has a substantial effect on the tumor microenvironment that influences systemic processes. In vivo mouse studies have shown that radiation treatment can activate anti-tumor immune responses and synergize with immunotherapeutic agents [29]. Radiation releases cell death substrates that activate innate immune receptors that promote T cell priming [30]. Furthermore, the production of double-stranded DNA breaks and formation of micronuclei turn on the type I interferon pathway [31, 32]. These phenomena, which will be elaborated in greater detail later, are established mechanisms by which radiation stimulates tumor immunity, and they substantiate the beneficial role of radiotherapy as an adjuvant when combined with immunotherapy.

Immunogenic Cell Death

The contribution of radiation to anti-tumor immunity is partly due to how the malignant cells die and the associated signals that are released

into the microenvironment. Zitvogel and Kroemer reported that various cell death pathways can produce DAMPS, which are danger signals that activate innate immune receptors and ultimately trigger adaptive T cell activation against antigens from the dying cells. This type of cell death is categorized as "immunogenic cell death" (ICD) [33]. Strategic induction of ICD is an emerging therapeutic strategy to elicit activation of the immune system within the tumor. Three important DAMPs have been conventionally associated with cells undergoing ICD [34]:

1. Calreticulin, an endoplasmic reticulum protein, translocates to the extracellular surface of the plasma membrane. External exposure of calreticulin corresponds to endoplasmic reticulum stress and the molecule signals CD91 on DCs and macrophages, leading to phagocytosis of the dying cell [35].
2. HMGB2 is a chromatin-binding factor that is released from the cell. It signals TLR4 on DCs leading to maturation. Mature DCs upregulate costimulatory molecules such as CD80, efficiently phagocytose dead cells, and cross-present exogenous antigens [36].
3. ATP is secreted by the dying cells, which recruits professional APCs and stimulates IL-1β production by DCs, thus promoting antigen cross-presentation.

Altogether, ICD facilitates anti-tumor immunity by producing an array of DAMPs that promote tumor infiltration and activation of APCs, engulfment of dead and dying tumor cells, and effective cross-presentation and priming of tumor-specific T cells.

The discovery that some cell death pathways promote adaptive immunity has led to evaluation of various anti-neoplastic therapies for their immunogenicity. Among various chemotherapy classes, anthracyclines, cyclophosphamide, and oxaliplatin have been demonstrated to induce ICD in vitro and in vivo [37]. Classic tumor vaccination/re-challenge assays have also shown that radiation induces ICD. Mice injected with irradiated cells fail to grow tumors following a second challenge injection. Importantly, this finding was not recapitulated when the experiment was repeated in immunodeficient mice, bolstering the causal relationship between adaptive immunization and protection against tumor growth. Golden et al. evaluated levels of ICD biomarkers produced in tumor cell cultures and found that tumor cell radiation results in release of ATP and HMGB1 and promotes externalization of plasma membrane calreticulin, all in a dose-dependent fashion [38]. These studies have shown that radiation of tumor cells induces bona fide ICD with production of the hallmark DAMPs.

Radiation Upregulates MHC and IFN-β

Radiation also promotes tumor MHC:peptide antigen presentation. Reits et al. showed that radiation of human melanoma cultures increased the level of tumor MHC class I molecules in a dose-dependent fashion. Radiation was also shown to upregulate MHC expression on normal host tissues in vivo [39]. An orthotopic murine glioma model demonstrated that whole-brain radiation upregulated MHC-I expression on GL261 tumor cells, which improved the efficacy of concomitant vaccination [40]. Radiation also broadens the antigen peptide pool by activating mammalian target of rapamycin (mTOR), which promotes processing of proteins into peptide fragments and increases synthesis of new proteins. Moreover, radiation of different types of human tumor cells demonstrably increased the production of cancer-testis antigens, including MAGE-A1 and NY-ESO-1, which lead to activation of corresponding T cells reactive against these epitopes. These findings taken together show that radiation promotes MHC display with a diverse ensemble of peptide antigens.

Radiation of tumors also stimulates an innate immune pathway that leads to type I interferon production. Specifically, production of double stranded DNA (dsDNA) breaks followed by cell mitosis generates micronuclei that contain chromosome fragments. The cGAS molecule senses these dsDNA fragments and activates downstream STING, which ultimately leads to transcription of type I interferon [41]. Production of IFN-β stimulates maturation of DCs with

increased expression of costimulatory molecules and efficient cross-presentation of antigens to T cells, which enhances priming of adaptive immunity. Combinatorial therapy with radiation and checkpoint blockade relies on IFN-β activation of Batf-3-dependent DCs to cross-prime $CD8^+$ T cells and generate effective anti-tumor responses [32]. An in vivo mouse model of breast cancer utilizing combination anti-CTLA-4 and tumor radiotherapy showed that doses greater than 12–15 Gy per fraction attenuated anti-tumor immune responses. Mechanistically, higher doses of radiation induce expression of the nuclease, Trex1, which degrades cytosolic dsDNA and thereby removes the immune signal for activation of the cGAS-STING pathway [31]. This model demonstrated the significance of radiation dose and fractionation for immunotherapy applications.

The immune-activating effects of radiation have provided a basis for models combining tumor radiotherapy with immune targeting drugs. One of the first preclinical models testing this concept utilized Flt-3 ligand, a growth factor for DCs, together with radiation to treat mice challenged with Lewis lung carcinoma. The cohorts that received monotherapy of either agent alone showed limited survival because of lung metastases. However, a combination of radiation with Flt-3 ligand reduced the number of pulmonary metastases and improved overall survival [42]. Subsequently, Demaria and Formenti showed a bona fide abscopal effect with a combination of radiation and immunotherapy. In mice with bilateral flank tumors of mammary carcinoma (67NR), radiation of one tumor and Flt-3 ligand treatment reduced the growth of the contralateral tumor [43]. This effect was abrogated in athymic mice lacking αβ T cells, highlighting a synergy of the two therapies for the adaptive immune response.

Immune Regulation Induced by Radiation

Radiation also activates homeostatic mechanisms of the immune system that play an important role in suppressing immune attack. Irradiated tumors increase HIF1-α expression, TGF-β production, and activation and release of chemokines that recruit T_{regs}, MDSCs, and macrophages. These phenomena have prompted research into regimens combining radiation with immunomodulatory drugs to "release the brakes" from these regulatory signals. TGF-β is a prominent target for this objective; it diminishes cross-priming by APCs, reduces activation of $CD8^+$ T cells, and increases the prevalence of T_{regs}. A preclinical model with 4T1 breast cancer evaluated tumor radiation and TGF-β blockade, which showed increased activation of anti-tumor T cells, decreased tumor growth and metastases, and improved survival [44]. This approach was incorporated in a clinical trial for metastatic breast cancer: patients received three fractions of 7.5 Gy to one lesion and either low- or high-dose anti-TGF-β antibody; receipt of the high dose of immunotherapy boosted memory $CD8^+$ T cells and was associated with improved overall survival [45]. Chemokine receptor 2 (CCR) is also a relevant target for combination therapy. Radiation signals through cGas-STING to increase intratumor levels of chemokines that bind CCR2 and attract MDSCs to the tumor microenvironment. Notably, tumor-challenged mice treated with radiation and CCR2 blockade demonstrated enhanced $CD8^+$ T cell-mediated tumor rejection versus cohorts receiving radiation alone [46]. Overall, radiation has both stimulatory and suppressive effects on the immune system. Strategic molecular targeting of potent regulatory pathways together with radiotherapy can successfully elicit anti-tumor immunity.

Immune Checkpoint Inhibitors

Clinical trials have demonstrated the efficacy of checkpoint inhibitors for several tumor types and thus established immunotherapy as a mainstream modality in oncology. New applications continue to emerge, and at present, most are focused on metastatic or locally advanced disease. Allison and colleagues originally elucidated the T cell regulatory molecule, CTLA-4, and demonstrated that antibody blockade (anti-CLTA-4) unleashed anti-tumor immunity. Mice that were

challenged with characteristically immunogenic tumors showed pronounced rejection of the tumors after receipt of anti-CTLA-4 antibody [47]. An in vivo study with melanoma demonstrated that anti-CTLA-4 therapy contributed to tumor immunity by amplifying effector T cell function and minimizing T_{reg} cell activity [48]. Notably, a subsequent study using anti-CTLA-4 to treat the poorly immunogenic melanoma, B16-BL6, showed minimal ability to inhibit tumor growth. It was only when mice received anti-CTLA-4 therapy combined with a vaccination injection of irradiated B16-BL6 cells modified to express GM-CSF that elimination of tumor could be achieved in vivo [49]. These results highlighted that most tumors may require multiple sources of immunogenic stimuli for a therapeutic response. The preclinical work characterizing anti-CTLA-4 ultimately translated to clinical applications with ipilimumab. In the first major phase III trial with a checkpoint inhibitor, the drug showed improved overall survival for metastatic melanoma, which set the stage for further development of checkpoint inhibitors in oncology [50].

The PD-1 signaling axis is the second T cell checkpoint pathway that has been successfully incorporated for tumor immunotherapy. Several established human tumors such as lung, ovary, colon, and melanoma increase expression of PD-L1 to suppress T cell activity in their microenvironment [51]. Immune cells recruited by tumors, including MDSCs, can also express PD-L1 [52]. When surface PD-1 is engaged by the ligand, T cells adopt an exhausted phenotype and display diminished activity. Anti-PD-1 antibodies block this signal and help revive tumor infiltrating T cells, thus facilitating adaptive anti-tumor responses. PD-1 checkpoint inhibitors have demonstrated success and are approved for use in an increasing number of malignancies, including advanced stage melanoma, non-small cell lung cancer (NSCLC) urothelial carcinoma, Hodgkin's disease, and head and neck squamous cell cancer, as well as microsatellite instability-high cancers [53]. Though cohorts of cancer patients receiving checkpoint inhibition have improved clinical outcomes as a group, most patients do not achieve a significant response to treatment. New approaches to increase the proportion of responders are needed, and radiotherapy is being investigated for this purpose.

Recent trials have assessed whether combined checkpoint inhibition may synergistically enhance clinical anti-tumor responses. Checkmate 067 was a phase III clinical trial evaluating monotherapy checkpoint inhibition versus a combination of ipilimumab and nivolumab administration for patients with metastatic melanoma [54]. The cohort receiving combined therapy had a longer progression-free survival (PFS) and higher objective response rate compared to the cohort receiving ipilimumab alone, albeit at the price of increased toxicity. Notably, most of the trials utilizing immunotherapy for advanced stage cancer have excluded patients with brain metastases. However, Margolin and colleagues reported a phase II study of dual checkpoint inhibition with nivolumab and ipilimumab for patients with melanoma brain metastases. Combined therapy resulted in a high response rate of 56%. Complete response was seen in 26% of patients [55]. These impressive results provide a foundation for exploring checkpoint inhibition for different types of brain metastases.

Combination of Checkpoint Inhibitors with Radiation

Radiation of tumors associated with off-target responses (abscopal effect) has been described in a small number of case reports dating back several decades. This includes patients with a wide variety of tumor types such as melanoma, renal cell carcinoma, and lymphoma [56–58]. The impact of radiation on systemic tumor responses may be related to anti-tumor immunity. As previously described, radiation induces stimulatory immune danger signals that create an in situ vaccine effect in the tumor microenvironment, which helps prime adaptive T cell responses. Potential synergy of these effects with checkpoint inhibition has been extensively explored in preclinical studies [59]. Formenti and Demaria showed that mice challenged with 4T1 breast carcinoma derived minimal benefit from treatment with radiation or anti-CTLA-4 monotherapy. Yet, combined treatment with both agents significantly reduced the

number of lung metastases in recipients and improved survival [60]. This approach has also demonstrated efficacy in an orthotopic glioma mouse model: combinatorial therapy with anti-PD-1 and a single fraction of 10Gy to the tumor resulted in a significant improvement in survival over either treatment alone [61]. Minn et al. showed that dual checkpoint therapy with anti-PD-1 and anti-CTLA-4 in addition to tumor radiation provided complementary, non-redundant immune activation signals. The anti-tumor TCR repertoire was expanded by radiation. PD-L1 blockade revived exhausted $CD8^+$ T cells, and CTLA-4 blockade decreased T_{regs}. Thus, dual checkpoint blockade increased the ratio of CD8/Treg cells [62]. Rudqviist et al. also found that CTLA-4 blockade and radiation therapy for tumor-challenged mice synergized to expand the TCR repertoire within tumor-infiltrating lymphocytes (TIL). Their evaluation identified an increased diversity and number of CDR3 motifs among the population of receptors [63]. The evidence from these and several other preclinical models have provided a compelling rationale to explore combinatorial strategies with radiation and checkpoint inhibitors (Fig. 25.2).

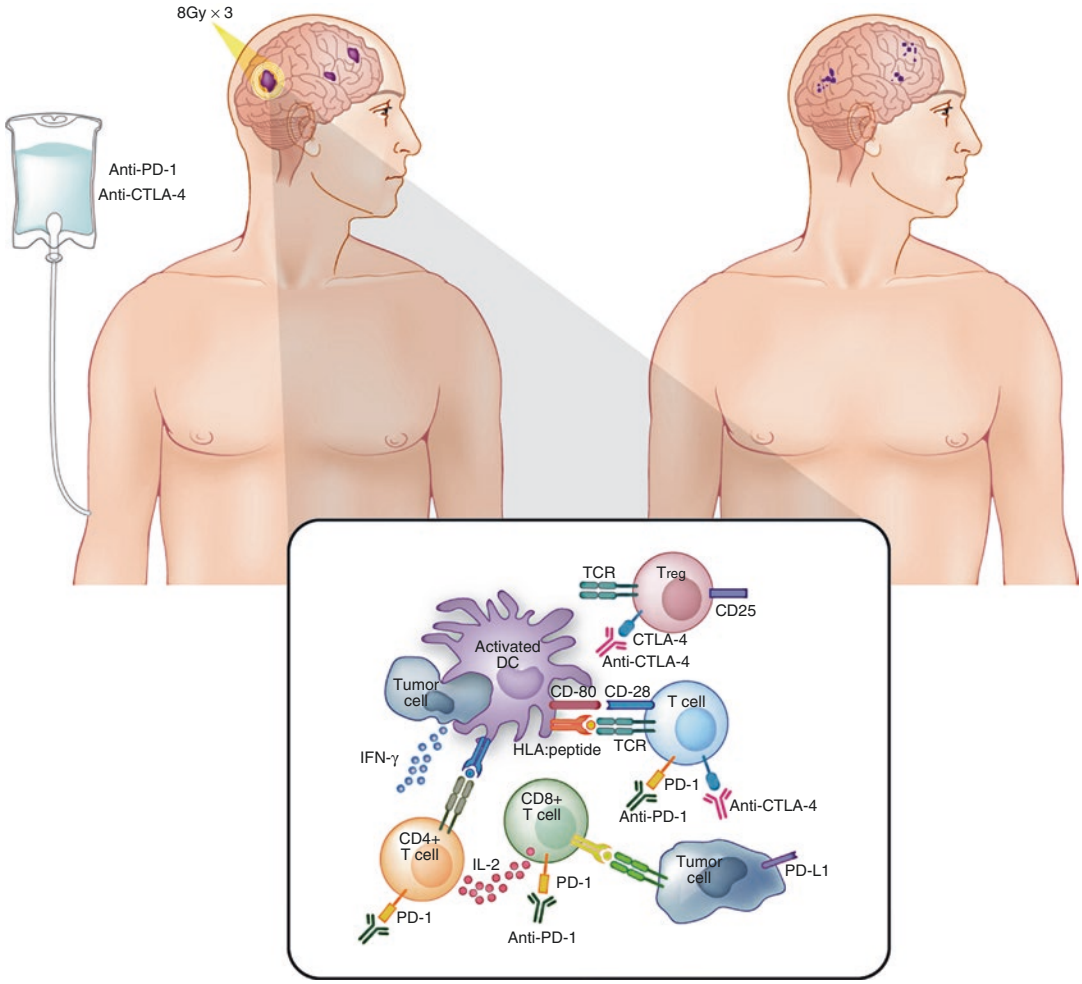

Fig. 25.2 Immunotherapy with anti-CTLA-4 and anti-PD-1 monoclonal antibodies activates non-redundant mechanisms that promote clonal expansion of T cells and revive exhausted effector cells. Tumor radiation enhances MHC antigen presentation and increases the diversity of the anti-tumor T cell repertoire. Clinical trials are exploring paradigms for combining immunotherapy with tumor radiation to synergistically activate and expand anti-tumor T cells that mediate systemic tumor rejection

Results from preclinical data have influenced new oncology trials for patients incorporating synchronous immunotherapy and radiation. Most of the findings are limited to small cohort studies or anecdotal case reports. For example, a melanoma patient who reportedly progressed after receipt of ipilimumab received palliative radiation in three fractions for a spinal metastasis. Within 3 months, distant hilar metastases, and splenic lesions responded, representing nearly a complete disease regression [64]. Also a phase II study treating Merkel cell carcinoma with pembrolizumab reported that two patients who received palliative radiation following disease progression had subsequent off-target tumor response [65]. Formenti and colleagues recently reported the results of a trial for patients with NSCLC who, after failing chemotherapy, went on to receive radiation therapy to a single metastasis and concurrent ipilimumab. Notably, two previous prospective randomized trials of CTLA-4 blockade with chemotherapy failed to demonstrate significant activity in advanced NSCLC [66, 67]. However, in Formenti's trial combining ipilimumab with focal radiotherapy, 31% of the patients achieved disease control, and 18% demonstrated an objective response [68]. One patient who achieved a complete response after originally presenting with synchronous lung cancer and brain metastases was found to have a clonal expansion of T cells recognizing a mutation within his tumor. This result demonstrated translational success of radiotherapy in inducing neo-antigens and converting the tumor into an in-situ vaccine. As ongoing combinatorial trials continue to mature, more sophisticated conclusions can be reached regarding the efficacy of combining tumor radiation with immune checkpoint inhibitors.

Optimal Radiation Parameters for Immunotherapy

The optimal dose and fractionation of radiotherapy in combinatorial regimens with checkpoint inhibitors are yet to be determined. Several cases reported in the literature utilized a hypofractionated course, though no standard prescription has emerged. One core question is the comparative efficacy of different doses per fraction of radiotherapy. In preclinical work with B16 melanoma, a single fraction of 20Gy activated anti-tumor $CD8^+$ T cells in mice, whereas this response was not seen in a comparison cohort treated with 5 Gy × 4 fractions [69]. On the other hand, Vanpouille-Box treated mice bearing two subcutaneous TSA breast carcinomas with anti-CTLA-4 and various radiation regimens directed only to one tumor. Cohorts that received 8 Gy × 3 demonstrated abscopal tumor response (measured in the non-irradiated tumor) and increased survival compared to those that received a single fraction of 20 Gy. In this model, the abscopal response from radiation diminished as doses were escalated above 12 Gy per fraction [31]. This trend paralleled dose-dependent induction of Trex-1, an exonuclease that digests cytoplasmic dsDNA and removes the substrate for cGAS/Sting, which attenuates induction of type I interferon.

With no consensus dose established for immunotherapy applications, clinical trials are utilizing a variety of radiation prescriptions. Chmura et al. conducted a phase I clinical trial treating metastatic solid tumors with pembrolizumab and SBRT doses from 30 to 50 Gy. They reported a favorable toxicity profile, but the objective response was only 13.2%, which was similar to the outcome of pembrolizumab alone in an unselected cohort of patients with metastatic disease. The median PFS was 3.1 months [70]. In comparison, the Netherlands Cancer Institute reported preliminary phase II results from NSCLC patients, who were randomized to pembrolizumab alone versus pembrolizumab with a sub-ablative radiation dose of 8 Gy × 3. The pembrolizumab alone cohort achieve a 19% response rate, while the cohort receiving combination therapy had a 41% objective response. Also, the median PFS was 1.8 versus 6.4 months, respectively [71]. These preliminary findings suggest that a dose/fraction effect may govern the immune activating potential of radiotherapy. Further investigation is needed to validate this phenomenon and,

if confirmed, determine whether this is due to Trex-1 induction or other signals.

Modern clinical trials have not yet reported high-level data for combinatorial regimens with checkpoint inhibitors and radiation of brain metastases. Standard whole-brain radiation prescriptions include 30 Gy in 10 fractions and 20 Gy in 5 fractions as palliative options for extensive disease. Stereotactic radiosurgery (SRS) using a single-fraction ablative dose has demonstrated excellent local control for patients with a limited number and size of brain metastases. SRS also has superior preservation of long-term cognition compared to whole-brain radiation. Furthermore, Knisely and colleagues reported findings that bolstered the prospect of combination SRS and checkpoint inhibition. In a retrospective analysis of cases of melanoma brain metastases, they showed that the cohort of patients who received ipilimumab in addition to SRS had an overall survival of 21.4 months versus 4.9 months for patients who received SRS alone [72], a significant difference even if the retrospective nature of the study likely reflects patient selection. Additionally, hypofractionated regimens may have comparable efficacy to SRS for larger brain tumors >2 cm. A meta-analysis of 24 trials showed similar 1-year local control for patients receiving SRS versus multi-fraction RT. The most common multi-fractionation regimen utilized was 27 Gy in three fractions [73], a prescription that aligns well with the preclinical data from Vanpouille-Box modeling optimal immunogenic doses to induce tumor production of type I interferon.

In addition to dose and fractionation, the optimal sequencing of radiation and immunotherapy continues to be evaluated. Preclinical work comparing different sequences showed that upfront checkpoint blockade with anti-CTLA-4 followed by radiotherapy achieved the greatest tumor treatment efficacy. The study concluded that early depletion of T_{regs} facilitated immune priming of $CD8^+$ T cells when tumors were irradiated [74]. Limited results from currently available trials suggest that overlapping or close sequencing of checkpoint blockade with radiotherapy is likely to be the most effective approach. For melanoma brain metastases, a retrospective analysis showed that patients receiving anti-PD-L1 and anti-CTLA-4 therapy followed by stereotactic radiosurgery within 4 weeks of checkpoint blockade demonstrated a greater median reduction in lesion volume compared to patients with a longer separation of treatments. However, this result could be attributable to patient selection since progression through ipilumimab may correspond to more aggressive metastatic disease [75]. An unplanned analysis of the Pacific Trial for NSCLC found that patients who received durvalumab (anti-PD-1) after responding to platinum-based chemo-radiation had improved PFS. The finding was particularly significant if checkpoint blockade was administered within 2 weeks from completion of chemoradiation [76]. Also, Chiang and colleagues reported retrospective data of melanoma patients with brain metastases who were treated with SRS and immune checkpoint inhibition. Administration of immune checkpoint therapy within 4 weeks of SRS resulted in greater reduction in tumor size compared with patients who received treatment that was not concurrent [77]. Going forward, results from clinical trials that are currently underway will provide a clearer understanding of the significance of dose/fractionation and sequencing to the overall success of therapy.

Lymph Nodes as an Organ at Risk (OAR)

Utilization of radiotherapy for tumor immune activation will elevate the importance of lymphocytes and lymph nodes as organs at risk for treatment planning. Functional lymph nodes provide an interface for T cells and APCs draining from tumors to interact and receive priming signals for activation and proliferation. Marciscano and colleagues examined the impact of radiation target fields that included tumor-draining lymph nodes in a preclinical model. Mice were challenged with flank tumors and treated with checkpoint blockade and a single fraction of 12 Gy that either included or omitted the regional draining lymph nodes. The cohort that received radiation with a field encompassing their draining lymph nodes had a diminished tumor infiltrating lym-

phocytes population and worse survival compared to the cohort where draining lymph nodes were avoided [78]. A second area of consideration is the impact of fractionated radiation on lymphocytes in the peripheral blood. Ford and colleagues modeled the radiation dose to the circulating pool of lymphocytes. In their calculation, a single fraction of 2 Gy would deliver 0.5 Gy to 5% of circulating cells. Notably, a 30-fraction course would result in ≥0.5 Gy to 99% of circulating blood cells. These studies support a strategy of lymph node sparing and the utilization of hypofractionated courses of radiation to best protect the host T cell pool if attempting to stimulate an anti-tumor immune response. For radiation of the brain, an additional consideration could be the anatomic avoidance of the previously described lymphoid drainage network that traces along the sinuses to the cervical nodes. Louvea and colleagues showed that ablation of meningeal lymphatics reduces T cells and inflammatory responses in the brain in a model of multiple sclerosis [79]. It has not been determined how treatment such as whole-brain radiation impacts the integrity of the brain lymphatic channels and, furthermore, what impact this has on anti-tumor T cell responses within the brain. Future preclinical studies may be needed to explore how brain radiation specifically impacts all of these variables.

Summary

Immunotherapy is transforming the practice of oncology and rapidly integrating into mainstream treatment paradigms. The utility of radiotherapy as an adjuvant with immunotherapy is well established by preclinical data showing how tumor radiation releases danger signals that may convert the irradiated tumor into an in situ vaccine. The rarity of abscopal effects confirms the evidence of the robust immunosuppressive microenvironment of established tumors. Tipping the balance by adding immunomodulators to local radiotherapy, such as checkpoint inhibitors, can create a synergistic effect that promotes therapeutic anti-tumor T cell responses. Brain metastases present a unique challenge because the brain has a distinct immune profile. Furthermore, many clinical trials with checkpoint inhibitors have excluded such patients. Additional data regarding optimal dose, timing, and targeting with radiation is rapidly emerging. This data should be incorporated into new clinical trials for brain metastases to ultimately develop the most effective combinations of stereotactic radiation and immunotherapy.

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Salvage Irradiation for Patients with Recurrent Brain Metastases

26

Christian Iorio-Morin, Laurence Masson-Côté, and David Mathieu

Introduction

Brain metastases (BMs) are the most common tumors of the central nervous system. Their exact incidence is difficult to assess, since they are not part of the data collected by national registries such as the Surveillance, Epidemiology, and End Results (SEER) [1] and the Central Brain Tumor Registry of the United States (CBTRUS) [2]. In prospective cohorts, 10–50% of patients with cancer have been reported to be diagnosed with BM before their death [3]. Given that, in 2020, 1,806,590 new cases of cancer are projected to occur in the United States alone [1], the annual number of new BM is considerable.

Historically, a BM diagnosis was an indication for palliative care and the prognosis was typically <6 months. The development and iterative refinement of prognostic models such as the original recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) trials [4] and the subsequent Disease-Specific Graded Prognostic Assessment (DS-GPA) [5] led to a paradigm shift in BM management. These tools highlighted the wide range of outcomes observed in BM, such as a median overall survival of 4 years from the diagnosis of BM in ALK-rearranged NSCLC [6], compared to 3 months in SCLC with the lowest DS-GPA score [3]. By allowing reliable outcome prediction before the start of therapy, these tools enabled clinicians to identify patients who might benefit from aggressive treatment despite a diagnosis of BM. In turn, aggressive treatment of BM also led to the realization that, once treated, patients tend to die of their systemic, rather than their neurologic disease [7–9]. As survival improved and active and aggressive treatment of BM became mainstream, recurring BM became an additional challenge in the management of cancer patients.

Recurrent Brain Metastases

Depending on the treatment modality and goal of therapy, recurrence of BM can be assessed as either a global process encompassing all BM of a given patient (i.e., the cerebral disease response) or at a metastasis-specific level (i.e., the local response). Studies of systemic therapies and whole-brain radiation therapy (WBRT) will usually report outcomes in terms of disease response, whereas studies of local therapies such

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Table 26.1 RANO-BM CNS disease response criteria for brain metastases

	Complete response	Partial response	Stable disease	Progressive disease[a]
Target lesions	None	≥30% decrease in the sum of the longest diameters of all target lesions relative to the baseline	Between the partial response and progressive disease criteria	≥20% increase in the sum of the longest diameters of all target lesions relative to the smallest measurement obtained during follow-up after treatment
Nontarget lesions	None	Stable or improved	Stable or improved	Unequivocal progression
New lesion	None	None	None	Present
Corticosteroids	None	Stable or decreased	Stable or decreased	Not applicable
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse

Adapted from Lin et al. [10]

[a]All listed criteria are required for the CNS disease to be considered in complete response, partial response or stable. If any criteria listed under the progressive disease column are met, the CNS disease is considered to be progressing

as surgical resections, stereotactic radiosurgery (SRS), and laser interstitial thermal therapy (LITT) will focus on the local response of the treated lesion. This distinction is important when interpreting the literature on recurrent BM. Furthermore, the definition of response and progression varies considerably across clinical trials, making meta-analyses challenging to produce. The most recent response assessment criteria for BM have been proposed by the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) working group [10] and are presented in Table 26.1. These criteria are built on the older RECIST [11], Macdonald [12] and WHO [13] criteria and define *progressive disease* as any patients in whom target lesions are progressing, nontarget lesions are progressing, new lesions are appearing, or clinical status is worsening. A *progressive lesion* is defined as a ≥20% increase in the longest diameter relative to the smallest measurement obtained during follow-up after treatment [10]. An exception exists for lesions treated by SRS or immunotherapy, because transient increase in lesion size or edema can often be observed in lesions which will eventually respond. These treatment effects should not be mistaken for recurrence [10]. In addition, radiation necrosis can be seen as a complication of SRS-treated lesions and does not constitute recurrence. A presumed diagnosis of radiation necrosis can be supported by advanced imaging modalities such as perfusion MRI, magnetic resonance spectroscopy, or FLT, FET, MET, or FDG-PET [14, 15], although no approach has been proven sufficient to reliably distinguish radiation necrosis from true progression in all patients [10].

In light of these challenges, unless a surgical resection is performed and pathology is available, progressive BMs are usually diagnosed by the clinical judgment of a multidisciplinary team.

Therapeutic Options for Recurrent Brain Metastases

Management of recurrent brain metastases depends on the pattern of recurrence, the previously employed modalities, as well as patient factors, such as his or her functional status, systemic treatment options, and personal preference.

Patient factors are used to estimate the usefulness of pursuing further treatments in the setting of recurrent, incurable disease. For most patients with a poor functional status with recurrent brain disease, palliative care should be considered. When patients have a good functional status, more aggressive BM management can be considered because the short-term impact of treatment on QOL might be outweighed by a better long-term prognosis.

In the National Comprehensive Cancer Network (NCCN) guidelines [16], recurrence is conceptually addressed as either local (i.e., the progression of a previously known and treated lesion) or distant (i.e., the appearance of a new

lesion during follow-up of a patient with other known BM). The CNS disease is further defined as limited, extensive, or leptomeningeal. The threshold between limited and extensive disease is not specified. Philosophically, this stratification is used to distinguish patients in whom SRS would be "equally effective and offers significant cognitive protection compared with WBRT" (limited disease), from those in whom SRS is not thought to be advantageous or feasible (extensive disease) [16]. Randomized controlled trials currently support the advantage of primary SRS in up to four metastases [17–19] although some centers have reported results for many more lesions [8].

For patients with recurrent previously irradiated BM and for whom active treatment is pursued, therapeutic options include surgical resection, laser interstitial thermal therapy (LITT), systemic chemotherapy, and repeat irradiation with either SRS or WBRT. We will now discuss the various combinations of repeat irradiation in the setting of recurrent BM.

Rationale for Repeat Irradiation

The majority of patients with recurrent BM will have undergone previous SRS or WBRT, as sole primary treatment modality or as adjuvant therapy following surgical resection. Distant recurrences are new lesions that have not previously been exposed to radiation, although the surrounding brain parenchyma might have been. Salvage irradiation in this setting is therefore thought to have the same efficacy on each individual lesion as if it was a primary treatment, albeit with an increased risk of adverse radiation effects on the surrounding tissue. For locally recurrent lesions, however, the rationale for repeat irradiation is different. The mechanism of action of SRS is not completely understood and lesion response is different than that seen after WBRT. Inherently radioresistant histologies, such as melanoma, renal cell carcinoma, and sarcoma BM, which have a significantly higher recurrence rate following WBRT have been shown to respond to SRS. Moreover, for vestibular schwannomas, the response after a second SRS has been shown to be as good as the response after a first SRS [20], suggesting that failure might be a random event not necessarily related to intrinsic tumor characteristics. This peculiarity is relevant to the management of BM, because a previous failure might not be predictive of a future failure. For BM patients where the maintenance of short-term quality of life is critical, the option of repeating SRS and sparing the patient a surgery is appealing.

We will now discuss various re-irradiation paradigms with a special focus on their impact on survival and functional outcomes.

SRS After SRS

Eight series have reported the use of repeat SRS on the same lesion (Table 26.2). Because of the retrospective nature of these series, heterogeneous inclusion criteria and the lack of standardized definition of radiation necrosis and tumor control, aggregation of data, and meta-analysis are not feasible. Reported 1-year local control ranged from 61% to 83% and median survival after the second SRS ranged from 8 months to more than 2 years. Some series were heavily biased toward melanoma [28] or SCLC [24], while others were more representative of standard BM histologies [22]. We recently analyzed our personal series, which consisted of 75 recurrent lesions in 56 patients. We used the standardized RANO criteria to define outcome. Patients were treated using a median dose of 20 Gy (range 14–24) for the first SRS and 18 Gy (range 12–20) for the second. Actuarial local control at 1, 2, and 5 years was 68%, 54%, and 54%, respectively, and median survival was 14 months (Journal of Neuro-Oncology, https://doi.org/10.1007/s11060-019-03323-8). Factors associated with failure of the repeat SRS were an absence of initial response observed after the first SRS, a lower KPS, a lower maximal dose, and having an uncontrolled primary cancer at the time of the second SRS. Other authors associated a volume >4 cc with poor local control [24]. Radiation necrosis occurred in 5–30% of patients across all series. Risk factors identified for radiation necrosis included a treatment volume >7 cc [22] and the volume of lesion

Table 26.2 Series reporting SRS after SRS

References	*n*	Median first SRS dose (Gy)	Median second SRS dose (Gy)	One-year local control	Median survival from last radiation treatment (months)	% of patients with symptom improvement	% of radiation induced effects
Iorio-Morin et al. [21]	56	20 (14–24)	18 (12–20)	68%	14	18%	5% RN
Moreau et al. [22]	30	18 (12–20)	18 (12–20)	68%	14.2	NR	10%
McKay et al. [23]	32	20 (12–24)	20 (14–22)	79%	>24	NR	30%
Koffer et al. [24]	22	18 (17–20)	15.5 (10–20)	61%	8.7	NR	16.7%
Minniti et al. [25]	43	NR	3 × 7–8	38–78%	10	NR	19%
Trifiletti et al. [26]	24	20	18	NR	12.2	NR	9%
Jayachandran et al. [27]	19	22 (16–24)	17.3 (14.5–24)	83%	26	NR	21%
Terakedis et al. [28]	37	20 (15–24)	20 (14–24)	81%	8.3	NR	16%

receiving 40 Gy [23]. Previous WBRT was associated with an increased risk of radiation necrosis in one series [22] while two others did not show a significant correlation [24].

Together, these studies demonstrate the feasibility and safety of a repeat course of SRS for locally recurrent BM. Given the lack of standardized response assessment and the concurrent administration of other treatments in most series (including subsequent WBRT and systemic chemotherapy), the level of efficacy of the second SRS alone remains to be determined. However, in properly selected patients, repeat SRS can be used to control locally recurrent BM and postpone WBRT or surgery.

SRS After WBRT

For historical reasons, the combination of SRS and WBRT is the most studied double BM irradiation paradigm. In the 1990s, multiple randomized controlled trials demonstrated the benefit of BM surgical resection on survival [29, 30] as well as the role of WBRT to reduce recurrence [31], establishing resection followed by adjuvant WBRT as the standard of care of the time. When SRS for BM was introduced, it was proposed as an alternative to surgical resection [32]. Patients with 1–3 BM in the landmark RTOG 9508 trial were treated with WBRT (37.5 Gy in 15 fractions) with or without SRS (15–24 Gy at the margin). This trial showed improved KPS at 6 months and improved survival in RPA class 1 patients with the combination therapy. Importantly it also demonstrated that toxicity did not differ between both groups [32]. This led to a subsequent study of SRS with or without WBRT which further supported the safety of combined irradiation [33]. Multiple series have since been published assessing SRS as a salvage treatment (i.e., not as a boost) for patients who previously underwent WBRT (Table 26.3).

Survival in this setting ranged between 4 and 11.7 months from the SRS. As discussed, survival can be biased by heterogeneous inclusion criteria and practice across studies. The largest study included 310 patients [37]. The median survival in this series was 8.4 months overall, and 12.0 versus 7.9 months in patients with a single or multiple retreated BM. Favorable prognostic factors depended on the primary cancer histology. For breast cancer, factors identified were an age <50, a smaller total target volume, and a longer interval between WBRT and SRS. For NSCLC, factors were a smaller number of BM, a KPS >60, and a controlled primary. In melanoma, the only favorable prognostic factor was having a smaller total target volume [37].

Table 26.3 Series of salvage SRS after WBRT since 2000

References	*n*	Median WBRT dose (Gy)	Median SRS dose (Gy)	Median time to local failure (months)	Median survival from last radiation treatment (months)	% of patients with symptom improvement	% of radiation induced effects
Huang et al. [34]	39	40 (30–50)	17 (12–25)	6.5	11.4	43%	NR
Lucas et al. [9]	293	NR	NR	14.8	4	NR	NR
Kurtz et al. [35]	106	NR	21 (12–24)	6.2	11.7	NR	NR
Hsu et al. [36]	78	30 (20–30)	24 (12–24)	NR	11.2	NR	NR
Caballero et al. [37]	310	30 (19.8–60)	18 (7.5–22)	NR	8.4	NR	NR
Kelly et al. [38]	76	NR	18 (16–20)	5.7	9.8	NR	NR
Gwak et al. [39]	46	32.7 (18–54.9)	23 (10–36)	21	10	NR	4% of RN
Chao et al. [40]	111	37.5 (30–50)	23.6 (9.6–25.4)	8.4–15.3	9.9	NR	2%
Noël et al. [41]	54	NR	17.2 (11–22.9)	>24	7.8	NR	0% RN

Local control was heterogeneously reported across studies. Median time to local failure ranged from 5.7 months to more than 2 years, and control was shown to be improved in patients with a favorable histology (NSCLC) [40], an interval between WBRT and SRS >14 months [41] and a SRS dose >22 Gy [40]. In breast cancer, overall cerebral disease control was affected by HER2 status [38] and the systemic disease status [38].

As discussed, the safety of the combined irradiation was prospectively demonstrated in multiple randomized controlled trials of the SRS boost paradigm [32, 33]. WBRT has recently fallen out of favor for most BM patients with limited brain disease. However, it is still commonly used for patients with disseminated BM, so the ability to salvage new lesions arising after the end of WBRT remains relevant as systemic treatments and overall survival improve. The studies in Table 26.3 confirm the relevance of this approach.

WBRT After WBRT

Fourteen studies have described repeat WBRT after WBRT (Table 26.4). Reported median survival ranged from 2 to 6.9 months. The largest study included 205 patients from nine Canadian centers [42]. The median treatment dose was 20 Gy (range 12–48 Gy) for the first course and 20 Gy (range 4–30.6 Gy) for the second. Median survival in this series was 3.6 months (range 0.2–45) from the second treatment with 14% surviving less than a month after the second WBRT. Prognostic factors associated with poor survival at the time of the second WBRT were an SCLC histology, the presence of extracranial metastases, a KPS <80, an interval between both WBRT courses <9 months and an uncontrolled primary. These five factors were combined to create a reirradiation score in which each factor is worth 1 point, and in this series, patients with 4–5 points had a median survival of 2.2 months compared to 3 months for patients with 3 points, and 7.2 months for patients with 1–2 points [42]. This system allowed better prognostication than histology or RPA class alone, although it still requires external validation.

The relevance of WBRT after WBRT is challenged by the lack of studies reporting patient-centered outcomes. With a significant neurocognitive decline observed as soon as 3 months after the first course of WBRT [17], there is concern that any gain in terms of BM control or survival provided by a second course of WBRT could be offset by a worsened quality of life resulting from poor cognitive function. Improvement in symptoms after repeat WBRT has been reported in 14% [48] to 80% [47], highlighting inconsistent definitions, reporting standards, and follow-ups of these

Table 26.4 Series of WBRT after WBRT

References	*n*	Median dose at first WBRT (Gy)	Median dose at second WBRT (Gy)	Median survival from second WBRT (months)	% of patients with symptom improvement
Logie et al. [42]	205	20 (12–48)	20 (4–30.6)	2.2–7.2	NR
Aktan et al. [43]	34	30 (25–30)	25 (20–30)	5.3	24%
Scharp et al. [44]	134	30 (30–40)	20 (20–30)	2.8	39%
Ozgen et al. [45]	28	30 (20–30)	25 (20–30)	3	39%
Akiba et al. [46]	31	30 (26–42)	30(30–40)	4	68%
Son et al. [47]	17	35 (28–40)	21.6 (14–30)	5.2	80%
Karam et al. [48]	37	NR	NR	6.9	14%
Sadikov et al. [49]	72	30 (20–30)	NR	4.1	31%
Abdel et al. [50]	15	30 (30–55)	30 (30–35)	NR	60%
Wong et al. [51]	86	30 (1.5–50.6)	20 (8–30.6)	4	NR
Cooper et al. [52]	52	NR	NR	5	42%
Hazuka et al. [53]	44	30 (30–36)	25 (6–36)	2	27%
Kurup et al. [54]	56	NR (18–30)	20	3.5	NR
Shehata et al. [55]	35	NR	NR	NR	NR

terminally ill patients. In addition, the assessment of adverse radiation effects is unreliable because most patients in these studies did not undergo follow-up imaging. Given the safety and probable efficacy of the other previously discussed paradigms, WBRT after WBRT should be reserved for symptom relief in patients with a very short expected survival not otherwise eligible for SRS, and in whom this approach is believed, based on individual clinical judgment, to be superior to best supportive care alone with steroids.

Conclusion

As systemic therapies for cancer are improving, keeping cerebral metastatic disease under control will become increasingly important. Salvage irradiation of previously irradiated tumors is a useful strategy to achieve this goal. Multiple paradigms have been studied, including SRS after SRS, SRS after WBRT, WBRT after SRS, and WBRT after WBRT. All have been shown to be feasible and safe in properly selected patients. The choice of salvage strategy depends on the initially chosen management modalities. For patients with a good functional status and a limited intracranial disease, multiple courses of SRS, irrespective of a previous WBRT, are likely to provide the best results, sparing cognitive functions, and maximizing local control. WBRT remains an option for patients with disseminated intracranial disease unresponsive to systemic therapies, or with poor performance status who require palliative symptom control not achievable by best supportive care alone with steroids. In the end, patient survival still mostly depends on the control of primary cancer. As such, when selecting the best management plan for BM, clinicians should consider not only optimal local control but also target the quality of life and symptoms control—issues poorly assessed in current studies.

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Applications of Stereotactic Radiosurgery for Brain Metastases

27

Akshay V. Save, Dominique M. O. Higgins, Mark D. Mayeda, and Tony J. C. Wang

Introduction

Radiation therapy has been a mainstay of managing brain metastases for decades. In the past, clinicians have relied on whole brain radiotherapy (WBRT) and in some instances partial brain radiation therapy to deliver conformal radiation dose distributions using MRI and CT-guidance to plan treatment. The dose limitations of various critical structures of the brain and treatment-induced neurocognitive side effects made intracranial treatment challenging. However, the development and popularization of stereotactic radiosurgery (SRS), including Gamma Knife stereotactic radiosurgery (GKRS) and linear accelerator (LINAC)-based SRS, has had a profound impact on the field of neuro-oncology. As the name suggests, SRS typically uses a method of immobilization to maintain a particular patient position for the duration of treatment. While this method of immobilization has traditionally been an invasive, rigid frame placed onto a patient's head, with newer technical advances, frameless treatments with masks have become feasible without sacrificing accuracy. In this chapter, we outline seven particularly interesting applications in which SRS was used to increase the likelihood of achieving local control in patients with a variety of brain metastatic lesions.

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Case 1: Skull-Base Metastasis

History

This is a 43-year-old woman with history of stage IIIA cT3N2M0 right-sided invasive ductal breast carcinoma with ER+/PR+/HER2+ status who underwent neoadjuvant chemotherapy, mastectomy, adjuvant irradiation of the right chest wall and internal mammary lymph nodes, and adjuvant herceptin and anastrazole. Over a year after this initial treatment, she developed multiple brain metastases, for which she received memantine and hippocampal-sparing WBRT. Several months later, she represented with new metastatic brain lesions which were treated with GKRS. Four months after completing her treatment, she was found to have interval enlargement of a right cerebellar lesion in the posterior fossa adjacent to the skull base. Her case was discussed at a multidisciplinary conference and the consensus was that she should receive repeat GKRS (Fig. 27.1).

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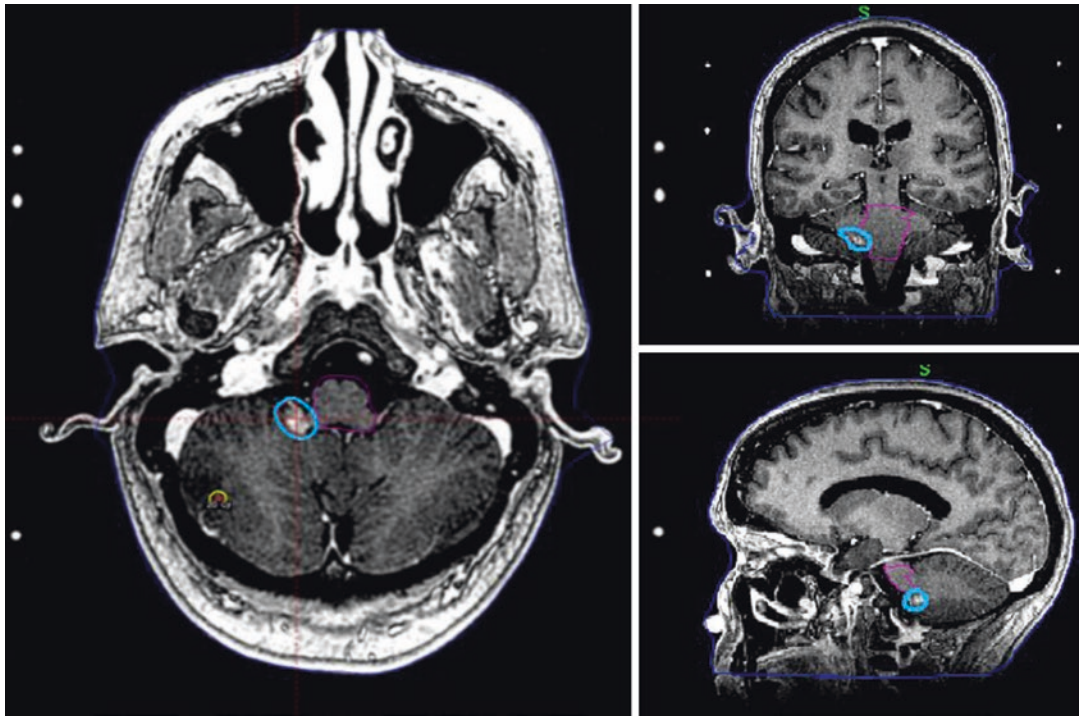

Fig. 27.1 Gamma Knife stereotactic radiosurgery treatment plan for breast cancer metastatic to the skull base of the posterior fossa

Radiosurgery for Skull Base Tumors

While metastases to the skull base are less common than metastases to the cerebral hemispheres, they present a unique challenge for management. Retrospective case series have found that lung, breast, and prostate cancers have the highest incidence of skull base metastasis [1, 2]. Though prostate cancers rarely metastasize to the brain, a large review of the French and English case literature found that 38% of reported skull base metastases were from primary prostate cancers and 20% were from primary breast cancers [1].

In general, skull base tumors are challenging to treat due to their proximity to critical neural structures. Surgical resection can be limited or even impossible due to the risk of damage to the brainstem or cranial nerves [3]. This is further complicated in the case of metastasis due to the frequency of multifocal disease. SRS provides the ability to selectively deliver high doses of radiation to tumor regions, with sharp dropoffs in dosage that minimizes the toxicity to surrounding tissue [3]. GKRS has been shown to have an excellent 1-year local control rate of 89% in a series of calvarial and skull base lesions [4]. Further, GKRS can be repeated with minimal consequences in the case of disease progression. Overall, SRS has become an attractive option for patients with inoperable skull base tumors or an overwhelming burden of disease.

Dosage and Treatment Considerations

This patient received single-fraction GKRS of 20 Gy to the lesion, which, although it is not physically within the clivus or petrous bone, shares with tumors in those sites the issues of relative surgical inaccessibility and concerns about tolerance of cranial nerves emerging from the brainstem. Approximately 2 weeks after treatment, she developed nausea and vomiting, which resolved after treatment with dexamethasone. Repeat imaging 2 months after treatment showed resolution of the treated lesion.

Case 2: Re-irradiation GKRS After WBRT

History

This is a 34-year-old woman who presented postpartum with fevers, persistent abdominal and pelvic pain, abdominal distension, and dark urine. Abdominal imaging revealed multiple hypodense lesions in the liver with biopsy revealing poorly differentiated carcinoma consistent with a primary ER-/PR 10%+/HER2+ breast cancer. She began treatment with paclitaxel, trastuzumab, and pertuzumab, but began experiencing visual field deficits. MRI at the time revealed numerous lesions diffusely distributed throughout the brain. Given the overwhelming burden of disease, she was treated with WBRT, 3750 cGy in 15 fractions, instead of SRS. Over time, she developed new metastatic lesions and was referred for GKRS to prevent progression of disease (Fig. 27.2).

Re-irradiation After Whole Brain Radiotherapy

In the setting of diffusely distributed metastatic disease to the brain, WBRT remains the mainstay of treatment. One of the advantages of WBRT is the ability to preemptively treat microscopic preclinical lesions before they become symptomatic or even radiographically evident. However, despite this, many patients progress and develop new lesions. In that setting, salvage therapy options include SRS or repeat WBRT. In general, clinicians have avoided repeat WBRT because of the concerns for violating normal brain organ constraints and also the increased risk of neurocognitive deterioration. In this setting, SRS has had promising results in several trials.

The RTOG trial 90-05 set out to determine the maximum dose of focal radiation that could be delivered without causing significant CNS toxicity in a large cohort of recurrent high-grade

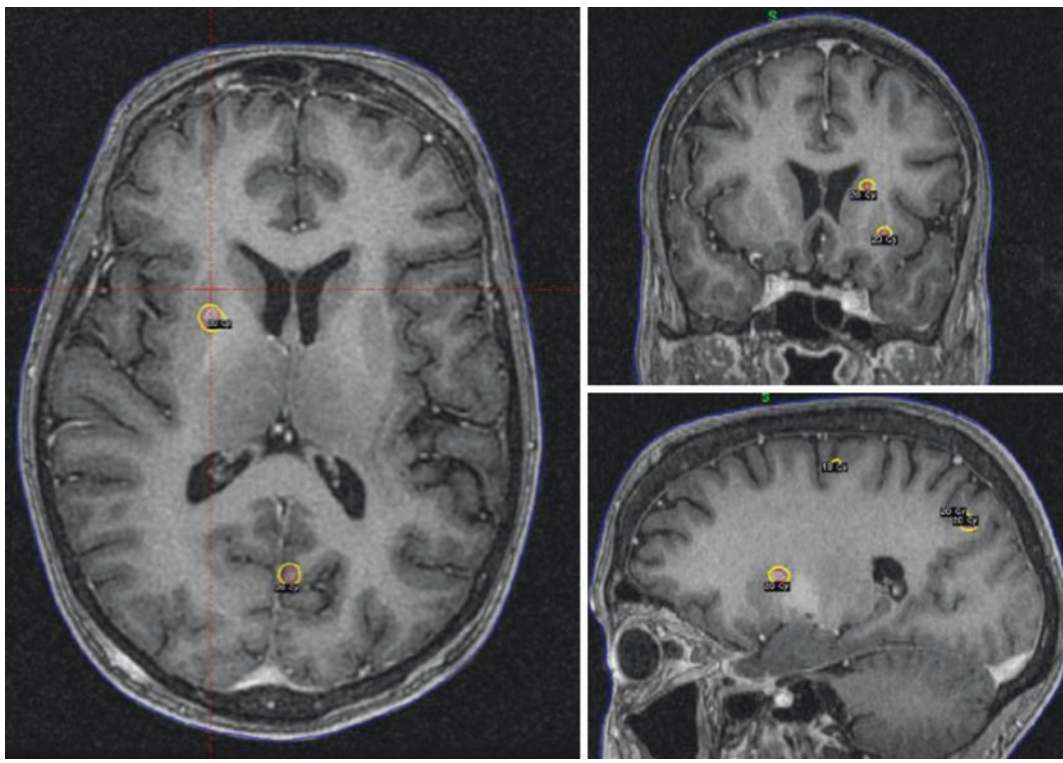

Fig. 27.2 Gamma Knife stereotactic radiosurgery after prior WBRT for patient with multifocal metastases. All lesions were treated to between 18 and 20 Gy in one fraction

gliomas and brain metastases. For tumors ≤20 mm, 21–30 mm, and 31–40 mm in maximum diameter, the highest safe dose for previously irradiated brains were 24 Gy, 18 Gy, and 15 Gy, respectively [5]. The most common severe CNS toxicities were irreversible cerebral edema requiring steroids and radiation necrosis requiring craniotomy. Increased tumor volume was associated with increased CNS toxicity.

In a dedicated series for SRS to patients with brain metastases that had failed WBRT, response rates were 91%, with a 1-year local control rate of 74%. Re-irradiation was found to be safe and effective with low rates of radiation necrosis (6%). Chao et al. found that patients who had sustained responses to initial WBRT tended to have longer survival after SRS treatment [6]. Based on these results, SRS after WBRT has been shown to provide high rates of local control without significant side effects [5–8].

Case 3: Whole Brain Versus Stereotactic Radiotherapy for Multiple Metastases

History

This is a 44-year-old woman with history of left-sided poorly differentiated invasive ductal breast carcinoma with ER+/PR+/HER2- disease, initial stage unknown. She underwent bilateral mastectomies with chemotherapy and unilateral radiation to the left chest wall. Several years after treatment, she presented with persistent cough and chest pain. Comprehensive imaging studies at the time revealed pleural nodules and several areas of dural enhancement. Shortly after, she had an episode of right scalp, face, and arm numbness followed by loss of consciousness. Imaging revealed multifocal metastases in the frontal lobes, right parietal lobe, right cerebellar hemisphere, left corona radiata, and right temporal lobe. Her case was discussed at multidisciplinary conference, and given her young age and good performance status, the consensus from the panel was to recommend GKRS without WBRT with close interval follow-up (Fig. 27.3).

Treatment Considerations for Multifocal Metastases

The development of SRS has made a considerable impact on the management of patients with multiple brain metastases. Standard treatment for multiple metastases had traditionally been WBRT. However, high rates of neurocognitive deterioration and memory deficits have made WBRT a less attractive option, especially considering the accuracy and local control rates achievable with modern SRS.

In 2014, a large prospective observational study compared the overall survival of patients receiving SRS, stratified by the number of metastases. This multi-institutional study enrolled 1194 patients over a 3-year period and provided a median follow-up of 20.9 months. Fairly high-functioning patients, with a KPS >70, with evidence of newly diagnosed metastatic lesions and a cumulative tumor volume less than 15 mL, who were treated with SRS without WBRT, were included in the study. Patients who had one metastatic lesion were found to have better overall survival (13.9 months) compared to patients with more than one metastasis (10.8 months). However, importantly, the authors found no difference in survival between patients that had five to ten metastatic brain lesions compared to those with two to four, with both groups having a median survival of 10.8 months [9]. Furthermore, univariate analysis of volumetric data found that dimension-related factors such as a maximum diameter of the largest lesion greater than 1.6 cm and a cumulative tumor volume greater than 1.9 mL were associated with worse overall survival. Though these factors were not statistically significant predictors in the multivariate analysis, these findings together suggest that volumetric factors may be more important than the absolute number of metastases in clinical decision-making for patients with multiple metastases [10, 11].

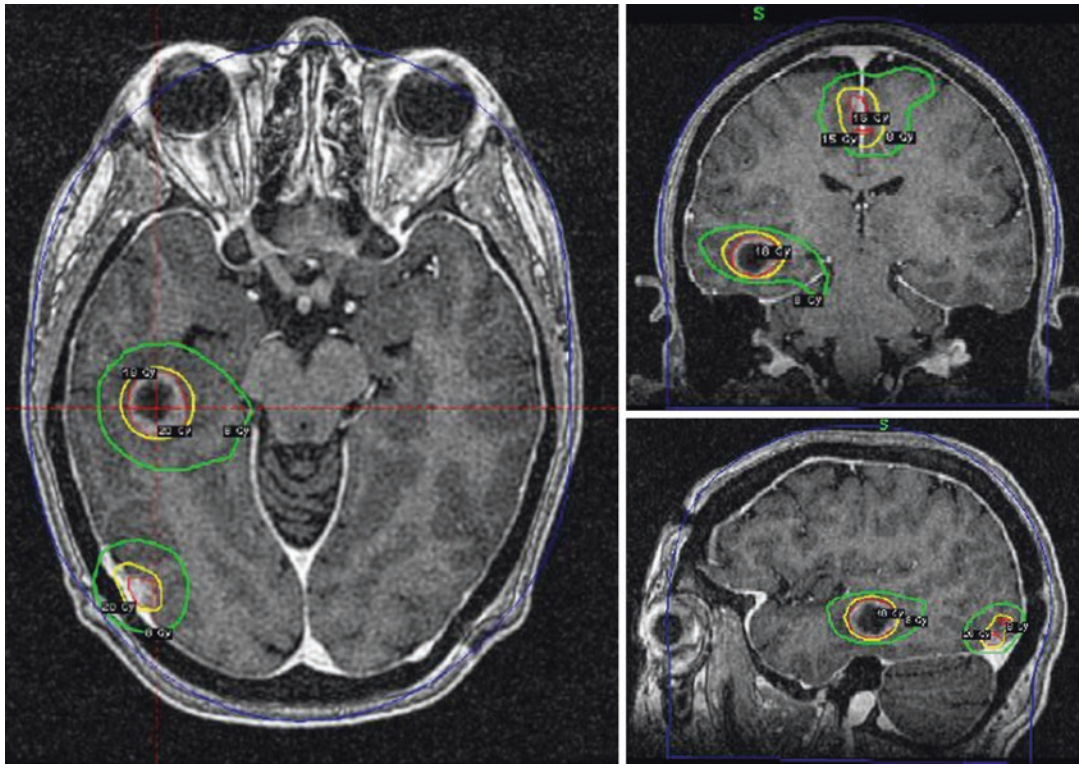

Fig. 27.3 Gamma Knife stereotactic radiosurgery treatment plan for a patient with multifocal metastatic breast cancer. All lesions were treated between 18 and 20 Gy each

Case 4: SRS for Neurocognitive-Sparing Treatment of Multifocal Disease

History

This is the case of a 43-year-old woman with a history of ER-/PR+/HER2-invasive ductal carcinoma complicated by multifocal, multisite metastases for which she has undergone several radiotherapy regimens. She presented to her oncologist with worsening headaches, fatigue, and confusion, with neuroimaging showing six brain lesions distributed throughout the temporal lobe, occipital lobe, and cerebellum with compression of the fourth ventricle. She was initially treated with GKRS, but over time she developed additional metastases. At the time, she wished to avoid WBRT. Given her young age, good performance status, and effective response to prior SRS, she was considered to be a good candidate for continued SRS. Several months after her second course of GKRS, she progressed and developed widely disseminated lesions with significant changes to her baseline, including visual field deficits, headaches, nausea, vomiting, and debilitating lethargy leaving her wheel chair bound. At this point she decided to pursue WBRT and was considered for enrollment in an ongoing clinical trial for hippocampal-sparing WBRT with memantine (Fig. 27.4).

Treatment Considerations for Neurocognitive Sparing Radiotherapy in Patients with Good Performance Status

Though recent evidence suggests that SRS may provide similar rates of local control for up to ten

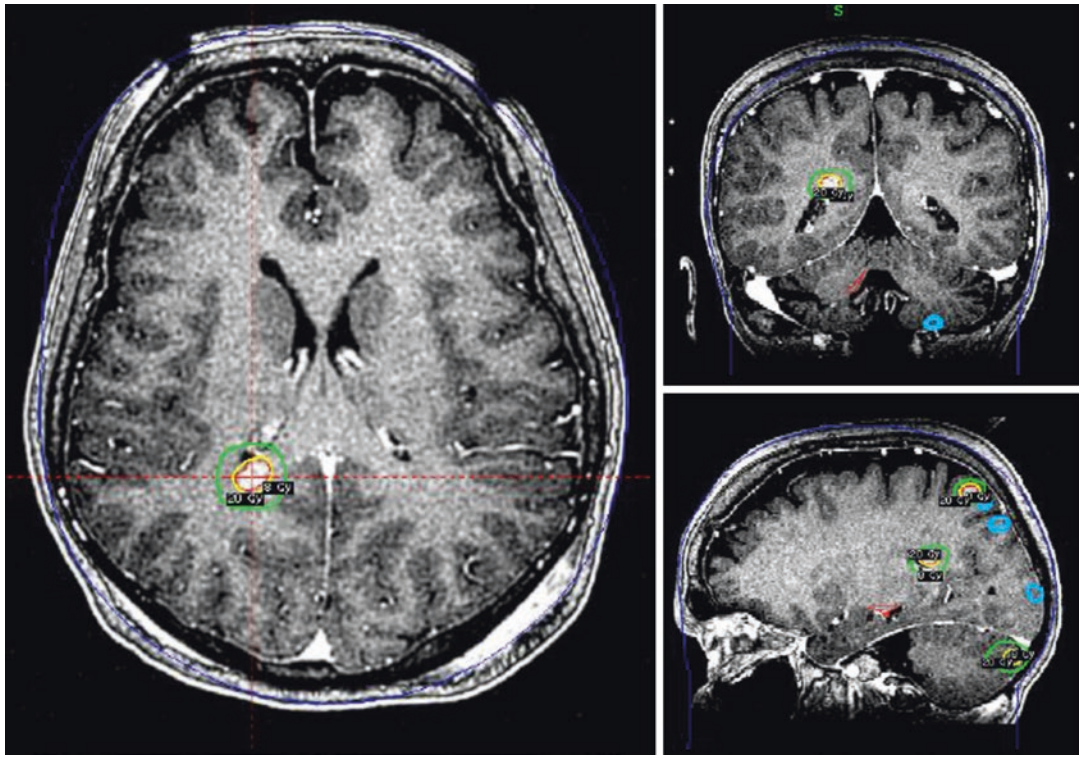

Fig. 27.4 Gamma Knife stereotactic radiosurgery plan for multifocal metastatic disease rather than WBRT for neurocognitive protection. All four lesions were treated to 20 Gy

brain metastases, whole brain radiotherapy (WBRT) remains the mainstay treatment for widely disseminated metastatic disease. The rationale for WBRT is to minimize symptom burden from the current lesions and also to preemptively treat distant sites of subclinical disease. Conventional fractionation schedules for WBRT involve 20 Gy in 5 fractions, 30 Gy in 10 fractions, and 37.5 Gy in 15 fractions, which have similar overall survival and preservation of neurological function probabilities [12]. While two studies looked at accelerated schedules of 40 Gy in 20 twice-daily fractions and found better rates of local control with slower time to progression, they were unable to find any benefit in terms of overall survival [12–14].

WBRT is effective in treating multifocal brain metastatic disease; however, it has been associated with long-term neurocognitive and memory deficits in a large percentage of patients. To minimize these toxicities, neurocognitive agents such as donepezil and memantine have been studied. Donepezil has been shown to prevent decline in memory and motor dexterity, though it did not change the overall neurocognitive testing score [15]. Memantine slowed the cognitive decline in patients undergoing WBRT for metastatic disease, though the study failed to meet statistical significance ($p = 0.059$) likely due to a relatively low rate of patient follow-up [16]. Additionally, a phase II multi-institutional trial studied the effects of hippocampal-sparing WBRT and found significant preservation of memory and quality of life compared to previous studies [17]. Preliminary results from an ongoing phase III trial suggest that hippocampal avoidance provides a cognitive benefit that is noticeable as early as 3 months into treatment, most notably in executive function and total recall and recognition. However, there have been no statistically significant differences in terms of intracranial progression or overall survival. Despite the evolving role of SRS, whole brain radiotherapy remains an important treatment option in the management of multifocal brain metastases.

Case 5: Frameless SRS to Post-resection Cavities

History

This is a 64-year-old woman with stage IIIA cT1aN2M0 lung adenocarcinoma with mutated KRAS treated with three cycles of carboplatin/pemetrexed, left upper lobectomy with complete thoracic lymph node dissection, and post-operative radiation therapy to the chest. Almost 3 years later, she began experiencing daily severe holocephalic headaches that would wake her up from sleep in the morning. She underwent neuroimaging, which revealed a large 3.9 × 2.7 × 3.8 cm peripherally enhancing, centrally necrotic mass in the right parietal lobe with substantial vasogenic edema causing 6 mm midline shift. This mass was resected with pathology consistent with a poorly differentiated metastatic carcinoma. Her postoperative brain MRI showed minimal surrounding enhancement that could not be distinguished between scarring or residual neoplasm. Given the large size of her brain metastasis, she was referred for post-operative SRS of the resection cavity for treatment of suspected residual disease (Fig. 27.5).

Stereotactic Radiosurgery for Post-resection Cavities

Two landmark trials in the 1990s showed that WBRT after surgical resection of a single brain metastasis offers better progression-free survival than either WBRT or surgical resection alone [18, 19]. As such, radiation to the post-operative resection cavities has been a mainstay in the treatment of large single metastases that are amenable to surgery. However, as previously described, WBRT carries a higher risk of neurocognitive decline, which has prompted increased research in the role of SRS for treatment. SRS to the resection cavity in fewer than four metastases

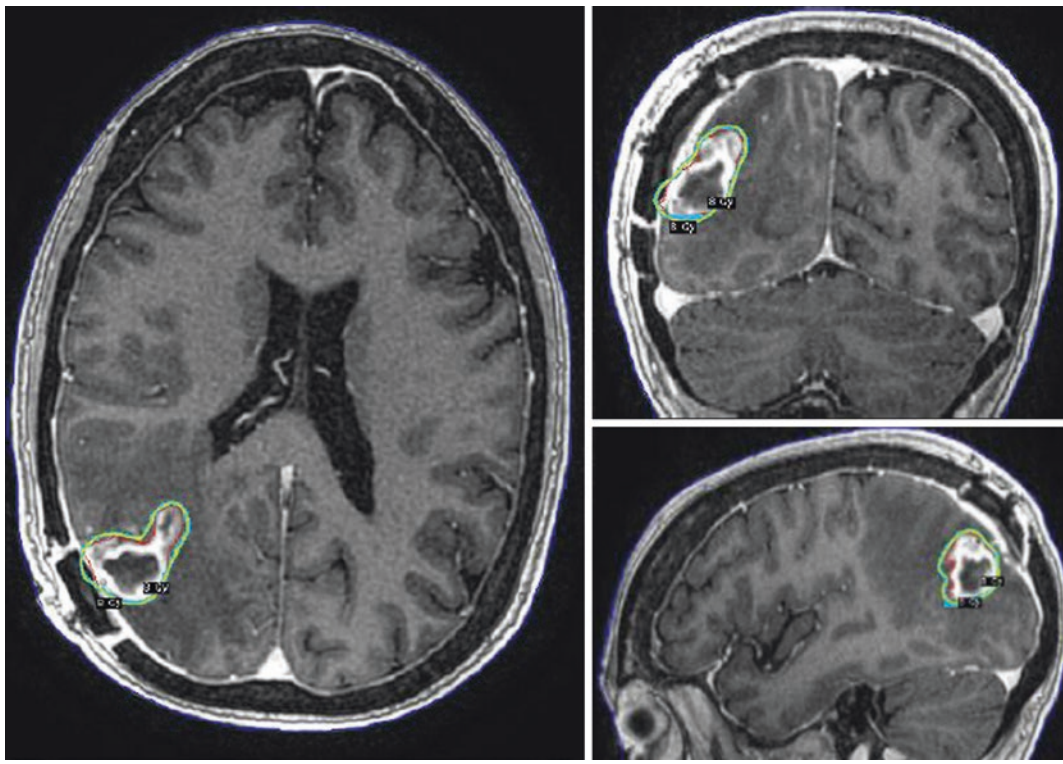

Fig. 27.5 Gamma Knife radiosurgery plan for the post-operative resection cavity

results in longer time to progression compared to observation alone [20]. Additionally, a phase III study compared SRS and WBRT in patients after resection of metastatic disease [21]. Though patients in the SRS cohort had worse local and distant control compared to patients with WBRT, there were no differences in overall survival between the treatment groups. Further, patients treated with SRS had less frequent decline in cognition and a better quality of life compared to patients who received WBRT. A systematic review and meta-analysis of the literature found that SRS may be associated with a higher rate of leptomeningeal disease compared to WBRT; however, both treatment options provide similar survival and disease control rates [22].

The largest clinical concern for using SRS over WBRT is the risk of recurrent disease at distant sites. Factors associated with distant brain failure are uncontrolled systemic disease, melanoma lesions, and higher numbers of brain metastases [23]. Interestingly, size of the pre-operative metastatic lesion or post-operative resection cavity is not associated with a differential response to SRS versus WBRT. A comparison of patients with large tumors (>4 cm) compared to smaller tumors (≤4 cm) found no statistically significant difference between 1-year rates of local control, radiation necrosis, or overall survival [24]. Thus, post-operative SRS to the resection cavity should be considered as a main treatment option for patients with single metastases.

Frameless GKRS for Fractionated Treatment

The advent of frameless GKRS has made treatment with GKRS more acceptable to patients because it obviates the need to place an invasive stereotactic Leksell G Frame. Placement of stereotactic frames can be uncomfortable and can rarely result in infections or persistent pain at the insertion sites. Our institution published a case series on the first 100 consecutive patients that were treated with frameless GKRS on the Gamma Knife Icon [25]. In our experience, using the frameless mask for treatment resulted in improvements in our workflow and an increase in the number of patients eligible for treatment with GKRS. The ability to fractionate treatment provides a radiobiological advantage to local tumor control by exploiting the relative dysfunction of DNA-repair pathways in tumor cells compared to healthy cells. Additionally, the ability to better manage constraints to critical organs such as the brainstem, optic pathways, and cochlea through fractionation minimizes toxicity. While the concern of frameless treatment is a decrease in treatment accuracy compared to treatment with a stereotactic frame, we found that the use of real-time monitoring with an infrared camera was able to successfully ensure that the patients remained in the stereotactic space. Whenever rare deviations are greater than a pre-set threshold, a new cone-beam CT is required prior to re-starting treatment. LINAC mask-based radiosurgical systems employing image guidance in the treatment room provide the same ability to fractionate treatments and may have some advantages in terms of rapidity of treatment delivery to larger target volumes and target volumes that are spatially separated from each other.

Dosage and Treatment Considerations

This patient was treated with 24 Gy in three fractions of frameless GKRS. She experienced some fatigue in the weeks after treatment, but tolerated the procedure without significant issues.

Case 6: Management of Brainstem Lesions

History

This is a 49-year-old woman with a past smoking history who presented to an outside hospital with complaints of worsening abdominal pain, decreased appetite, bloating, dyspnea, and nonproductive cough. She was found to have multiple nodules in her lung fields, lesions in the liver, moderate ascites in the abdomen and pelvis, and bone lesions, findings consistent with diffusely metastatic disease. Bronchoscopy and biopsy revealed lung adenocarcinoma. Comprehensive imaging revealed an 8 mm

lesion in the midbrain in the left cerebral peduncle, and three other lesions between 5 and 7 mm in both frontal lobes, and she was referred for consideration of SRS.

Use of SRS for Management of Brainstem Metastases

SRS plays an important role in treating lesions in eloquent brain regions. Although the recommended maximal dose tolerance for the brainstem is 12–12.5 Gy in a single fraction and radiation dose to the margins of radiosurgically treated tumors routinely can exceed that amount. Despite this concern, the sharp drop-off in radiation with SRS at a sub-millimeter level still makes it an attractive option for brainstem metastases. Though some studies have been insufficient powered to determine a statistically significant relationship between tumor margin dosage and local control rates, Trifiletti et al. showed that higher radiation doses at the tumor margin provided superior local control in their cohort [26]. Based on a large multi-institutional series, estimated rates of severe toxicity after brainstem SRS are 7.4%, with the most common reported adverse effects being radiation necrosis, intra-tumoral hemorrhage, and symptomatic peri-tumoral edema [27]. Prior whole-brain irradiation has been shown to increase the risk of severe toxicity in patients undergoing SRS for brainstem metastases [27]. Tumor location further sub-localized within the brainstem has not been definitively shown to predict for toxicity [28]. Overall, SRS for brainstem lesions has been shown to be a safe and effective treatment with high rates of local control and low toxicity [26–31].

Dosage and Treatment Considerations

This brainstem lesion was treated to 15 Gy in 1 fraction (Fig. 27.6). The mean dose to the brainstem was 1.9 ± 2.2 Gy. About 1% of the

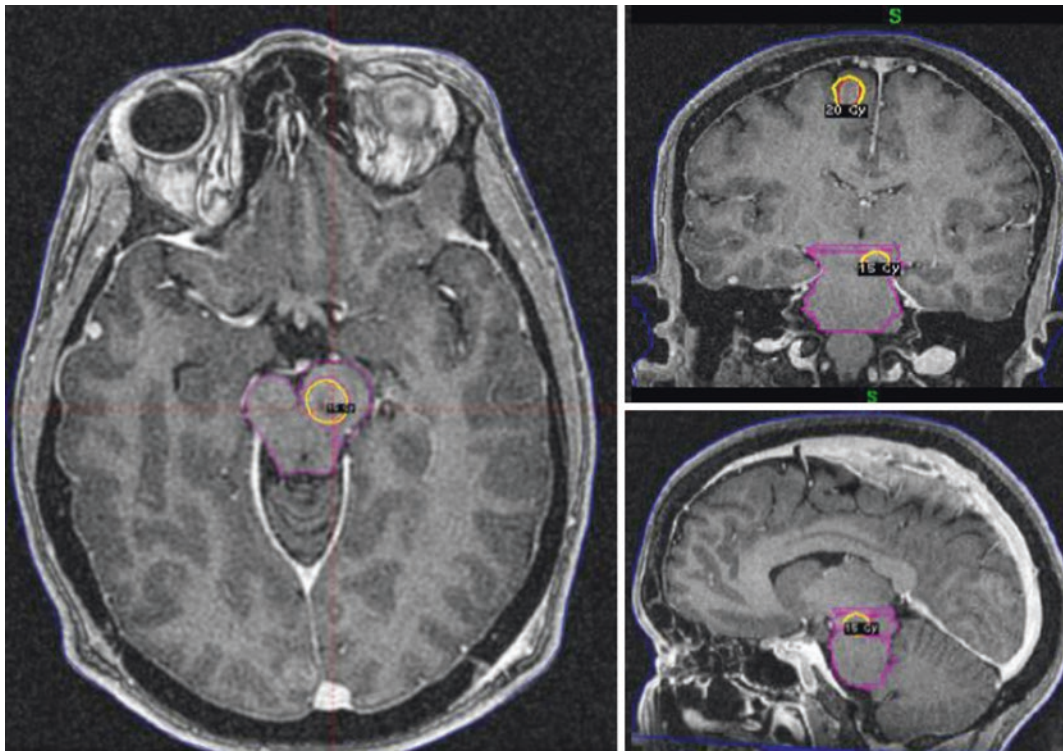

Fig. 27.6 Gamma Knife stereotactic radiosurgery plan for brainstem metastatic lesion

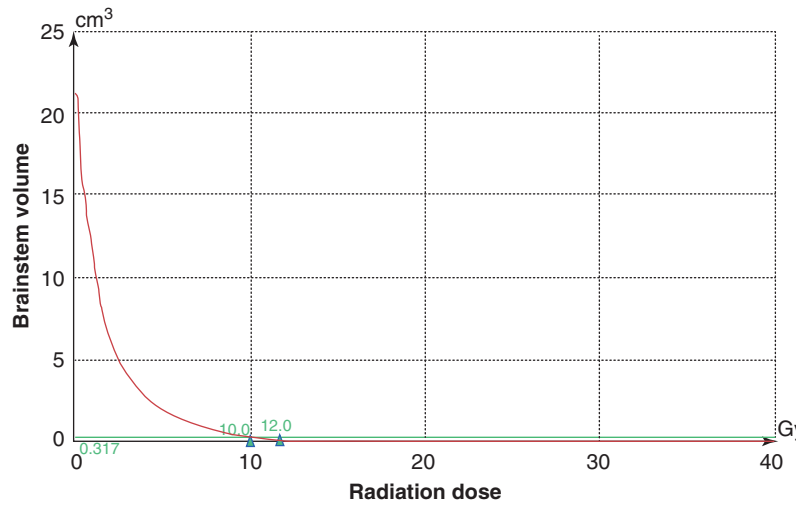

Fig. 27.7 Dose-volume histogram for the brainstem, outlined in pink on MRI

brainstem volume received a dose ≥10 Gy and less than 0.5% received more than 12 Gy (Fig. 27.7).

Case 7: Multiple Melanoma Metastases in Elderly Patient with Comorbidities

History

This is an 88-year-old man with a past medical history of diabetes mellitus, hypertension, and hyperlipidemia who presented to an outside hospital with several months of worsening imbalance on his left side resulting in several bicycle accidents. Initial imaging studies revealed a lung mass and several brain lesions. Bronchoscopy with biopsy of the lung lesion revealed pathology consistent with melanoma. He also underwent biopsy and resection of the main brain lesion. Subsequently, he developed additional lesions, which were treated with GKRS. He progressed both intra-cranially and systemically despite treatment with pembrolizumab and was started on ipilimumab and nivolumab. Despite treatment, he developed worsening disease causing loss of mental acuity, confusion, as well as worsening imbalance. On latest imaging, he was found to have five new brain metastases lesions for which he was referred for SRS (Fig. 27.8).

SRS for Multifocal Radio-Resistant Disease

Different tumor histologies often have varying expected responses to radiation therapy. Radiosensitive tumors include breast, prostate, ovarian, and neuroendocrine carcinomas, whereas traditionally radio-resistant tumors include renal cell carcinoma, sarcoma, and melanoma [32, 33]. Of these radio-resistant tumor histologies, melanoma is the most common to metastasize to the brain. Generally, radio-resistant tumors cannot be adequately treated with whole brain radiotherapy and require SRS to deliver the high doses of radiation for successful local control. In a large retrospective study of patients undergoing SRS, our institution found no difference in local control or overall survival in patients with radiosensitive versus radio-resistant histologies, suggesting that upfront SRS may be the optimal treatment strategy for brain metastases with radio-resistant histologies [33].

The introduction of anti-PD1 and anti-CTLA4 immunotherapy has had a significant impact on survival in patients with advanced melanoma. However, initial studies on the effects of immune checkpoint inhibition in melanoma excluded patients with brain metastases. Some estimates suggest that almost 50% of patients with metastatic melanoma will have brain metastases [34]; therefore, optimizing the treatment strategy for

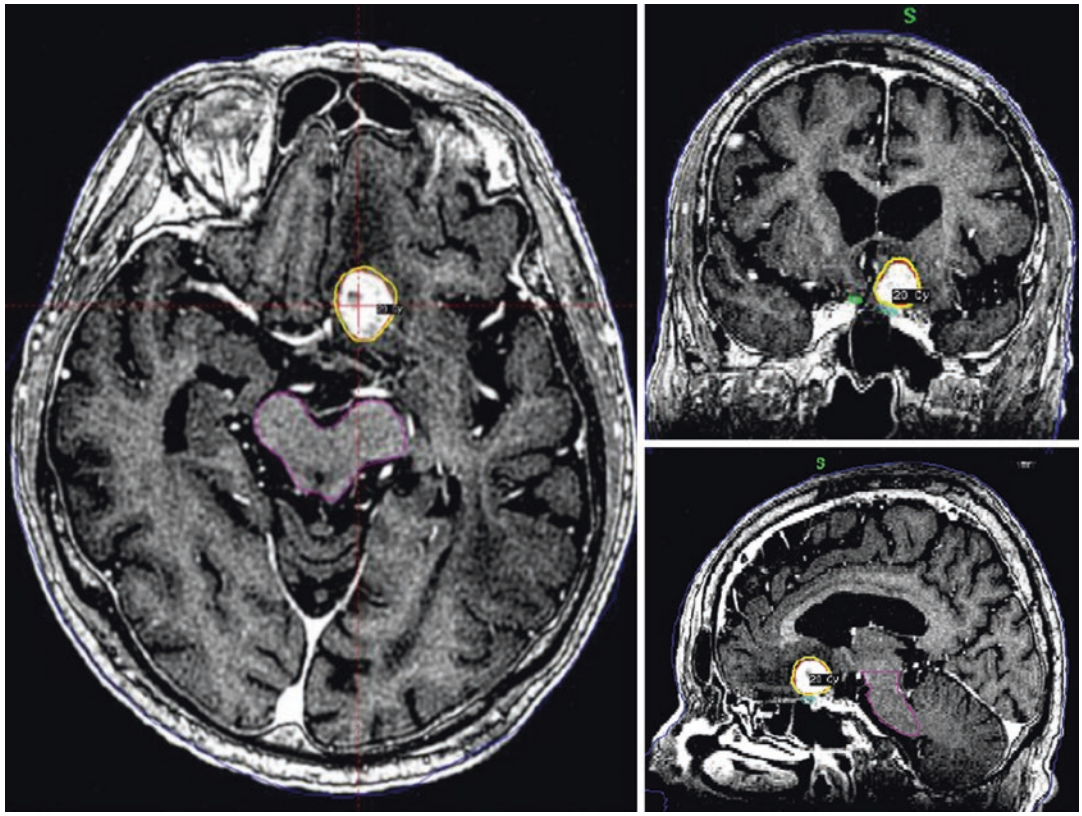

Fig. 27.8 Gamma Knife radiosurgery plan for treatment of a large intracranial lesion consistent with metastatic melanoma. This lesion was treated to 30 Gy in five fractions

this patient cohort will have a significant clinical impact. A recent multicenter phase II trial studied the effect of combined dual anti-PD1 and anti-CTLA4 immunotherapy on melanoma patients with non-radiated brain metastases. The authors reported that 57% of patients had an intracranial response with dual therapy [35], whereas reported results for monotherapy of immune checkpoint inhibitors have response rates of 20–24% [36, 37]. Additionally, 64% of patients were progression-free at 6-month follow-up. Unfortunately, 55% of patients experienced grade 3 or 4 toxicities including hepatic and CNS toxicity, with one patient dying from immune-related myocarditis.

Given this high level of toxicity experienced in patients undergoing dual immune-checkpoint inhibitor therapy, studies are looking at the synergistic effect of immunotherapy and radiotherapy in the management of melanoma brain metastases. This would allow de-escalation of immunotherapy to decrease systemic toxicity, while maintaining high rates of intracranial control. Preclinical and clinical data suggest that radiation therapy may enhance the effects of immunotherapy by increasing the extent of lymphocytic infiltration into diseased tissue or by the abscopal effect. The abscopal effect is a form of activation of the adaptive immune system whereby local tumor death releases tumor-specific antigens that initiate a systemic immune response [38]. Retrospective studies have found a survival benefit when combining radiation therapy and immune checkpoint inhibition in terms of lesion volume [39], regional control rates, time to progression, and overall survival [40, 41], Results from ongoing prospective clinical trials that specifically aim to understand this synergism and the most effective scheduling of treatments are pending; however, at this time,

combined radiation and immune therapies are an active and exciting area of research in the management of brain metastases.

Conclusion

SRS is a versatile technique that should be used in the management of metastatic disease to the brain. The ability to selectively deliver high levels of concentrated radiation without irradiating surrounding normal brain allows for excellent rates of local control while minimizing toxicity. Recent technical advances have made frameless treatments with the Gamma Knife feasible and successful, which will undoubtedly increase the applicability of SRS for a wide variety of indications, including fractionated treatments.

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28

Radiation Necrosis Following the Radiosurgical Treatment of Brain Metastases

Stephanie M. Robert and Veronica L. Chiang

Introduction

Radiosurgery is a growing treatment strategy for numerous neurological pathologies, including vascular lesions, brain tumors, trigeminal neuralgia, as well as functional procedures for the treatment of epilepsy, Parkinson's disease, and essential tremor. In the 1950s, Lars Leksell, a Swedish neurosurgeon, began using photon and proton beams directed into the brain, in an attempt to treat neurological diseases. Over the centuries, his protocol and methods has been refined and developed into what is now broadly referred to as stereotactic radiosurgery (SRS) [1].

Although SRS is used to treat many different neurological conditions, its use has grown exponentially in the field of neuro-oncology as a result of improved cancer survival and increased surveillance imaging for intracranial metastasis. As more intracranial lesions are identified and treated, radiation-induced side effects increase in tandem. The term adverse radiation effect (ARE) is a radiological definition used to describe these post-radiation changes identified by imaging modalities. AREs are further distinguished based on length of time from exposure. Early/acute AREs occur within days of radiation exposure. Early-delayed (also known as pseudoprogression) is typically seen less than 12 weeks post-radiation, and late effects occur months to years after treatment. Most concerning of these effects are late AREs, which include leukoencephalopathy and radiation necrosis. Unlike earlier effects, late changes are typically irreversible and more often symptomatic and progressive [2]. Furthermore, because of the time course of development and appearance on imaging, differentiating radiation necrosis from tumor progression is an important and growing challenge.

Development of Radiation Necrosis

Although one of the most common side effects of SRS, the true incidence of radiation necrosis remains unclear, largely due to the challenges that exist in defining and diagnosing this pathology. The reported incidence of AREs ranges from 5% to 68%, depending on the imaging and clinical criteria used. Furthermore, the duration of time patients are followed clinically, or with additional neuroimaging, varies, and significant heterogeneity exists in the degree of symptomatology that manifests clinically. In addition, the incidence can be highly variable depending on whether the number of cases of radiation necrosis is reported relative to the number of lesions treated, the number of patients treated, or the number of at risk patients (i.e., only survivors) over a variety of time points

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after radiosurgical treatment. Symptomatic cases have been reported to occur less often with a less variable incidence ranging between 2% and 14% [2, 3].

Risk factors for the development of radiation necrosis is an active area of investigation. Although still poorly understood, a few independent factors have been identified. Treatment platform, including LINAC and Gamma Knife, has not been shown to affect rates of radiation necrosis development. The most consistently identified factors found to be associated with development of radiation necrosis are increased dose of radiation, larger volume of treated tissue – as measured by target volume or 12Gy (V12) and 10Gy (V10) volumes – and concurrent chemotherapy administration [4–7]. Furthermore, risk of radiation necrosis also increases with repeated SRS treatment. Sneed et al. showed that risk increases significantly with size and volume of lesion; however, a 20% 1-year risk of symptomatic lesions was found with prior SRS to the same area. In comparison, risk of prior whole brain radiotherapy (WBRT) or concurrent WBRT are 4% and 8%, respectively [8].

The use of chemotherapy in conjunction with radiation to enhance tumor killing properties is often used in the treatment of cancers outside the brain, such as neoadjuvant therapy for gastrointestinal cancers, skull base tumors, and primary treatment of non-operative lung cancers, as well as many other malignancies. For treatment of brain metastases, combining chemotherapy with whole brain radiation therapy (WBRT) results in unacceptable rates of normal tissue toxicity without improved survival [9] and therefore chemotherapy is traditionally put on hold while WBRT is being administered. With the increasing use of SRS rather than WBRT, it is less clear how much separation is needed between radiation treatment and chemotherapy. In malignant glioma, SRS in combination with temozolomide increases the incidence of radiation necrosis [10, 11]. Sneed et al. (2015) reported that the only chemotherapy agent to independently increase the rate of radiation necrosis was capecitabine [8]. Systemic immunotherapy, frequently used in metastatic cancer, significantly increases the risk as well. This will be discussed later in the chapter. Interestingly, Colaco et al., in a single-institution retrospective review, found that while 37.5% of patients treated with systemic immunotherapy developed radiation necrosis, 25.0% of patients receiving targeted therapy also developed radiation necrosis which was significantly higher than the 16.9% rate in those receiving chemotherapy [12]. Of particular concern is the BRAF-inhibitor vemurafenib, a proven pre-clinical radiosensitizer. Patel et al. reported that the rate of both radiographic and symptomatic radiation necrosis was significantly increased if SRS was administered concurrently with vemurafenib (radiographic – 22 vs. 11.1% at 1 year, $p < 0.001$; symptomatic 28.2 vs. 11.1%, $p < 0.001$) [13]. In comparison, second-generation BRAF-inhibitor dabrafenib does not seem to have the same increased risks. Despite this, consensus guidelines from the Eastern Cooperative Oncology Group recommend holding BRAFi and/or MEK inhibitors for three days or more before and after fractionated radiotherapy, and one day or more before and after radiosurgery [14].

In addition, varied reports have also suggested that radiation necrosis rates are increased in lung cancer patients with oncogenic driver mutations (EGFR or ALK) or in those patients receiving tyrosine kinase inhibitors [15]. Kim et al. (2017) retrospectively reviewed 1650 patients treated for 2843 brain metastases across all histologies and found that radiation necrosis developed in 8% of lesions overall [15, 16]. Concurrent systemic therapy significantly increased the rate of radiation necrosis if administered with upfront SRS with WBRT (8.7% compared with 3.7%, $p = 0.04$), and the specific agents most likely to be associated with radiation necrosis were VEGFR tyrosine kinase inhibitors (TKIs) and EGFR TKIs (14.3% and 15.6%, respectively, compared with 6% for non-TKIs). The differences were particularly notable when comparing cumulative incidences suggesting that the increased duration of survival in patients receiving these agents probably also contributed to their increased risk of development of radiation necrosis.

Pathophysiology of Radiation Necrosis

Currently, no data is available on the pathophysiology of pseudoprogression. Radiation necrosis by strict definition is the death of healthy tissue caused by radiation therapy; however, it is the downstream pathological side effect of this initial tissue death that is now more loosely defined by this term. Histologically, the key changes found in specimens containing radiation necrosis are regions of coagulative necrosis surrounded by demyelinated white matter containing vessels with thickened, sclerosed and hyalinized walls, reactive astrocytosis, and extensive macrophage infiltrates [3]. In addition, a process referred to as delayed radiation-induced vasculitic leukoencephalopathy (DRIVL) has been reported in radiation necrosis specimens. Diffuse infiltrates of both CD4+ and CD8+ T lymphocytes are widely present in SRS-treated tissue. T cells are commonly found diffusely scattered throughout the tissue; however, Rauch et al. also demonstrate the presence of transmural infiltration into small- and medium-sized vessels, suggesting an immune-driven, active vasculitis present in SRS-treated tissue [17].

The underlying biology and pathophysiology of radiation necrosis remains a widely debated topic. Radiation necrosis has not only been reported following the high dose radiation treatment of both malignant glioma and brain metastases, but also following the radiosurgical treatment of arteriovenous malformations and other benign brain tumors. Because of this, the implicated mechanisms underlying the development of radiation necrosis include radiation-induced neuronal/glial cell damage, vascular injury, and immune-mediated changes. Two models have been proposed to explain the development of radiation necrosis – primary injury to endothelial cells versus primary injury to glial cells (predominantly oligodendrocytes). Early studies of rodent and human tissue support both vascular and glial injuries underlying the pathophysiology. Currently, it is thought that endothelial injury is the initial insult, which then leads to the development of intravascular thrombosis and subsequent ischemia, causing coagulative necrosis. As a result of either ischemia or intrinsic injury from radiation, oligodendrocyte damage and demyelination also occur [18, 19]. Interestingly, these changes may explain the radiographic characteristics seen in radiation necrosis that makes it difficult to distinguish from tumor progression.

The resulting ischemia and cellular injury likely induces the activation and release of microglial, macrophage, and lymphocyte cytokines. Upregulation of pro-inflammatory cytokines, such as IL-1 alpha, TNF-alpha, and IL-6, can initiate chemokine networks such as the CXCL12/CXCR4 axes, which then likely contributes to much of the progressive nature demonstrated by these lesions [20]. Specifically, hypoxia-inducible factor-1 alpha (HIF-1α) is released by activated microglia, and may lead to upregulation of vascular endothelial growth factor (VEGF). VEGF is known to be elevated in the areas of radiation necrosis [20], is detected as early as 4 weeks post-treatment, and has been shown to increase over time in a mouse model of radiation necrosis [21]. VEGF overexpression is known to promote angiogenesis, resulting in the development of leaky blood vessels. This effect contributes to the permeability of the blood–brain barrier and the resulting vasogenic edema seen with these lesions [22].

One of the most challenging aspects of radiation necrosis is to understand its delayed presentation and progressive nature. Realistically, given that neither current model fully explains the histological changes seen in radiation necrosis tissue, it is likely that a combination of these mechanisms, as well as yet unknown mechanisms, underlies the true pathophysiology of this disease process. Furthermore, beyond vascular-induced changes, diffuse cellular infiltration, including T cells and activated macrophages, is commonly seen in SRS-treated tissue. These infiltrating macrophages readily express pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNFα) and IL-6 [22], possibly supporting an important immunological aspect of radiation necrosis.

Oligodendrocytes are exquisitely radiosensitive, resulting in demyelinating lesions seen in radiation necrosis [23]. Interestingly, one hypothesis that may explain the late-onset and progressive nature of the

disease is an underlying autoimmune etiology. As oligodendrocytes are damaged, and as a result lyse open, exposure of the brain's immune cells to released intracellular components, such as myelin basic protein (MBP), which can be detected in cerebrospinal fluid months after radiation exposure, may trigger ongoing demyelination and further inflammation [17]. Furthermore, albeit rare, a few cases of radiation necrosis remote from the site of SRS treatment have been reported [23, 24]. The involvement of the corpus callosum and periventricular subependymal areas in these cases further supports oligodendroglial injury from an autoimmune-type response after initial SRS exposure. Lastly, the reporting of the vasculitic changes seen in the entity called DRIVL, as discussed above, may also lend support to the autoimmune theory. Further work is necessary to identify the antigen(s) to which the T-cells are primarily reactive.

Regardless of the underlying pathophysiology, radiation necrosis, then, is defined as a high-dose radiation-induced, self-perpetuating, inflammatory, and demyelinating process that surrounds a central core of coagulative necrosis.

Diagnosing Radiation Necrosis

The dilemma in the diagnosis of pseudoprogression and radiation necrosis is differentiating it from tumor recurrence after initial response to treatment with radiosurgery. As discussed, pseudoprogression and radiation necrosis are thought to be similar entities, differentiated by the timing of their presentation. Both tumor and radiation necrosis then can manifest similarly, both clinically and radiographically; however, treatment options for the two diagnoses are very different. What can also be very different about the two diagnoses is their potential course. With tumor recurrence, growth will be persistent and always requires intervention, whereas many cases of radiation necrosis can be self-resolving even if presenting with symptomatology, and therefore may not always require intervention.

Interestingly, patients with radiation necrosis many develop significant changes on imaging, without developing concurrent symptomatology [25]. If they do occur, development of symptoms is usually concurrent with radiographic regrowth of the radiosurgically treated lesion. Just like with tumor growth, the symptoms of radiation necrosis can be highly variable but are typically either related to increased intracranial pressure (headache, confusion, and altered mental status), focal neurological dysfunction (such as motor weakness, sensory loss, dysphasia, gait imbalance), or seizures. Further, as with tumor, symptomatology is determined by the size, extent of edema, and location in the brain, rather than the underlying pathology. It has been suggested that fatigue and cognitive dysfunction in areas such as memory and concentration are more likely related to radiation injury, but this data has not been validated [25]. In the majority of patients, initiation of steroids and anticonvulsants results in good initial control of symptoms, regardless of underlying pathology.

Given that symptomatology often does not differentiate tumor regrowth from radiation necrosis, it is important then to try to accurately differentiate radiation necrosis from tumor recurrence by some reliable method to appropriately guide management and treatment decisions for patients. Conventional, first-line imaging, which consists of computerized tomography (CT) and magnetic resonance imaging (MRI), often shows indistinguishable imaging changes for both tumor recurrence and radiation necrosis. One of the challenges in using MRI to differentiate tumor versus radiation necrosis lies in the similarities in the pathophysiology of these lesions. MRI analysis of intracranial tumors relies heavily on the breakdown of the blood–brain barrier in regions with malignancy-induced neovascularization, which appears as contrast enhancement on imaging. Radiation necrosis, as an inflammatory process, similarly disrupts the blood–brain barrier, therefore showing similar enhancement on contrast-enhanced MRI scans [26]. Characteristically, gadolinium-enhanced T1-weighted MRI shows a rim-enhancing lesion with central necrosis with mass effect, and FLAIR imaging will show significant perilesional edema around the area previously targeted by SRS. As previously described, central necrosis is seen in all cases of radiation necrosis, but many tumors also contain significant areas of necrosis, further confusing interpretation on imaging. Lastly, because of its delayed onset, radiation necrosis typically

presents in a similar time period as does tumor regrowth, therefore, timing of lesion development is not a realiable indicator to differentiate between these pathologies.

In the largest study of brain metastasis-related radiation necrosis by Sneed et al. [8], the authors showed that of their 2200 metastatic lesions treated, 9.2% of regrowth was tumor recurrence, 5.4% was isolated radiation necrosis, and 1.4% was a combination of tumor and necrosis. The finding that in a certain percentage of cases these lesions likely contain a component of both radiation necrosis and tumor tissue further complicates diagnosis. Further, the percentage of lesions that may show mixed pathology may vary across institutions depending on the radiosurgical dosing across institutions depending on the radiosurgical dosing, surgical aggressiveness, and a host of other factors. In a study by Alomari et al., 36 consecutively identified lesions that regrew after radiosurgical treatment required surgical resection for either diagnosis or management of symptomatology [27]. Pathology was consistent with tumor regrowth in 31% and radiation necrosis in 36%; for the remaining 33%, there was less than 2% of tumor within the specimens. In determining the clinical significance of this finding, a subsequent publication by Nath et al. showed that only patients in whom pathology showed absolutely no tumor had increased survival and that even in patients with 2% tumor in their specimen subsequently went on to have tumor progression at the previously treated site [28].

Extensive research continues to focus on identifying new imaging modalities and protocols to accurately diagnose radiation necrosis without the need for invasive procedures to obtain tissue for pathological evaluation. Advances in the development of novel MRI sequences are leading the field currently, with new protocols and techniques such as perfusion protocols and spectroscopy. As yet, however, there is no gold standard imaging technique that provides sufficient accuracy in predicting radiation necrosis versus tumor regrowth in the clinical setting.

Based on T1 gadolinium-enhanced MRI, use of lesional morphology has been well document to frequently be insufficient for differentiation of the two diagnoses [29] although some lesions do show the characteristic "Swiss cheese," "cut bell pepper," or "soap bubble" changes (Fig. 28.1) described by Kumar et al. in gliomas treated using high-dose fractionated radiation [23].

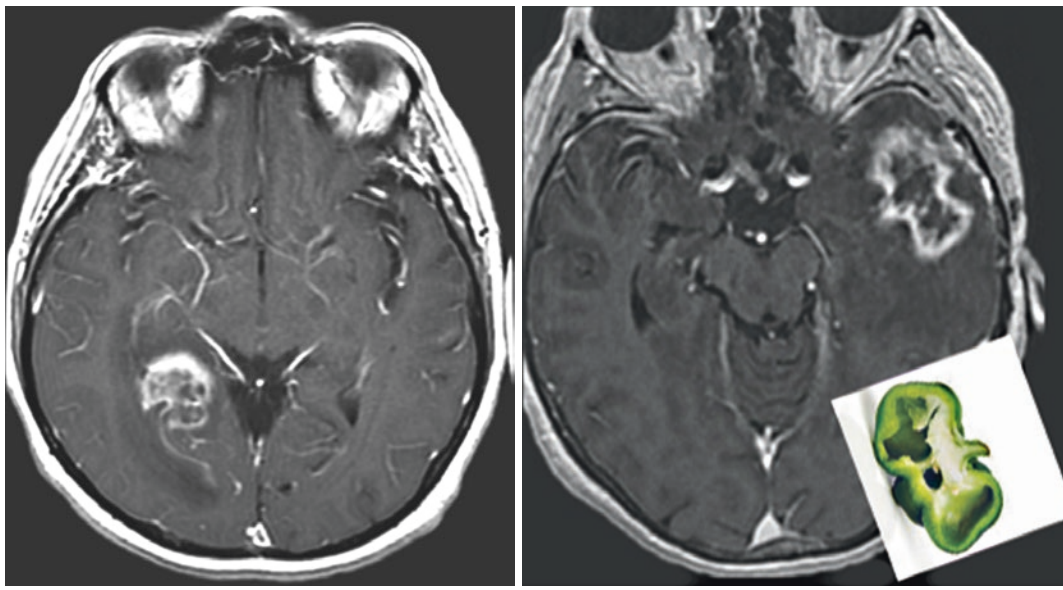

Fig. 28.1 Lesional morphology of radiation necrosis on T1 gadolinium-enhanced MRI. The characteristic "Swiss cheese," "soap bubble," and "cut bell pepper" appearance of radiation necrosis lesions. (These imaging characteristics were described by Kumar et al. [23] in gliomas treated with radiosurgery)

Apparent diffusion coefficient (ADC) is an MRI sequence based on diffusion-weighted imaging that was initially hypothesized to differentiate tumor versus radiation necrosis based on hypercellularity of tumor-bearing regions relative to necrotic areas. In theory, tumor recurrence should cause restriction of water diffusion due to the increased number of cells compared to radiation necrosis. However, recurrent tumors have variable cellularity, and many regrowths have significant necrotic cores, preventing the development of clear parameters for diagnosis [30]. Similarly, T1/2 mismatch, initially developed and proposed by Dequesada et al., has been ultimately shown to have a poor positive predictive value in distinguishing radiation necrosis from tumor recurrence [31, 32].

The most promising MRI-based technique currently available takes advantages of the subtle differences in pathophysiology of radiation necrosis and tumor regrowth, using MR spectroscopy combined with MR perfusion. These modalities measure metabolism and physiology, and together are more likely to accurately predict the pathology of the lesion. MR perfusion uses dynamic susceptibility-weighted contrast-enhanced imaging to determine relative cerebral blood volume (rCBV). As a measure of microvascular density, rCBV is typically decreased in radiation necrosis given the small-vessel injury that underlies its development. In contrast, tumor regrowth promotes angiogenesis for cell nutrition and survival, therefore enhancing rCBV and increasing perfusion on MRI [26].

MR spectroscopy evaluates the chemical makeup of the brain tissue, and using the ratio of metabolites N-acetyl aspartate (NAA), choline (Cho), and creatine (Cr) measured, further insight into the pathology of lesions can be gathered. NAA is a marker of neuronal function, and a decrease in this metabolite indicates neuronal injury. Increase in choline suggests increased cellular proliferation, as it is a component of the cellular membrane. Creatine, a marker of energy reserve, remains stable and is used as a control for comparison. To differentiate tumor versus radiation necrosis, Cho, NAA, and Cr ratios are compared. Tumor regrowth tends to have higher Cho/NAA and Cho/Cr ratios, and lower NAA/Cr ratios [23, 33]. However, there is a significant variability in the ability of MR spectroscopy and MR perfusion to accurately predict tumor versus radiation necrosis in the literature, and therefore their sensitivity and specificity are currently debated [34, 35].

Lastly, nuclear medicine imaging is becoming more widely used, and is specifically being investigated for use in identifying tumors and metastatic lesions. Techniques using positron emission tomography (PET) in combination with 2-deoxy-[18F]fluoro-D-glucose (FDG) allows measurement of cellular metabolism by detecting glucose uptake. Malignant lesions, with higher metabolic activity, show up as brighter lesions given their enhanced glucose uptake [36]. Unfortunately, due to the high basal glucose metabolism in brain tissue, FDG-PET is not as useful as in extracranial lesions. PET scans using radiolabeled amino acids have shown promise at several centers for differentiating radiation necrosis and tumor, specifically with the ^{11}C methionine-PET-labeled isotope. However, due to its short half-life and need for an on-site cyclotron, its use remains relatively limited [37].

Given the lack of any specific imaging test to reliably differentiate radiation necrosis from tumor regrowth, our institution still relies heavily on histological analysis of tissue as studies have shown accuracy to be >98% to distinguish radiation necrosis from tumor recurrence [38–40]. In those patients in whom surgical management is not possible, serial imaging with standard T1-weighted gadolinium-enhanced MRI and FLAIR sequence MRI over a 3- to 6-month period ultimately also allows for differentiation of diagnosis with the majority of cases of radiation necrosis being self-limited.

Surveillance for Radiation Necrosis

As seen in the radiological study by Patel et al. (2011), of 500 metastases after SRS treatment, the authors found that up to one-third of SRS-treated lesions regrew after an initial favorable radiographic response [41]. Radiation necrosis

can develop as early as 2 months post-radiation, and as far out as 10 years after exposure, although imaging changes begin most commonly between 7 and 11 months post-SRS [7, 42–44].

In a recent study by Fujimoto et al. (2018), the authors retrospectively reviewed imaging for all their radiosurgically treated brain metastases patients to identify patients who had lesional regrowth beyond 18 months after radiation. A total of 13 patients with 19 problematic lesions were identified with a median follow-up of 48.2 months and a median overall survival of 73 months. Of the 19 lesions, 12 were identified as radiation necrosis (either by demonstration of spontaneous resolution on serial imaging or by pathology) and 7 were tumor recurrence. The radiation necrosis cases demonstrated first concerning imaging changes at a median of 33.2 months (range 18.5–63.2 months) and therefore the latest case occurred at 5.3 years. In comparison, the tumor recurrence cases occurred at a median time of 23.6 months (range 19.8–45.3 months), with the latest case occurring at 3.8 years [45].

This study highlights the need for continued imaging surveillance for both tumor recurrence and radiation necrosis and the need for recognition that both diagnoses can still occur many years after radiosurgical treatment. This issue will become increasingly important as patients with brain metastases experience improving survival durations from newer systemic therapies that also may have variable central nervous system penetration. Within our institution, post-radiosurgical surveillance includes serial MR imaging at 6 weeks, and then 3, 6, 9, 12, 18, and 24 months after radiosurgical treatment as long as systemic control is maintained. MR imaging is performed more frequently (usually every 6 weeks) if there is recurrence of systemic disease or if neurological symptoms arise and are associated with new changes on MRI. Beyond 2 years, yearly MRIs are advisable. Given that the first change often seen on MRI is the development of perilesional edema, it may also be reasonable to perform surveillance imaging using serial CT scans of the brain to minimize imaging costs and then to follow up any concerning CT findings with an MRI of the brain.

Immunotherapy and Radiation Necrosis

Monoclonal antibody immunotherapies, specifically PD-1 inhibitors alone or in combination with CTLA4 inhibitors, are being increasingly used in many types of cancer but most commonly currently for patients with small cell and non-small cell lung cancer, melanoma, and renal cell carcinoma. Brain metastases occur in all of these cancer types and therefore, as SRS is also being increasing used as a therapeutic modality for brain metastases, the interaction between immunotherapies and the development of radiation necrosis is an important new focus of research. Studies have shown that radiation therapy enhances the innate immune response within tumors as well as within the immune system of the patient [46], and that combining SRS with immune checkpoint inhibitors may enhance antitumor activity [47, 48].

These immune therapies, also known as checkpoint inhibitors, block inhibitory checkpoints in the immune response, allowing the immune system to generate a more robust response to malignant lesions, enhancing antitumor activity [49]. The brain has traditionally been known as an "immunologically privileged site" referring to its ability to limit the entrance of peripheral immune cells due to the presence of the blood–brain barrier (BBB). Activated T cells however have been shown to be able to cross this barrier [50], and furthermore it has been suggested that not only do brain metastases have a disrupted BBB, but SRS may further disrupt the BBB, allowing enhanced crossing of peripheral immune cells into the central nervous system (CNS), an effect that in animal studies has been found to last as long as a month post-treatment [51]. Recent data by Qian et al. [52] has shown an improved therapeutic response of brain metastases in melanoma patients when radiosurgery is delivered concurrently with immunotherapy, supporting the idea of

increased T-cell penetrance and/or efficacy in the brain following radiosurgery [52].

The negative consequences of combining SRS and immunotherapy, however, remain unclear. Given that one of the pathophysiological mechanisms proposed in the development of radiation necrosis was autoimmune reactivity, it is feasible that immunotherapy may accentuate the risk for development of radiation necrosis. During the era when the anti-CTLA4 agent ipilimumab was commonly used for melanoma, there was no clear evidence that risk of radiation necrosis was increased, although a study by Colaco et al. (2016) showed that when all immunotherapies were aggregated together, the majority of which included ipilimumab, the rates of radiation necrosis were higher than the rates seen in patients treated with either targeted therapies or chemotherapies [12]. This finding however was not supported by a recent study by Diao et al. (2018) who studied acute toxicity specifically in 91 patients treated concurrently with ipilimumab and radiosurgery [53].

Similarly discrepant results are being reported for anti-PD-1 and combination immunotherapies used in conjunction with radiosurgery, uncovering an association between the development of radiation necrosis and the use of concurrent immunotherapy. A recent study by Martin et al. (2018) found a higher incidence of radiation necrosis in patients treated with combined immunotherapy and SRS. Their patient population included those with lung cancer, melanoma, and renal cell cancer, and interestingly, the increased risk of radiation necrosis was heavily biased toward the melanoma population [54]. Similar results were found by Kaider-Person et al. (2017) in their 58-patient population with melanoma brain metastases [55]. In contrast, Fang et al. did not find any increase in the rate of radiation necrosis in their study of 137 melanoma patients treated with radiosurgery to 1094 lesions especially when compared to rates of radiation necrosis seen in patients treated with chemotherapy [56].

Given the conflicting data currently in the literature, larger multicentered studies, particularly either standardized or stratified for the many clinical variables in the care of each patient, may be required to determine the true interactive effect of immunotherapy and radiosurgery. In our own center, we see examples of radiation necrosis developing immediately after GKSRS + immunotherapy treatment, as well as delayed effects (Fig. 28.2). Interestingly, radiation necrosis is seen to develop immediately after immunotherapy (Fig. 28.2a), in a delayed fashion (Fig. 28.2b), and even years later, seen in long-term survivors (Fig. 28.1c). Although data is suggesting significant interactions between immunotherapy and radiation necrosis, more research is needed to provide insight into the mechanisms underlying the intricate interaction between immunotherapy and SRS in the treatment of malignant lesions and development of radiation necrosis.

Treatment of Radiation Necrosis

Interestingly, and unlike tumor regrowth, many radiation-induced lesions spontaneously resolve without intervention. Although no clinical or imaging parameters have been shown to predict the likely evolution of the lesion, the likelihood of improvement of radiation necrosis increases with time, with up to 76% of lesions resolving 18 months after initial diagnosis. However, up to 25% of these lesions may not improve with medical treatment alone, necessitating surgical intervention [42].

Management and treatment of radiation necrosis therefore varies depending on symptomatology. If the patient's clinical scenario and imaging seem most consistent with radiation necrosis, then asymptomatic, small, and non-progressive lesions can be managed conservatively.

First-line medical therapy for symptomatic radiation necrosis is corticosteroids. Steroids are presumed to contribute anti-inflammatory effects, stabilize the blood–brain barrier, and decrease edema. Steroids, however, are not required unless symptoms arise, as steroids alone have not been shown to change the course of radiation necrosis. If symptoms arise, however, then the lowest dose of steroids allowing management of symptoms should be administered and recurrent attempts to

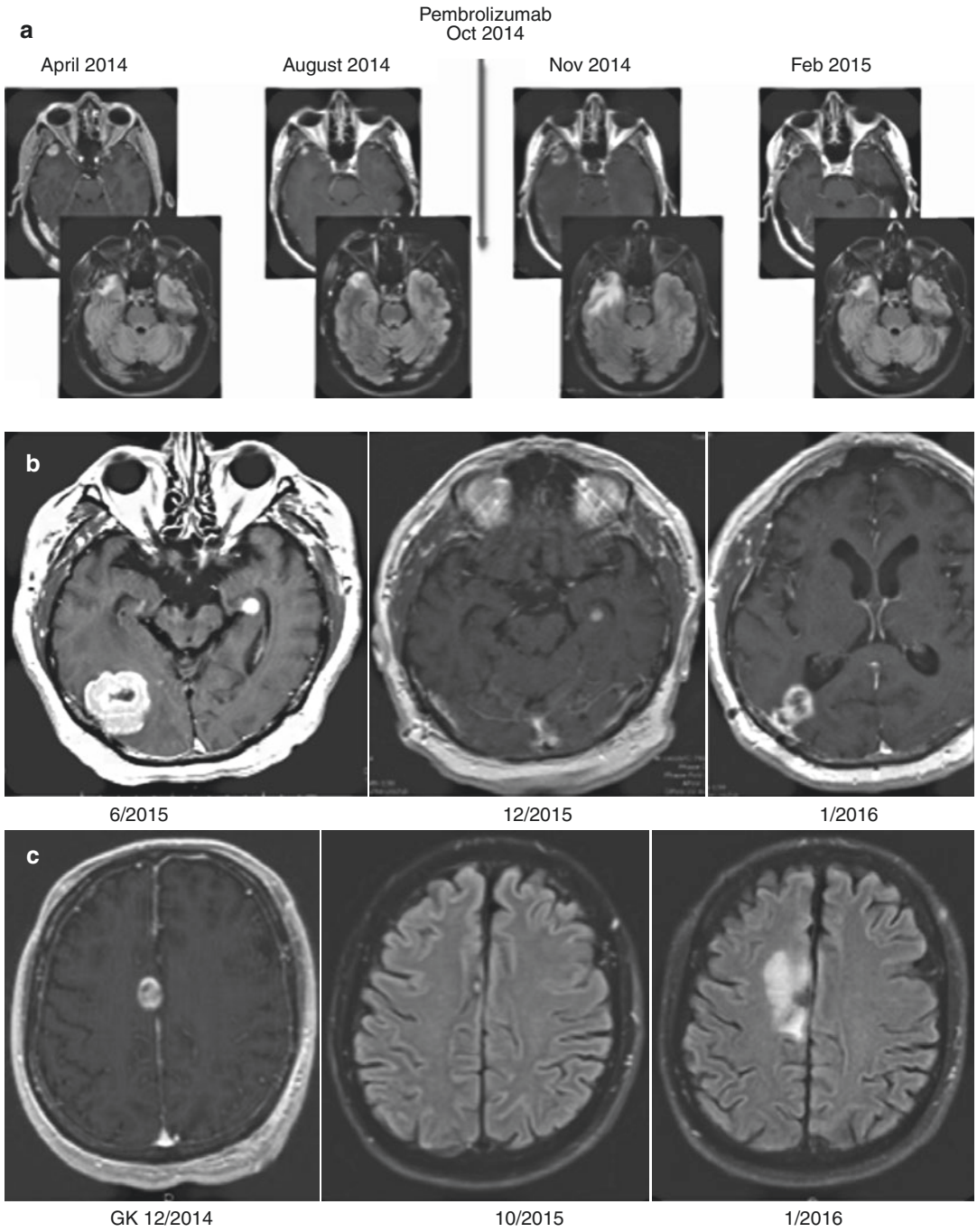

Fig. 28.2 Immunotherapy and the development of radiation necrosis in three patients with melanoma. The first patient (**a**) had previously received Gamma Knife stereotactic radiosurgery (GKSRS) several times with improvement in her right temporal lesion. However, 1 month after receiving pembrolizumab, she developed progressive radiation necrosis that required resection. In the second patient (**b**), the initial lesion was resected, with GKSRS to the post-op cavity only, in combination with immunotherapy. He showed good response for 8 months; however, he then developed radiation necrosis in the GKSRS cavity only. This lesion was then surgically resected. For the last patient (**c**), GKSRS was provided to a single lesion, followed by immunotherapy, which provided good response for 2 years until the development of radiation necrosis in the previous area of GKSRS treated lesion. This phenomenon is seen in many long-term survivors of peripheral cancers

wean steroids should occur until the lesion or symptoms resolve [26]. Unfortunately, some patients are unable to tolerate this medication due to its side effects, and others continue to experience symptoms in spite of treatment.

Bevacizumab, a humanized monoclonal antibody, has shown efficacy in studies of central nervous system radiation necrosis. While it is unclear how bevacizumab works to resolve radiation necrosis, as a VEGF-inhibitor, it is a highly effective non-steroidal therapy for management of perilesional edema. In a randomized, placebo-controlled study of 14 patients with radiation necrosis, all treated patients showed improvement, both on imaging and symptomatically, while none of the patients in the placebo group showed improvement [57]. Similarly, Gonzalez et al. (2007) showed that treatment with bevacizumab reduced the MRI fluid-attenuated inversion-recovery (FLAIR) abnormalities and T1-weighted post-Gd-contrast abnormalities in radiation necrosis. These findings suggest that vessel leakage and associated edema is decreased as a result of this treatment strategy. Bevacizumab use also enabled a reduction in daily dexamethasone dose required for these patients [58]. Notably, however, this treatment strategy has significant side effects and again is not tolerated by all patients.

Aspirin, non-steroidal agents, anticoagulation, and vitamin E supplementation have all been anecdotally reported to have efficacy in the treatment of radiation necrosis although consistent results have not been replicable. Hyperbaric oxygen is a less commonly used treatment, in large part because of the limitations of delivery. This therapy enhances angiogenesis in hypoxic tissue and oxygen delivery. Although no large-scale studies have been performed, smaller trials have also shown improvement in imaging and symptoms in patients undergoing hyperbaric oxygen [26].

For lesions that do not respond to medical therapies, or those in whom a tissue diagnosis is needed to rule out regrowing tumor, surgical resection can be performed. In addition to providing definitive pathology, removal of the lesion is frequently the most rapid mechanism to relieve neurological symptoms by immediately reducing mass effect and edema, and allowing for a quicker taper of steroid dosing. This approach is preferred for readily accessible lesions in the brain, and for patients healthy enough to undergo a more invasive surgical procedure. Furthermore, surgical resection has been shown to provide complete local control of the lesion [28].

For less surgically accessible lesions, a more recent technique called laser interstitial thermotherapy (LITT) has been developed to address both the need for tissue diagnosis and the treatment of radiation necrosis. Since its introduction, it has been increasingly used for patients with lesions amenable to standard craniotomy because of its minimally invasive technique. Using this procedure, through a small scalp incision and a 5 mm twist drill hole made in the skull, a biopsy can first be obtained to provide a diagnosis, and then the lesion can be ablated using a diode laser introduced into the center of the lesion. Light emitted from the laser is converted in the surrounding tissues into heat. The progression of heat delivery is monitored using continuous intra-operative MR gradient echo imaging, and through the use of proprietary software, a real-time ablation map is created corresponding to the amount of time each imaging voxel has been at an elevated temperature.

One of the significant advantages of using LITT for regrowing lesions after SRS is the success it has shown in treating both radiation necrosis and regrowing metastatic lesions. Multiple retrospective studies have demonstrated the efficacy of LITT regardless of diagnosis [59, 60]. Furthermore, since it provides a minimally invasive alternative to an open surgical approach, it allows more patients to undergo treatment. Many cancer patients with metastatic lesions are poor surgical candidates or have lesions located in brain regions too deep to justify the morbidity that would result from open surgical resection. A recent prospective, multi-center study (Laser Ablation After Stereotactic Radiosurgery [LAASR]), looked at longer-term results of using LITT for regrowing SRS-treated lesions. Interestingly, they found that for biopsy-confirmed radiation necrosis lesions, local control at 6 months was 100%; however, for regrowing tumor lesions, control was less at 74%. These findings suggest that LITT is an effective option for treatment of both radiation necrosis

and tumor regrowth, with the caveat that further surveillance and treatment may be needed post-LITT for recurrent metastatic lesions [20].

Conclusion

Radiation necrosis is a growing problem due in large part to the success of SRS in treating a vast number of intracranial pathologies. Although SRS-induced radiation necrosis has been described following treatment for benign and non-tumor lesions, given its increasing use in malignant primary and metastatic brain tumors, important questions remain unanswered for the field of neuro-oncology.

Furthermore, newer evidence strongly suggests a significant immunologically mediated component underlying the development of radiation necrosis. Combining the current proposed models, immune activation likely occurs in response to the vascular and cellular injury created by radiation treatment. As such, as both radiosurgery and immunotherapy/targeted therapies become more heavily utilized and combined clinically, and as more metastatic brain lesions are identified and treated, the incidence of radiation necrosis will likely continue to grow. Fortunately, there are a number of effective treatment options for patients to treat radiation necrosis. However, a better understanding of the pathophysiology of radiation necrosis is needed to guide treatment decisions and patient management, both before radiation necrosis develops, as well as how best to treat once it occurs.

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29 Neurocognitive Effects of Brain Metastases and Their Treatment

Karine A. Al Feghali, Mariana E. Bradshaw, Caroline Chung, and Jeffrey S. Wefel

Introduction

Brain metastases are the most common intracranial tumors. The overall frequency of parenchymal brain metastases in cancer patients was found to be as high as 15–17% on autopsy studies [1, 2]. The cancers that are the most prone to metastasize to the brain are lung, breast, melanoma, renal, and colorectal [3–6], with incidences as high as 60% in patients with small-cell lung cancer (SCLC) [7] and EGFR-mutated or *ALK*-rearranged non-small-cell lung cancer [8, 9]. The emergence of new and more effective systemic therapies and the development of better radiation therapy techniques have significantly improved locoregional rates and overall survival in cancer patients. These advances have paradoxically led to an increased incidence of brain metastases [7, 10, 11], as these typically emerge later in the disease course, and most therapies do not substantially cross the blood–brain barrier.

Multidisciplinary management of brain metastases consists of surgery, radiation therapy [stereotactic radiosurgery (SRS) or whole brain radiation therapy (WBRT)], and/or systemic therapy. Unfortunately, patients are sometimes plagued with debilitating and life-altering neurocognitive adverse effects due to off-target or on-target/off-tumor toxicity. Efforts to prolong survival can indeed come at the detriment of cognitive dysfunction and/or impairment of functional independence. A decline in neurocognitive function (NCF) after WBRT in patients with brain metastases has been shown to precede deterioration in the quality of life (QoL) by 9–153 days [12], although this association has not always been demonstrated across all studies [13]. It is sometimes challenging for the clinician to isolate the effect of a specific treatment on cognitive function, as cognitive decline is most often multifactorial, resulting from the interplay of different therapies and from the central nervous system (CNS) disease itself. Balancing the benefits and toxicities of brain metastasis treatment is a challenging task that medical, radiation, and surgical oncologists face daily.

Radiation therapy, chemotherapy, and surgery can affect processing speed, attention, learning and memory, executive function, and motor dexterity among other brain functions. These changes can occur in the acute setting, such as

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with encephalopathy [14–16], and in the chronic setting, such as in neurotoxicity due to delayed white matter tract damage [17]. Neurocognitive side effects from treatment are often partially or completely reversible, but can also be irreversible. Many factors, including age, comorbidities [18], and lower baseline pretreatment cognitive capacity, sometimes called "cognitive reserve" [19, 20] can increase the risk of chronic neurotoxicity.

The pathophysiology of radiation-induced neurotoxicity is not well understood. However, animal studies have demonstrated that radiation blocks neurogenesis in the dentate gyrus of the hippocampus [21]. Chemotherapeutic agents such as paclitaxel have also been shown to reduce neurogenesis in the hippocampus [22]. Advanced imaging techniques such as structural and functional MRI, as well as animal studies in rodents, have shaped our understanding of some of the neurobiological mechanisms underlying chemotherapy and radiotherapy-induced adverse neurological effects. The main culprits are believed to be oxidative stress causing DNA single-strand or double-strand breaks, increased apoptosis, vascular injury, damage to white matter tracts, and neuroinflammation [19, 23–26]. Imaging biomarkers are being investigated as surrogates for early assessment of RT-induced neurotoxicity. In particular, dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) can be used to detect early changes in vasculature and predict late neurocognitive dysfunction [27, 28].

The Impact of Baseline Brain Metastases Characteristics on Neurocognitive Function

NCF at baseline, i.e., before any treatment, is directly affected by tumor location [29], tumor burden [30–32], rate of growth [33], and extent of surrounding edema [31]. Paraneoplastic effects, prior neurologic disease, and use of certain medications can also play a role in impaired NCF at baseline.

Neurocognitive impairment at baseline has been extensively documented in the literature. The prevalence varies among studies, as it depends on the sensitivity of the cognitive tests employed, the measured endpoints (for example, some studies use dementia as an endpoint versus milder deficits in other studies), and the patient population included. In a trial randomizing patients with brain metastases to different radiation fractionation schedules, 16% of patients had dementia at baseline, and the average mini-mental status examination (MMSE) score was 26, which is considered at the lower quartile of normal for the United States population [34, 35]. In a pilot study of patients treated with SRS for one to three brain metastases, two-thirds of patients had impaired NCF at baseline, with impairments observed in measures of executive functioning, motor dexterity, and learning and memory [36]. Some evidence of neurocognitive dysfunction can be found at baseline in up to 90% of patients with brain metastases [30]. Neurocognitive testing done at baseline can differentiate the effect of the disease itself on patients' cognition from treatment side effects. It has also been suggested that a combination of tumor prognostic variables and brain function assessments is better at predicting survival than tumor variables alone in patients with brain metastasis and in those with leptomeningeal disease [30, 37, 38].

Tumor location is a factor that can affect the likelihood of developing neurocognitive impairment. Traditionally, patients with tumors in the frontal or temporal lobes were thought to have more propensity to demonstrate cognitive dysfunction than patients with tumors in less "eloquent" brain regions [29]. More recent work is challenging this "localizationist" view of cognition; it describes whole-brain network disturbances in patients with brain tumors, indicating that cognitive deficits cannot be explained by tumor location alone, but are rather reflections of the brain's intricate interconnecting neural networks [39].

Tumor burden, and more specifically the volume of the lesions, rather than the number of brain metastases, has been consistently associated with worse NCF at baseline. In a large trial of patients with brain metastases from a variety

of primary cancers, there was a statistically significant small-to-moderate degree of correlation between the indicator lesion volume at baseline and measures of memory, verbal fluency, fine motor control and executive function [30]. In a prospective study of 97 patients with brain metastases, patients with large tumor volume showed a trend toward worse verbal memory and information processing speed, whereas the number of brain metastases was not correlated with any of the seven cognitive domains studied [32]. Larger total tumor volume of brain metastases (≥3 versus <3 cm^3) and a larger extent of tumor edema at baseline were also shown to be associated with worse MMSE in a Japanese trial [31].

In patients with gliomas, the faster the rate of tumor growth, the more dramatic the cognitive changes [40–42], which is probably due to less chance for compensatory neuroplastic reorganization. Although not well established, this association may hold true in patients with brain metastases as well, in whom tumor "momentum" may be an independent predictor of cognitive changes [33].

The Impact of Surgery on Neurocognitive Function

As noted above, brain metastases may impact cognition prior to any intervention. Surgical resection of brain metastases may result in the improvement of these cognitive symptoms through relief of mass effect. However, there is also the potential to damage healthy tissue, resulting in some long-term neurocognitive impairment; this might occur through either direct focal damage or disruption of larger distributed networks. While the use of surgery is often a critical component of the treatment of brain metastases, particularly for solitary lesions, there is little information regarding functional outcomes after resection. When it has been assessed, functional outcome after surgical resection of brain metastases has generally been measured using broad ratings of performance status as opposed to more precise neuropsychological assessment. Patchell et al. found that patients treated with surgery in addition to WBRT maintained Karnofsky Performance Scores (KPS) of ≥70 significantly longer than those who were treated with WBRT alone [43]. In contrast, no significant difference was found in length of functional independence (again as measured by KPS) in patients who had surgery alone as compared to those who received surgery plus WBRT [44]. The impact of surgery on cognitive functioning in patients with malignant gliomas has recently been described in several publications. The incidence of cognitive decline has varied across studies with rates ranging from 20 to 60% [32, 45–48]. Domains commonly reported as most vulnerable to surgical impact include memory, executive function, processing speed, and attention. Further, language functions are at increased risk when lesions and resections involve the dominant hemisphere. While some studies have found an increased risk for surgically associated cognitive decline in patients with dominant hemisphere tumors, other risk factors have not been routinely identified.

The Impact of Systemic Therapy on Neurocognitive Function

Chemotherapy

Chemotherapy-induced cognitive side effects (coined "chemobrain" or "chemofog") are frequent occurrences in cancer patients, varying in frequency from 15% to 80% [15, 19, 49]. Many chemotherapeutic agents have been inculpated, including methotrexate, BCNU, melphalan, fludarabine, cytarabine, 5-fluorouracil, levamisole, cisplatin, and capecitabine [14, 50, 51]. Structural brain differences between patients who received chemotherapy and control patients have been demonstrated, as well as reductions in the volume of white and grey matter [52, 53]. A Dutch study utilized diffusion tensor imaging (DTI) MRI in chemotherapy-exposed breast cancer survivors to report on changes in white matter microstructural integrity over time as measured by fractional anisotropy, mean/axial/radial diffusivity and tractography. This study revealed that

these metrics of global and focal white matter organization significantly deteriorated over time following treatment [54].

It has been demonstrated that a disrupted blood–brain barrier around brain tumors (as opposed to healthy brain tissue) helps systemic agents gain access [55, 56]. There is also growing literature on ways to circumvent the blood–brain barrier, by inhibiting transporters that function in extruding drugs or toxins from the brain [57]. However, the literature on the impact of chemotherapeutic agents on cognition in patients with brain metastases specifically is scarce. Whether the addition of chemotherapy to radiation results in more cognitive dysfunction is uncertain. Few clinical trials have examined the role of chemotherapy versus chemotherapy with WBRT [58–61], but none reported on the endpoint of cognitive dysfunction.

Because of its good penetration in the brain and its proven efficacy in glioblastoma multiforme [62], temozolomide, an oral cytotoxic alkylating agent, was tested in brain metastases in few phase II studies and a phase III study, with or without WBRT or SRS. Its addition was associated with good overall response rates, but no survival benefit [63–66]. While a phase II trial suggested that the addition of temozolomide to RT might lead to greater neurologic improvement than RT alone [65], a phase III trial suggested increased toxicities that could lead to a possible survival detriment [61]. However, none of these trials performed a neurocognitive assessment for the patients included.

Emerging Role of Immunotherapy and Targeted Agents in Brain Metastases: Uncertain Impact on Neurocognition

Advances in genetic characterization of brain metastases have paved the way to new therapeutic avenues. Actionable mutations have been identified in secondary brain lesions, which are sometimes distinct from the mutations harbored by primary cancer [67, 68]. This genetic heterogeneity might have resulted in the differential therapeutic response intra-cranially and extra-cranially, which had traditionally been solely attributed to inadequate penetration of the blood–brain barrier. Nowadays, immunotherapy and targeted therapies play an increasingly important role in the management of patients with brain metastases. Tyrosine kinase inhibitors (TKIs), such as some of the *ALK*-TKIs, EGFR-TKIs, and HER2-TKIs, and other agents, such as BRAF inhibitors, anti-PD-1, and anti-CTLA4, have been shown to have good activity against CNS metastatic disease [69, 70]. The impact of these novel therapeutics on NCF is still not elucidated, as most phase 2 and 3 trials testing these new agents have not yet incorporated formal neurocognitive testing. Data on cognitive effects of immunotherapy or targeted therapy remain, therefore, very scarce. Although these options have been hypothesized to come at a lower cost to neurocognitive impairment [71], there is a lack of high-level evidence to prove this assumption.

There were also growing concerns on the safety of combining EGFR-TKIs with cranial irradiation in non-small cell lung cancer patients in terms of neurotoxicity. A systematic review on that topic concluded that although WBRT used concurrently with TKI did not seem to increase neurotoxicity, there was also a lack of high-quality evidence to support the use of these two therapies concurrently [72]. In fact, only one study included in this review used a formal neurocognitive battery of tests [73], and another one used MMSE, the EORTC QLQ-C30 cognitive function subscale and Trail Making Test Part B (for executive function) [74]. In both these studies, the addition of TKI (erlotinib and gefitinib) seemed to be well tolerated.

Checkpoint blockade directed against the programmed death-1 (PD-1) pathway has been shown to improve cognitive performance in murine models of Alzheimer's disease [75]. Whether this finding can be extrapolated to patients with brain metastases treated with anti-PD-1 remains to be proven. In a study with 36 patients with brain metastases secondary to NSCLC or melanoma treated with pembrolizumab, one patient developed grade 3 cognitive dysfunction, which could have resulted from per-

ilesional edema and not from the direct effect of the drug [76]. Some experts have hypothesized that there might be differences in individual susceptibility to cognitive impairments imparted by increased immune activation using some of these agents [77]. Many questions in the field of immunotherapy and cognitive side effects remain unanswered and there needs to be more neurocognitive assessment incorporated in trials testing these agents.

The Impact of Radiation Therapy Targeting Brain Metastases on Neurocognitive Function

Whole Brain Radiation Therapy

Whole Brain Radiation Therapy (WBRT) consists of two opposed-lateral treatment fields that encompass the entire brain (Fig. 29.1). It has long been considered the standard of care for patients with brain metastases, either postoperatively or as the sole treatment, especially for inoperable patients or in the setting of multiple brain metastases. Its impact on neurocognition can, however, be quite dramatic, ranging from mild cognitive impairment to full-fledged dementia.

In a secondary analysis of a trial including patients with multiple brain metastases receiving WBRT with or without thalidomide, both arms experienced a steady neurocognitive decline as assessed by the Folstein MMSE [13]. The limitations of MMSE will be discussed later in the chapter, but this study was performed before the RTOG's growing use of more elaborate neurocognitive batteries. In a study by Shibamoto et al. including 101 patients treated with WBRT (40 Gy in 20 fractions), there was a decrease in MMSE scores of ≥4 points in 7.4%, 11%, 20%, 12%, 5.9% of assessable patients at 3, 6, 9, 12, and 15 months, respectively. Brain atrophy was observed in 30% of patients but was not correlated with MMSE decrease [78]. In a study by Regine et al., accelerated fractionation (1.6 Gy twice a day to 54.4 Gy) was compared to standard WBRT fractionation (3 Gy daily to 30 Gy), with no difference in NCF between the two regimens as evaluated by MMSE [35]. Studies have reported neurocognitive dysfunction in 11–85% of patients treated with postoperative WBRT for brain metastases [79, 80]. These numbers vary depending on the assessment tool used and on the definition of neurocognitive deterioration in the different trials. Given these alarming numbers, the last decade has witnessed the decline of WBRT in favor of the less 'toxic' and more targeted stereotactic radiosurgery. The next section will offer an overview of the studies comparing the two techniques in terms of neurocognitive side effects. This decline in WBRT use was also potentiated by the recent advancement in systemic therapies [81] that have the potential to control microscopic disease, while surgery or

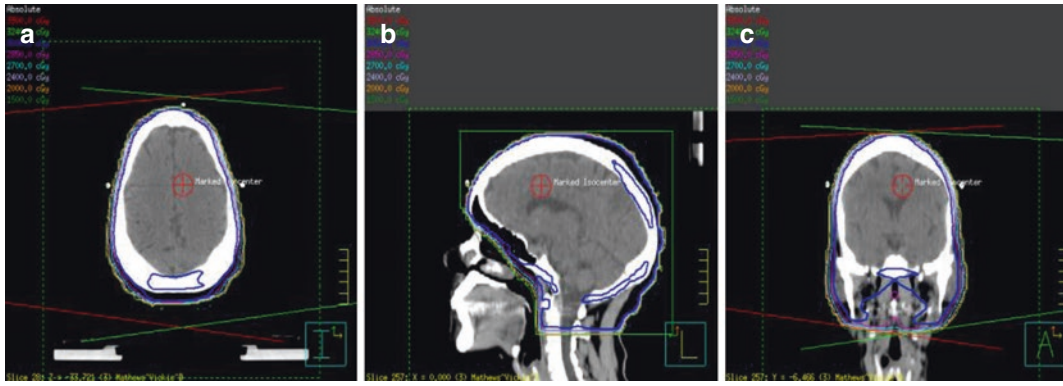

Fig. 29.1 Example of a whole brain radiation therapy plan with a dose prescription of 30 Gray in ten fractions. The three panels below represent cuts from the simulation Computed Tomography (CT) scans with isodose lines – Transverse (**a**), sagittal (**b**) and coronal (**c**) views

SRS is responsible for gross disease control. Even the role of WBRT in palliation (in patients who are not a candidate for surgical resection or SRS) has been challenged in the recent British QUARTZ trial, as optimal supportive care proved to be non-inferior [82].

Stereotactic Radiosurgery

Stereotactic radiosurgery is a form of local radiotherapy that precisely delivers a single high dose of radiation using multiple beams of high-energy x-rays, gamma rays, or protons that converge on a discrete treatment volume, while maximally sparing/minimizing the irradiation to the adjacent normal brain parenchyma and other surrounding normal structures [83] (Fig. 29.2).

SRS alone, when used for the treatment of brain metastases, is not associated with as many neurocognitive side effects as WBRT. Also, the number of metastases treated with SRS seems not to correlate with the extent of the decline in NCF. In a Japanese study comparing outcomes of patients with 1 (group A), 2–4 (group B), and 5–10 brain metastases (group C) treated with SRS, the incidences of MMSE deterioration were low overall and were not significantly different between the three groups. MMSE score was maintained in 92%, 91% and 89% of patients in groups A, B, and C, respectively [84].

Adding WBRT to SRS is associated with better local control and distant intracranial control, but not with improved overall survival as compared to SRS alone [79, 85]. It is, therefore, important to know whether this local control benefit outweighs the possible neurocognitive side effects of adding WBRT. Table 29.1 outlines the studies that compare neurocognitive side effects from SRS to those from WBRT with or without SRS.

In a randomized controlled trial of 58 patients at MD Anderson Cancer Center, those who received WBRT plus SRS showed a significantly greater decline in HVLT-R Total Recall at 4 months than patients treated with SRS alone (52% versus 24%, respectively), a difference which persisted at the 6-month follow-up. These patients also had a greater drop in executive functioning as compared to patients randomly assigned to the SRS alone arm [86]. These findings suggest that even though patients treated with SRS alone had higher rates of recurrences in the brain, WBRT neurotoxicity (a decline in verbal learning and memory) appeared to be worse than the cognitive decline associated with recurrences, as long as close surveillance with early diagnosis of recurrent brain metastases was performed.

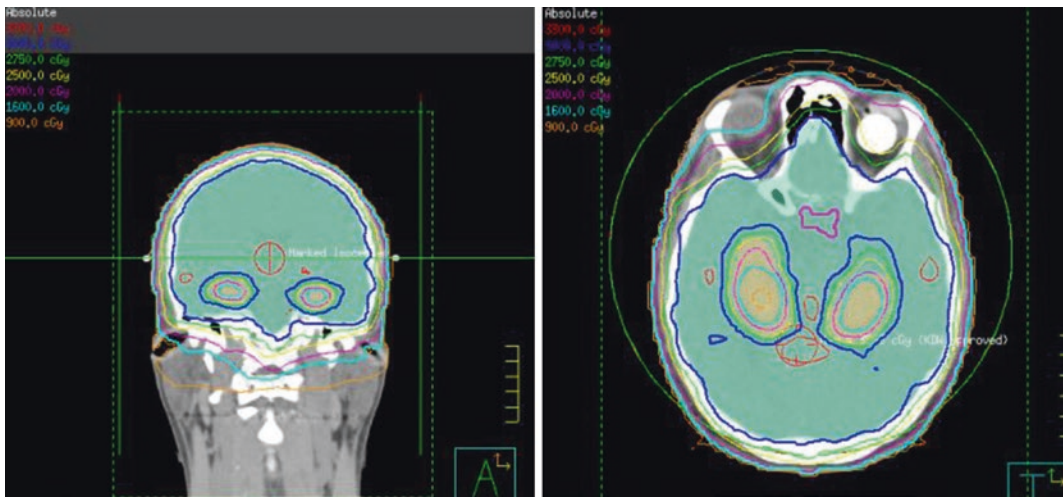

Fig. 29.2 Example of a hippocampal avoidance whole brain radiation therapy plan using intensity-modulated radiation therapy

Table 29.1 Neurocognitive side effects of stereotactic radiosurgery (SRS) versus whole brain radiation therapy (WBRT) alone or with SRS

	Study population	SRS dose	WBRT dose	Instrument for cognitive testing	Definition of the endpoint of cognitive deterioration	Results with SRS	Results with SRS + WBRT	Results with WBRT
Brown et al. 2016 [85]	213 patients with 1–3 brain metastases (no surgical resection)	18–22 Gy	30 Gy in 12 fx	Learning and immediate memory (HVLT-R Immediate Recall) Fine motor control (Grooved Pegboard Test) Verbal fluency (COWAT) Processing speed (TMT part A) Executive function (TMT part B) Delayed memory (HVLT-R delayed recall) Recognition (HVLT-R recognition)	Decline >1 SD from baseline on at least 1 cognitive test at 3 months	63.5% at 3 months	91.7% at 3 months	–
Chang et al. 2009 [86]	58 patients with 1–3 brain metastases (no surgical resection)	15–20 Gy	30 Gy in 12 fx	HVLT–R total recall	Deterioration (5-point drop compared with baseline) in HVLT-R total recall at 4 months	24% at 4 months	52% at 4 months	–
Aoyama et al. 2006 [88]	28 patients with 1–3 brain metastases (no surgical resection)	18–25 Gy	30 Gy in 10 fx	MMSE	Median MMSE change between pre- and posttreatment	Pretreatment MMSE: 27 Posttreatment MMSE: 28	Pretreatment MMSE: 28 Posttreatment MMSE: 27	–
Soffietti et al. 2012 [89]	341 patients with 1–3 brain metastases (no surgical resection)	25 Gy	30 Gy in 10 fx	Cognitive functioning as part of the EORTC QLQ-C30 (used as an HRQOL measure)	Differences between the two treatment arms for all post-baseline time points	10.7-point difference in cognitive function at 12 months between the two treatment arms, in favor of SRS alone (statistically significant)		–

(continued)

Table 29.1 (continued)

	Study population	SRS dose	WBRT dose	Instrument for cognitive testing	Definition of the endpoint of cognitive deterioration	Results with SRS	Results with SRS + WBRT	Results with WBRT
Aoyama et al. 2007 [31]	92 patients with 1–4 brain metastases (no surgical resection)	18–25 Gy	30 Gy in 10 fx	MMSE	3-point drop in the MMSE	59.3% at 1 year, 51.9%, at 2 years and 51.9% at 3 years The average duration until deterioration was 7.6 months	76.1%, at 1 year, 68.5%, at 2 years and 14.7% at 3 years The average duration until deterioration was 16.5 months	–
Brown 2017 [79]	213 patients with total/subtotal resection of a single BM	12–20 Gy	30 Gy in 10 fx or 37·5 Gy in 15 fx	Learning and immediate memory (HVLT-R Immediate Recall) Verbal fluency (controlled Oral word association test) Processing speed (TMT part A) Executive function (TMT part B) Delayed memory (HVLT-R delayed recall) Recognition (HVLT-R recognition)	Decline >1 SD from baseline on at least 1 cognitive test at 3 months	52% at 6 months		85% at 6 months
Kepka 2016 [80]	59 patients with total/subtotal resection of a single BM	15 Gy	30 Gy in 10 fx	MMSE	3-point drop in the MMSE	4.5% at 6 months		11% at 6 months

Abbreviations: SRS stereotactic radiosurgery, *WBRT* whole brain radiation therapy, *Gy* gray, *fx* fractions, *SD* standard deviation, *HVLT-R* Hopkins Verbal Learning Test–Revised, *COWAT* Controlled Oral Word Association Test, *TMT* Trail Making Test, *MMSE* Mini-Mental State Examination, *EORTC QLQ-C30* EORTC Quality of Life Questionnaire C30, *HRQOL* health-related quality of life

In the postoperative setting, a randomized trial of adjuvant WBRT vs. SRS also demonstrated better intracranial control with postoperative WBRT, at the expense of a greater cognitive decline associated with WBRT that persisted at the 12-month follow-up visit [79].

These randomized trials clearly demonstrate that WBRT compromises neurocognition more than SRS, without yielding a survival benefit [86–88]. It is thus reasonable to consider SRS first when a patient presents with a limited number of brain metastases and reserve WBRT as a last resort after the failure of one or several courses of SRS and surgical salvage. While SRS controls gross disease, systemic therapy might also be needed to control microscopic disease in the brain. A strategy of close follow-up and regular high-quality neuroimaging to detect recurrences is preferred nowadays over more aggressive treatment and is consistent with the trend towards personalized treatment. It is, however, dependent on the patient and medical team's willingness to adhere to a strict follow-up schedule.

It is difficult to quantitatively combine results from these different studies, as they use different definitions of neurocognitive deterioration and time to assessment, as well as different assessment methods, each with a different sensitivity. One study used self-reported measures, namely the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 [89]. The Japanese studies [31, 88] used a mini-mental status examination to compare cognitive outcomes between the different treatment modalities. Data from these studies should be interpreted with caution, as self-reporting and actual formal cognitive testing are poorly correlated, and MMSE has been deemed not sensitive enough in a brain tumor population [90]. The Food and Drug Administration (FDA) stated that objective assessment is preferred to subjective self-report in neuro-oncology, due to the challenges in assessing patient-centered outcomes in individuals with malignant brain tumors [91]. A battery of standardized neuropsychological tests is now recommended in clinical trials reporting on cognitive function, and this is what more recent studies are using [79, 85, 86, 92]. Table 29.2 lists a brief, core battery of neurocognitive tests that has been deemed appropriate for the clinical trial setting in patients with both CNS and non-CNS cancers [92, 93]. While not an exhaustive list of tests that would be appropriate for use with this patient population, these measures have been found to have appropriate psychometric properties and are sensitive to the effects of the tumor and anticancer treatment on the domains of memory and learning, information processing speed, and executive function.

Table 29.2 Clinical trial battery of neurocognitive tests recommended for cognitive function assessment in patients with brain metastases

Cognitive Domain	Test
Learning & Memory	Hopkins Verbal Learning Test-Revised (HVLT-R) [165]
Verbal fluency	Controlled Oral Word Association [166]
Executive functioning	Trail Making Test Part B [167, 168]
Information processing speed	Trail Making Test Part A [167]

The mechanisms underlying this differential neurotoxicity of SRS versus WBRT have been investigated using MRI. It has been found that delayed white matter leukoencephalopathy is very common in patients treated with WBRT, reported in up to 97% of patients [94, 95], whereas its incidence is much lower (1–3%) in patients treated with SRS [84, 94].

Neurotoxicity in the Setting of Prophylactic Cranial Irradiation

Studying the effect of prophylactic cranial irradiation (PCI) on cognitive function can help disentangle CNS toxicity inherent to the presence of CNS disease from the effect of radiation therapy itself.

PCI is considered standard of care in SCLC based on an individual patient data meta-analysis in limited-stage SCLC [96], and a seminal trial in extended-stage SCLC [97], showing an overall survival benefit with the use of PCI. The role of PCI in non-small-cell lung cancer (NSCLC) is

not as straightforward; no overall survival benefit has been demonstrated in the different randomized controlled trials randomizing patients with NSCLC to PCI versus no PCI [98–103], although a meta-analysis indicated a disease-free survival benefit in a subset of patients [104].

Late neurological complications from PCI have only been formally studied in three trials [103, 105, 106]. In RTOG 0214, a trial that randomized 340 patients with stage III NSCLC to PCI or no PCI, there was a trend toward a greater decline in patient-reported cognitive functioning in the PCI arm. There was no significant difference in MMSE scores between the two arms, except at 3 months. The only significant difference in the NCF analysis was in the Hopkins Verbal Learning Test (HVLT): patients who were treated with PCI had significantly greater deterioration in learning and memory at 1 year as compared to patients in the observation arm. There were no significant differences in QoL between the patients who received PCI and those who did not [105], unlike the sequential association between NCF decline and QoL deterioration noted earlier in this chapter in the setting of WBRT for brain metastases.

The RTOG 0212 trial randomized 265 patients with limited stage-SCLC and a complete response after chemotherapy and thoracic RT to either standard-dose PCI (25 Gy in 10 fractions) or higher-dose PCI (36 Gy). The 36 Gy cohort was secondarily randomized to receive PCI in either18 fractions of 2 Gy or twice daily in 24 fractions. Detailed neuropsychological test batteries were carried out on the study population. The baseline assessments prior to PCI demonstrated abnormalities in multiple parameters including language, visual and spatial scanning, attention, sequencing, and speed. Chronic neurotoxicity in this study was defined as the deterioration in at least one of the six cognitive domains without the development of brain metastasis at 12 months. The incidence of chronic neurotoxicity was significantly higher in patients treated with 36 Gy compared with 25 Gy (85 and 89% versus 60%, respectively, $p = 0.02$) [106].

A study by Gondi et al. pooled QoL and NCF results from the two RTOG randomized studies mentioned above: RTOG 0214, and RTOG 0212 [107]. As compared to observation, PCI was associated with a significant threefold higher risk of decline in self-reported cognitive functioning at 6 months and 12 months. PCI was also associated with a significant decline in HVLT-Total Recall and HVLT-Delayed Recall at 6 and 12 months. Interestingly, the decline in HVLT and decline in self-reported cognitive functioning were not closely correlated [108].

Radiation-Induced Neuroxoticity: Timeline and Risk Factors

Sheline's report in the 1980s was the first to subdivide radiation-induced brain injury into acute (early, during radiation), subacute (up to 6 months postradiation therapy), and late effects (chronic, more than 6 months postradiation therapy) [109, 110].

Acute encephalopathy, consisting of headache, nausea, vomiting, and fever with onset during treatment, occurs almost exclusively if a high dose per fraction is used, and not with the conventionally used dose of 3 Gray or less per fraction [111, 112]. This acute effect has been linked to edema formation secondary to blood–brain barrier disruption, due to apoptosis of endothelial cells [113–116]. Corticosteroids can help in treating these symptoms.

Subacute complications include somnolence syndrome, whose symptoms are transient and include excessive sleepiness, drowsiness, and anorexia, and are mainly documented in children receiving PCI for ALL [117, 118], or in adults receiving definitive doses of radiation therapy (45–55 Gray) for primary brain tumors [119, 120]. Another subacute effect is impairment in verbal memory function 6–8 weeks after PCI completion as demonstrated by Welzel et al. [121].

Late or chronic effects are the most dreaded of all radiation-induced injuries, as they are usually irreversible. Molecular mechanisms underlying the development of these chronic effects are inflammation [122, 123], hypoxia with vascular endothelial growth factor upregulation [124,

125], and neurogenesis inhibition [126]. This cascade of events can lead to radiation-induced demyelination and leukoencephalopathy that can occur months to years after irradiation [110], as well as radiation necrosis [127]. In long-term SCLC survivors, PCI has been shown to result in progressive ventricular dilatation or cerebral atrophy up to 8 years after therapy completion, as well as a slow decline in NCF [128, 129].

The incidence and severity of radiation-induced toxicities do not only depend on radiation dose but also depend on some patient-related factors, such as age, chemotherapy and existing comorbidities [110]. In RTOG 0212, age (>60 years) was the most significant predictor for the development of chronic neurotoxicity (p value = 0.005) [106]. Preexisting medical conditions, such as hypertension, have also been shown to accelerate vascular radiation damage [18].

Some patients may also have a genetic predisposition to develop more treatment-related neurocognitive toxicities. Based on the premise that the APOE e4 allele confers an increased risk of Alzheimer's disease, a retrospective analysis of RTOG 0614 evaluated the relationship between APOE e4 carrier status and NCF after treatment with WBRT in patients with brain metastases. Carrying the APOE e4 allele was shown to be a risk factor for worse memory function after treatment with WBRT (with or without memantine) [130].

Strategies to Mitigate Neurotoxicity

Some strategies have been tested to potentially mitigate the neurocognitive complications of brain irradiation [131]. One of them is the use of neuroprotective drugs, such as angiotensin-converting enzyme inhibitors [132], angiotensin type-1 receptor blockers [133], erythropoietin [134], and lithium [135, 136], all of which have been tested in vivo. Two of these potential neuroprotective drugs, memantine and donepezil, deserve special mention, as they have both been investigated in phase III clinical trials. The effectiveness of memantine, an N-Methyl-D-aspartate (NMDA) receptor antagonist, in preventing cognitive dysfunction has been tested in the phase III trial, RTOG 0614. There was a trend toward less decline in the primary endpoint of HVLT-R Delayed Recall at 24 weeks with memantine as compared to placebo, but this result did not reach statistical significance (p-value = 0.059), probably because of significant drop out, resulting in statistical power of only 35%. The patients on the memantine arm had a significantly longer time to cognitive decline, and better results in executive functioning and processing speed [137]. Donepezil, a reversible acetylcholine esterase inhibitor, has also been tested for its ability to improve cognitive dysfunction in a phase III trial in 198 adult brain tumor survivors, and although it did not show significant improvement in the overall composite cognitive score (primary endpoint), it showed significant benefit over placebo in some specific cognitive functions, such as memory, as well as motor speed and dexterity [138]. One of the limitations of this study was the low dose of donepezil used (10 mg/day), given that studies on patients with moderate-to-severe Alzheimer's disease showed significantly greater cognitive benefits with higher doses of donepezil 23 mg/day than donepezil 10 mg/day [139].

Another strategy to avoid cognitive dysfunction, and more specifically short-term memory loss, is hippocampal avoidance whole-brain radiation therapy (HA-WBRT) (Fig. 29.3). It uses conformal radiation therapy to avoid neural stem cells in the hippocampal dentate gyrus, which are mitotically active and radiosensitive, and are responsible for the formation of new memories [126, 140, 141].

This technique was tested in the phase II cooperative trial RTOG 0933, which showed significant memory preservation with hippocampal avoidance cranial irradiation, whereby relative decline in Hopkins Verbal Learning Test-Revised Delayed Recall at 4 months was 7% in the experimental arm, which was significantly lower than prespecified historical control of patients with brain metastases treated without hippocampal avoidance [142]. NRG-CC001 examined the combined use of HA-WBRT + memantine versus WBRT + memantine in patients with brain metastases. Recently reported results demonstrated a delay in the time to neurocognitive

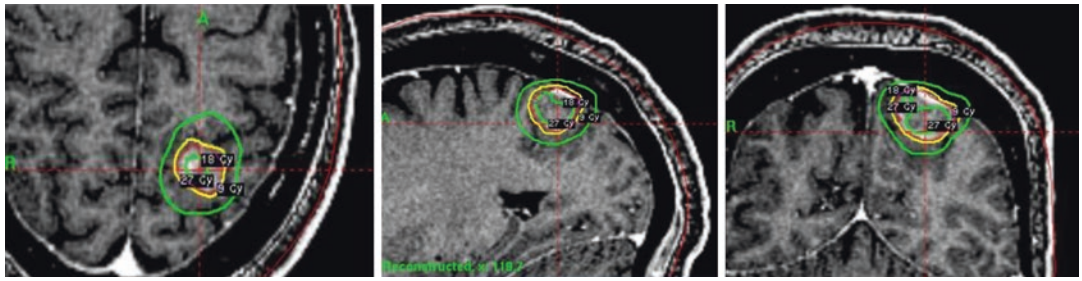

Fig. 29.3 Example of a stereotactic radiosurgery plan using Gamma Knife for a left parietal lesion, treated with a prescription dose of 18 Gy to the 50% isodose line

decline in the HA-WBRT + memantine arm with no difference in OS or PFS [143]. Two ongoing trials, NRG-CC003 (ClinicalTrials.gov Identifier: NCT01780675) and the Spanish PREMER trial (NCT02397733) [144], are currently examining the role of hippocampal avoidance in the setting of PCI for SCLC specifically.

Behavioral interventions have also been attempted to mitigate treatment-related neurocognitive impairment. Cognitive rehabilitation consists of clinic-based therapeutic programs designed to improve cognitive skills and functional capacity [145]. While to our knowledge these strategies have not been studied in patients with brain metastases specifically, there is evidence to suggest benefit in cancer patients, including those with brain tumors [146–148].

Studies have reported improvement in executive function, working memory, processing speed, and attention with the use of cognitive behavioral therapy among other interventions focused on self-awareness, mindfulness, and meditation [149–153]. A home-based, computerized Lumosity program has also been tested successfully in breast cancer survivors to improve executive function, processing speed, and verbal fluency [154], while patients with primary brain tumors failed to comply with the intervention and did not demonstrate improvements in cognitive function [155].

Limitations of the Existing Literature and Future Directions

In the development of new therapeutic agents, the endpoint of NCF is gaining increasing popularity, and the search for drugs that delay neurocognitive deterioration, without necessarily improving survival, is also on the rise. The new studies outlined in this chapter are helping in shaping better risk-versus-benefits evaluations for interventions targeted against brain metastases.

Although treatment-related cognitive deficits are being increasingly reported in clinical trials on cancer patients with brain metastases, their incidence and patterns are sometimes inconsistent between studies. This can be explained by different factors, such as the heterogeneity of the patient population included, the wide range of treatment modalities used, the different cognitive tests employed, and the various statistical methods used to measure and report neuropsychological changes (some more sensitive than others) [156, 157]. Some studies rely on self-reporting instead of objective neurocognitive testing. Self-reporting is problematic, as patients with cognitive impairments may not be fully aware of the extent of their cognitive problems [158]. Moreover, testing at baseline is not always available but it is critical to assess the effects of anti-cancer agents. Some studies have also struggled with patient compliance when it comes to follow-up neurocognitive testing [89], though feasibility of repeated neurocognitive assessment in this patient population has been demonstrated [86].

It is, therefore, difficult to draw meaningful conclusions when pooling these studies together. To make this task easier in the future, there is a need to make the tools used to evaluate cognition uniform across studies and to enforce a battery of validated tools. In light of these challenges, the "International Cognition and Cancer Task Force" was created and issued recommendations to harmonize studies of cognitive function in cancer patients [92]. The core

clinical trial battery represented in Table 29.2 and endorsed by the ICCTF was also endorsed by the RANO group [92, 159–163].

As brain function is multifaceted and subject to subtle changes over time, capturing it through formal and standardized neurocognitive testing is critical. The same battery of tests should be used consistently across studies, as a sensitive measure of brain functioning [90]. Improving the way the endpoint of NCF is reported can be critical, as a study has demonstrated that cognitive deterioration can precede radiological evidence of progression by around 6 weeks in patients with primary brain tumors [164]. Whether this finding can be extrapolated to patients with brain metastases remains to be studied.

As new therapies are currently revolutionizing cancer treatment, and allowing patients with brain metastases to live longer, the concern for delayed neurotoxicity is all the more real, and strategies to delay or prevent this life-altering morbidity all the more important. More efforts in the field of genetic characterization of brain metastasis should be deployed, which could permit the identification of actionable mutations and allow treatment personalization. In the future, this approach should be favored over the "one-size-fits-all" strategy.

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Part IV

Surgical Treatment of Brain Metastasis

30 The Role of Surgery in the Management of Brain Metastases

Jeffrey I. Traylor, Aditya Srivatsan, Rajan Patel, Rohan Ramakrishna, and Ganesh Rao

Background and Overview

Brain metastases are a devastating cause of cancer morbidity, comprising more than half of all intracranial malignancies. In the United States, brain metastases occur in more than 100,000 people each year, affecting between 10% and 30% of all patients with systemic malignancy [1]. Additionally, 2% of all cancer patients as well as 12.5% of patients with systemic disease will have brain metastases discovered at diagnosis [2]. Within this patient population, the most common underlying tumors are lung cancer (28%), melanoma (21%), and renal carcinoma (19%) with numerous other primary tumors contributing to the annual incidence [3].

The development of brain metastases represents a terminal stage in the management of the primary tumor with a prior median survival of 5 months from diagnosis [2]. However, there have been numerous advancements in the treatment of this disease process and median overall survival rates are now demonstrating a significant increase. Though a host of factors contribute to the overall outcome and response to treatment, management of these patients may be divided into four categories: systemic radiation, whole-brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and surgical resection. It also should be noted that newer targeted and immunotherapies have demonstrated efficacy for brain metastases as well [4–6]. Trials in the last two decades have illuminated primary prognostic factors that contribute to an overall management plan, including baseline neurologic status, often measured by the Karnofsky Performance Scale (KPS), combined performance status, and tumor histology measured by the Graded Prognostic Assessment (GPA), age (<65 years), and control of the primary malignancy [7]. Based on these and other variables, a combined therapeutic regimen may optimize patient outcomes.

Surgical resection has held a defined role in the management of brain metastases since the early 1990s. Since that time, numerous advances have been made in neurosurgical techniques with additional trials investigating the efficacy of this treatment option. A seminal study was reported in 1990, when Patchell et al. compared resection followed by WBRT to biopsy and WBRT in patients with a single brain metastasis. In addition to demonstrating improved survival in the combined treatment cohort, the authors reported an increased rate of local tumor control in the group undergoing resection [8]. The next major trial was completed 3 years later with a slightly

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larger cohort of 63 patients with single brain metastases showing similar findings. The authors reported increased survival in the cohort receiving combined resection and WBRT but also established that surgery was most beneficial for patients with stable extracranial disease [9]. Conversely, Mintz et al. reported no survival benefit for surgical resection of brain metastases in a 1996 trial [10]. However, these findings have since been disputed as a higher proportion of the cohort had significant extracranial disease and lower neurologic baseline than the subjects of preceding trials.

Studies have investigated the role of surgery in multiple and recurrent brain metastases. Wrónski et al. reported no outcome difference in patients with single and multiple cerebral metastases, and Iwadate and colleagues published comparable findings [11, 12]. Similarly, studies have revealed a survival benefit for reoperation in patients with tumor recurrence, further demonstrating the applicability and efficacy of surgical resection in this patient population [13–15]. More recent research has investigated the benefit of novel surgical techniques, incorporating stereotactic guidance as a means of more precise margination, advanced imaging sequences capable of delineating critical white matter structures, and the utility of surgery under awake conditions for tumor resections in eloquent cortical regions to minimize postoperative neurologic deficits [16].

Surgical resection for cerebral metastasis has become a mainstay for lesions that are accessible and of sufficient size to warrant removal. More recently, it has been established there may be a role for tissue sampling of brain metastases in an effort to genomically characterize these lesions as they can often be distinct from the primary tumor with brain-specific targetable mutations (this is not standard of care, however) [17]. Depending on the proximity of the tumor mass to eloquent cortical and subcortical structures, surgery carries a risk of worsening pre-existing neurologic deficits in addition to risks of hemorrhage and infection associated with any operative procedure. Even with these risks, neurosurgery for patients with the appropriate indications has been associated with shorter hospitalizations and overall improved neurologic outcomes.

Presurgical Evaluation

Cerebral metastases have numerous clinical manifestations and should be suspected in patients with underlying malignancy with neurologic symptoms or behavioral changes. In these patients, both mass effect and cerebral edema play a role in symptomatology. The tumor can compress adjacent structures resulting in corresponding neurologic deficits. Additionally, the cumulative mass of these lesions can further displace cerebral tissue and increase intracranial pressure. Should these masses interfere with normal cortical depolarization, new-onset epilepsy can occur which is often a presenting symptom. Vasogenic edema resulting from tumor disruption of the blood–brain barrier, allowing proteinaceous fluid into the extracellular space, is another mechanism by which metastatic lesions can contribute to increased intracranial pressure (Fig. 30.1). Yet another rare manifestation of intracranial spread of underlying malignancy is stroke, as the tumor can compress cerebral vasculature or hemorrhage. However, even within this high-risk patient demographic, the rates of brain metastases among those with new-onset neurologic symptoms are low, highlighting the importance of additional imaging and evaluation for underlying disease before establishing a concrete diagnosis [18]. More oncologists are recognizing the elevated risk of specific cancers to metastasize to the brain (e.g., lung and melanoma) and are frequently screening patients for brain metastases at initial presentation. Further, prophylactic cranial irradiation may be indicated with certain cancers that have an especially high risk of presenting with brain metastases (e.g., small-cell lung cancer).

Prognosis

The prognosis of a patient with brain metastases has a significant influence on the decision for operative intervention. Evaluation of a neurologic baseline is another important factor in determining whether surgery will improve the quality of life. To date, clinical trials have demonstrated better outcomes for patients with

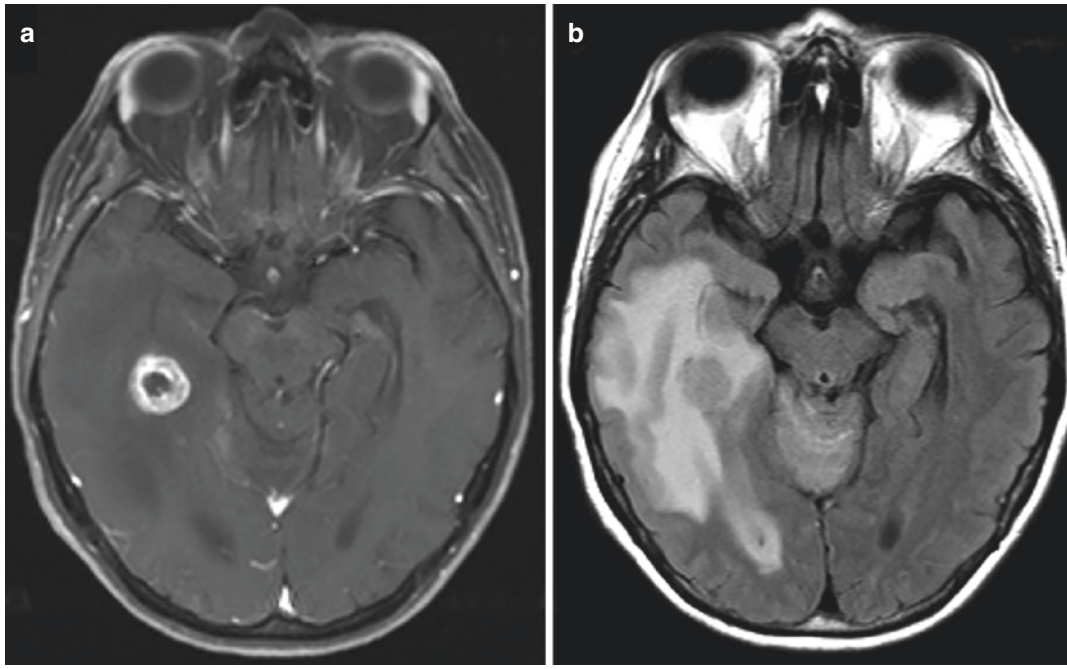

Fig. 30.1 (**a**) Axial T1-weighted postcontrast MRI of a temporal lobe metastasis. (**b**) Axial FLAIR MRI demonstrating significant perilesional edema

stable extracranial disease and good neurological function (usually defined as KPS ≥ 70). Other factors that contribute to operative management include surgical accessibility of the metastasis and lesion-induced deficit, with the potential for dramatic improvement in patient quality of life. Though Sawaya et al. first demonstrated the feasibility of resection of tumors in more critical cortical structures (e.g., the "eloquent" brain), deep-seated tumors in proximity to corticospinal or corticobulbar tracts are less amenable to resection with a high risk of worsened neurologic dysfunction [19]. Likewise, patients with poor prognoses and low KPS are less suitable for surgery and are conventionally managed with radiation, although the specific modality may vary depending on the size and number of lesions [20]. It is important, however, to distinguish poor performance status that results from symptomatic brain metastases versus poor performance status from systemic disease. The former may benefit from surgical excision while the latter may not.

Preoperative Risk Assessment

A preoperative risk assessment is crucial for determining surgical candidacy as the risks of undergoing a craniotomy must be weighed against the potential benefits of relieved tumor burden. Assessment of cardiovascular health to prevent intraoperative blood pressure fluctuations and myocardial ischemia as well as evaluation of baseline respiratory function is essential to good surgical outcomes and efforts should be made to optimize the function of these organ systems. Hyperglycemia has also been reported to increase perioperative morbidity after neurosurgical procedures and must be adequately controlled in advance of surgery and kept between 100 mg/dL and 150 mg/dLperioperatively[21, 22]. Reductions in hepatic and renal function also contribute significantly to surgical morbidity and must be properly evaluated. Clinical decision-making tools can provide insight into the feasibility of surgical management for patients with underlying organ disease [23]. Renal function also has implications on fluid and electrolyte

homeostasis and thus modulates the approach to maintenance of blood volume and osmolarity. This is especially significant for neurosurgical procedures where changes in plasma tonicity greatly influence cerebral volume. Additionally, the presence of peritumoral edema must be recognized and is generally managed with glucocorticoids to reduce the severity of neurological deficit or headache (Fig. 30.2). Evidence of significant intracranial pressure may require admission and more aggressive management including the administration of mannitol or hypertonic saline.

Surgery Versus Radiation

The decision to pursue radiation or surgery in the management of brain metastases often depends

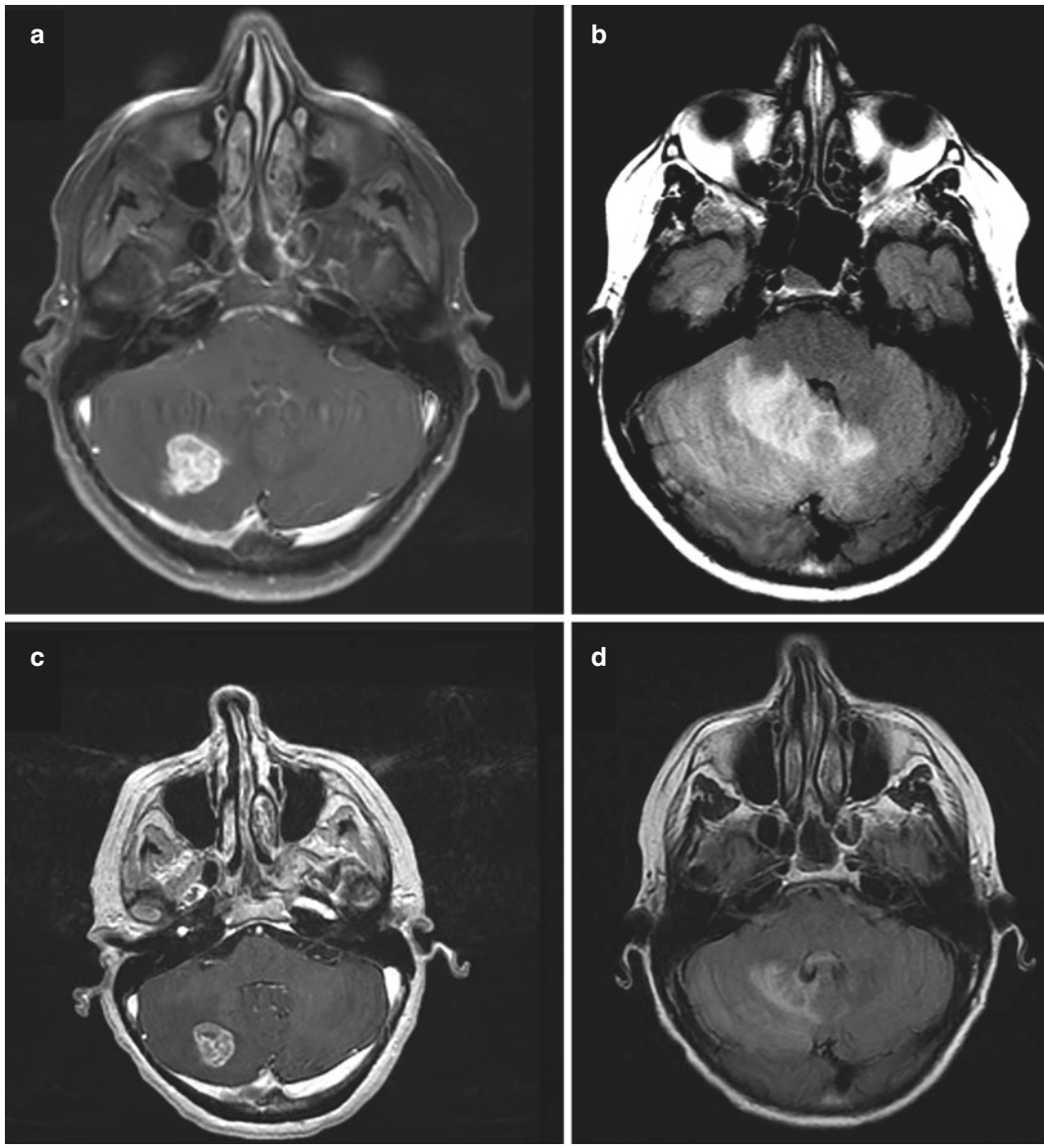

Fig. 30.2 (**a**) Axial T1-weighted postcontrast MRI of a right cerebellar metastasis from lung cancer. (**b**) Axial FLAIR MRI demonstrating significant perilesional edema with mass effect on the fourth ventricle. (**c**) After 10 days of dexamethasone, the lesion is considerably less edematous on axial T1-weighted postcontrast MRI and (**d**) axial FLAIR image showing less mass effect on the fourth ventricle

upon numerous factors including but not limited to tumor size, number, accessibility, and patient condition. As mentioned above, sometimes surgery can be utilized for brain metastasis sampling in an effort to identify unique, targetable mutations in patients with multiple lesions. In general, surgery is first-line therapy for single brain metastases of sufficient size to warrant resection, which may be 2 cm or greater. However, for lesions smaller in size or in locations not amenable to resection such as in close proximity to eloquent cortex, other approaches are utilized. Stereotactic radiosurgery (SRS) is another technique for treatment that is less invasive than conventional resection techniques. Though this therapy has emerged as an alternative to resection for cerebral metastases, particularly for small, deep-seated lesions, there is debate as to whether or not SRS is superior for single lesions less than 3.5 cm [23]. Multiple retrospective cohort studies have reported similar survival outcomes between the two while a study by Bindal and colleagues reported significantly longer survival times and reduced incidence of death from neurologic causes with surgical resection [13]. A prospective phase III trial comparing these modalities concluded SRS to have similar local tumor control to combined resection and WBRT, but with significantly less distant tumor control, though the study was prematurely discontinued due to inadequate patient accrual [24].

WBRT is often used as an adjunctive therapy with surgery or SRS, though it remains the treatment of choice for patients with numerous metastatic lesions. Altogether, WBRT has become less utilized as a single therapy as it may not improve overall survival [25]. Additionally, studies have demonstrated that WBRT advances cognitive decline in this patient population which also contributes to further selective implementation [26, 27]. In the context of this combined evidence, WBRT often serves as an alternative for poor surgical candidates and those with high intracranial tumor burden not amenable to more localized techniques.

Within the scope of operative therapy for brain metastases, there is a newly described, minimally invasive surgical technique: laser interstitial thermal ablation therapy (LITT). Though the concept for LITT has existed for decades, only recently has this technique been applied to the management of neurosurgical disorders, including brain metastases [28, 29]. However, because this therapy is relatively new, it is primarily utilized for the ablation of deep-seated tumors that are less accessible to standard resection techniques or in the management of recalcitrant radiation necrosis. It is typically not used in the management of newly diagnosed brain metastases.

Intraoperative Management

Stereotactic Navigation

Stereotactic navigation is a minimally invasive method for precisely locating targets of interest based on a three-dimensional (3D) coordinate system. Though the concept for this technique has existed for over a century, advances in imaging sequences and delivery systems have made stereotaxy an integral part of numerous neurosurgical procedures requiring anatomical precision. Initially, this technology was frame-based requiring application of a stereotactic frame to the patient's head. In recent years, frameless systems have been developed with increasing sophistication allowing the surgeon to register the volumetric MRI scan to the patient's head at the beginning of surgery. During the operation, the 3D coordinates of the navigation probes and registered instruments will be superimposed on preoperative imaging on the navigation suite screen in multiple planes. Throughout the operation, the surgeon will be able to reference the precise location of instruments to anatomical landmarks in real time in order to minimize collateral damage to adjacent structures and the associated morbidity. Additionally, the ability of modern stereotactic delivery systems to register compatible instruments has made it a core component of the LITT procedure; the precision offered by stereotaxy allows for real-time guidance of the ablation probe to the intracranial target.

Technological advances in the last two decades have made surgical resection a safer and more reliable option for the management of cerebral

metastases. These advances have spurred new research into the incorporation of these technologies into cerebral tumor resection and thus augmented the role of the neurosurgeon in the management of these patients. Advanced magnetic resonance imaging (MRI) sequences, real-time intraoperative imaging guidance, and novel cortical mapping techniques have all contributed to the modern landscape of neurosurgical oncology.

Functional MRI (fMRI)

The use of imaging for intracranial tumors is paramount to diagnosis, preoperative procedural planning, and postoperative surveillance. Increasingly available for preoperative assessment, functional MRI (fMRI) measures metabolic cerebral activity. The basis for fMRI is the quantification of changes in blood flow corresponding to neural depolarization based on the variable magnetic properties of hemoglobin depending on oxygen concentration, called blood oxygenation level-dependent (BOLD) imaging[30]. With conventional fMRI, the patient will perform tasks during a preoperative fMRI in order to map the corresponding cortex. These images are then closely referenced to the patient intraoperatively to avoid damaging cerebral loci critical to speech as well as motor planning and execution. Subsequent stereotactic navigation can then be superimposed on these images with real-time guidance for optimized procedural execution, based on these demarcated cortical and subcortical boundaries [31]. Though fMRI has advantages in being noninvasive, it is not as accurate as other techniques and thus cannot be solely relied upon for mapping cortical structures. Specifically, fMRI has a reported sensitivity and specificity of 61.7% and 93.7%, respectively, for motor mapping [32]. Although some studies have reported predictive value for language "lateralization" with fMRI, others have found significant discordance between fMRI and the gold standard Direct Cortical Stimulation (DCS) for cortical speech area mapping with sensitivities <60% [33, 34].

Diffusion Tensor Imaging (DTI)

Diffusion tensor imaging (DTI) is another MRI sequence that detects small movements of water molecules and is particularly useful for delineating critical white matter tracts, such as the corticospinal tract and arcuate fasciculus, due to their unique directionality; water molecules are more displaced along the directionality of the axon fiber than in the perpendicular direction [35]. Intraoperatively, DTI has been used to reduce postoperative neurologic morbidity by minimizing damage to these critical white matter tracts. By clearly visualizing these white matter bundles, surgeons can avoid their transgression intraoperatively [36]. Unlike fMRI, DTI does not rely on task-oriented feedback to display axon bundles. Instead, this unique MR sequence delineates critical subcortical white matter structures that can be superimposed on a neuronavigation model for real-time stereotactic feedback (Fig. 30.3). Though DTI mapping of white matter structures has been shown to improve the extent of resection and minimize postoperative neurologic deficits in patients with high-grade gliomas, there is much less utility and research into this modality for patients with brain metastases [37]. Because primary brain tumors, particularly high-grade ones, have a propensity to infiltrate neighboring white matter structures, DTI is often used to assess the extent of invasion and guide subsequent resection. On the other hand, intracranial metastases are better circumscribed and less likely to infiltrate adjacent neural tissue, making DTI less valuable in this patient population. Nevertheless, DTI remains a tool at the neurosurgeon's disposal for delineating nearby white matter structures at risk of damage during operative resection.

Transcranial Magnetic Stimulation (TMS)

Unlike fMRI and DTI, transcranial magnetic stimulation (TMS) is a method for cortical and subcortical mapping that does not rely on imaging data. Instead, TMS provides mapping

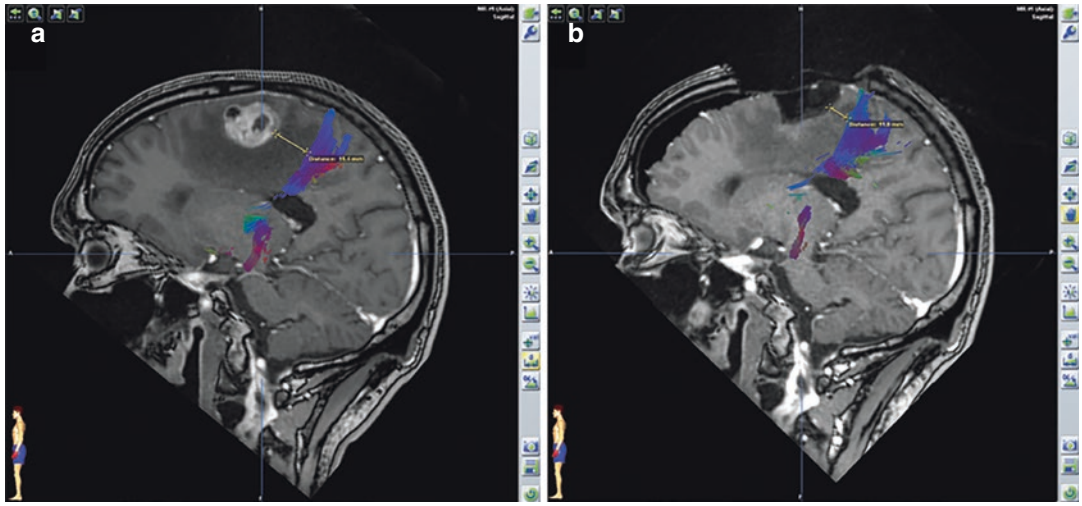

Fig. 30.3 (**a**)Sagittal T1-weighted postcontrast MRI demonstrating the proximity of a metastatic lesion to the descending corticospinal tract. (**b**) Post-resection, the distance between the tract and the resection cavity is reduced. The tract demonstrates continuity

information to neuronavigational models by correlating magnetic stimulation of cortical foci with motor activation. Thus, cortical mapping information is based on the response to TMS at various extracranial loci. Though TMS has existed for decades, it was not until it was combined with neuronavigation software suites (nTMS) that studies began to investigate its efficacy. Subsequent articles have reported significant accuracy in mapping the motor cortex in patients with primary brain tumors when compared to direct cortical stimulation (DCS) of these regions intraoperatively, thus making it a noninvasive and precise cortical mapping option for surgery on the eloquent cortex [38]. Later studies in patients with brain metastases have echoed these results expanding the potential role of this mapping technique [39].

Electrocorticography

Brain mapping during surgery under awake or asleep conditions offers the benefit of direct and immediate feedback on critical neurologic parameters such as language or motor function. This continuous observation allows the surgeon to monitor neurologic function as she begins the operation through the completion of resection [40]. While language mapping requires the patient to be awake, traditionally through the asleep–awake–asleep methodology, motor mapping can be performed either in the awake or sleep setting. If asleep, phase reversal between motor and sensory cortex is first assessed, followed by direct cortical stimulation of the brain to identify the motor gyrus. Continuous somatosensory and motor-evoked potentials can be run throughout the tumor resection to be certain of intact cortical-subcortical connectivity and function. If the patient is awake, a similar mapping procedure can be performed, with the added advantage of assessing active neurologic function. Brain mapping can thus serve to detect motor, sensory, and language deficits in early stages, preventing more significant neurologic morbidity. Since the emergence of "awake craniotomies" for tumor resection, a number of articles have reported success in minimizing postoperative neurologic deficits [40]. For the resection of brain metastases specifically, a 2018 systematic review of published data on the subject concluded that this technique can optimize outcomes for patients with lesions in eloquent cortical regions [41].

Method of Resection

Surgical resection is a mainstay of treatment for selected patients with brain metastases. A number of studies have examined the efficacy of various resection techniques and their respective associated complications. Current evidence suggests that 46% of resected, nonirradiated lesions eventually recur, highlighting the significant impact of the method of resection on the local recurrence rate [42]. Of these, en bloc and piecemeal resection represent the two categorized techniques for operative therapy of these lesions.

Local disease control and minimization of recurrence, coupled with optimized postoperative outcomes, are the goals of resection in these patients. Thus, en bloc resection is the preferred approach for resection as it reduces the risk of residual disease and local recurrence. Conversely, the piecemeal approach does not afford the same level of control of the tumor mass, though it is commonly utilized for lesions in otherwise inaccessible locations. Additionally, piecemeal resection may be necessary depending on tumor characteristics unique to the patient. If the tumor is friable or infiltrating eloquent regions, the required piecemeal resection may be unavoidable. Regardless of approach, a high-quality postoperative MRI is required to assess for residual disease and to plan potential radiation therapy.

Many studies have investigated the extent to which resection techniques afford local disease control and optimal patient outcomes in the postoperative period. Of these, a 2010 study by Patel et al. found that the type of resection and tumor volume were the two primary variables predictive of local tumor recurrence in a cohort of 570 patients with a solitary brain metastasis [3]. They reported specifically that piecemeal resection was associated with significantly higher local recurrence rates compared to an en bloc technique, though larger tumors were found to have higher rates of local recurrence regardless of the type of resection. Additional evidence to support en bloc resection comes from a later 2015 study by Patel and colleagues at MD Anderson Cancer Center [43]. The authors originally wanted to investigate the risk of potential complications associated with en bloc resection by retrospectively reviewing the outcome data of 1033 patients who received surgical resection of single brain metastases. However, they concluded that an en bloc approach was as safe as piecemeal resection with similar complication rates. This data further solidifies the preference for the en bloc technique in carefully selected patients.

Leptomeningeal disease (LMD) following the resection of cerebral metastases has become the subject of concern due to its aggressive nature. This devastating complication of intracranial malignancy results from contiguous spread of microscopic tumor components or seeding of the CSF. LMD has been associated with brain tumor progression and more recently by the technique employed during tumor resection. In 2008, Suki et al. reported an increased risk of leptomeningeal disease in a cohort of 260 patients who underwent piecemeal resection of cerebral metastases in the posterior fossa [44]. Ahn and colleagues reported similar findings—leptomeningeal seeding was significantly more likely to result from a piecemeal approach, particularly for lesions adjacent to CSF pathways [45].

In response to high rates of tumor recurrence in this patient population, Yoo et al. described a novel resection technique to supplement conventional en bloc and piecemeal approaches [46]. This technique for microscopic total resection involved utilization of an ultrasonic aspirator for removal of fine infiltrating tumor cells along the white matter margin following gross resection. When comparing this technique to gross total resections, the novel technique was associated with significantly fewer local recurrences suggesting the need for additional therapeutic methods for ensuring local control.

Postoperative Management

Good surgical candidates will often leave the hospital within a few days of surgery to either home or acute rehabilitation. One of the benefits of surgery is the ability to rapidly wean steroid medications, which are often given to minimize symptoms related to vasogenic edema. Once the tumor has been removed, steroids can be rapidly tapered, minimizing the complications of prolonged steroid

therapy. Patients should be quickly encouraged to ambulate, given their propensity for deep venous thrombosis following surgery.

In the context of brain metastases, progression of the primary malignancy often contributes to overall survival. However, it is important to devise a strategy for both local and distant brain control both to aid overall survival and improve the quality of life from neurologic complications. This often includes stereotactic radiosurgery, targeted medical therapy (i.e., EGFR inhibitors for EGFR mutant non-small-cell lung cancer), and less commonly whole-brain radiation therapy. As such, treating clinicians must be creative in the postoperative setting in devising an individualized treatment plan that addresses plans for both local and distant brain control.

As previously discussed, WBRT was historically considered standard of care for patients with a limited number of cerebral metastases until mounting evidence from randomized controlled trials (RCT) confirmed limited survival benefit and demonstrated a contribution to cognitive decline [25–27]. A 1998 RCT reported improved rates of local and distant control in patients receiving resection and WBRT compared to resection alone [47]. Though WBRT remains an option for patients who are not candidates for resection or radiosurgery, due to high intracranial tumor burden or contraindications to surgery, it does result in superior brain control globally at the expense of cognitive deterioration [48]. However, it does not clearly improve survival when added to surgery or SRS.

SRS is another radiotherapy technique often used as an adjunctive therapy to surgical resection that works by precisely intersecting multiple radiation beams at a 3D target. The precision of SRS has made it particularly useful for treating small, well-demarcated intracranial lesions in otherwise inaccessible loci. Because the rate of local recurrence following resection of brain metastases approaches 50%, SRS has been studied more recently as a postoperative adjuvant with positive results. A 2014 phase II trial found high rates of local control for small (<3 cm), deep-seated metastatic lesions, with higher rates of local failure for large, superficial tumors [49]. The results of a recent phase III trial by Brown et al. reported similar findings and concluded SRS should be the standard of care over WBRT in this patient population due to less frequently associated decline in cognitive function [27]. Moreover, Mahajan et al. reported lower risk of recurrence with SRS to the resection cavity and concluded that adjuvant SRS is an efficacious alternative to WBRT following resection of brain metastases (Fig. 30.4) [50].

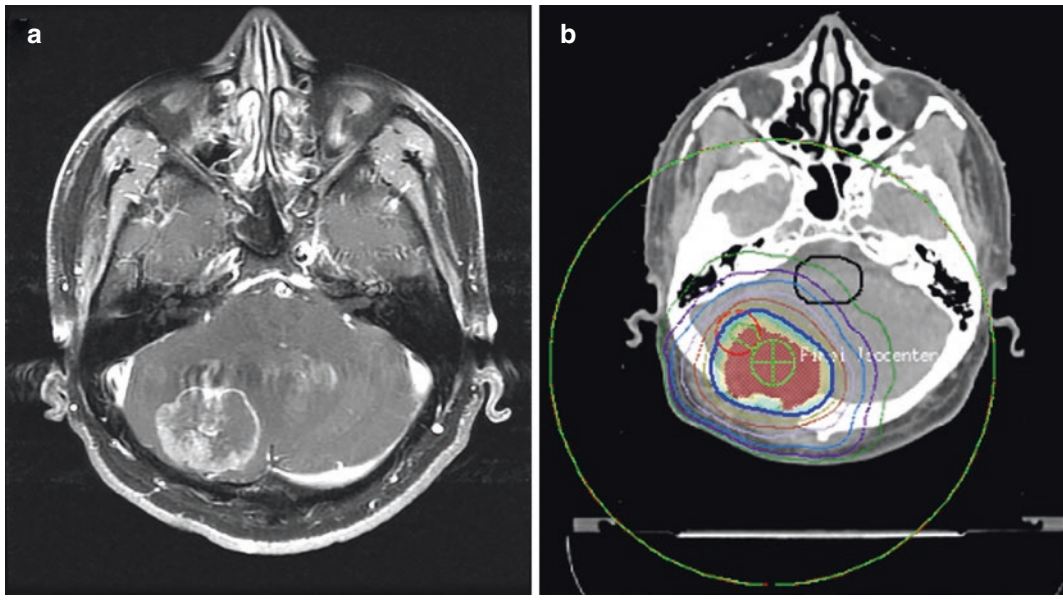

Fig. 30.4 (**a**) Axial T1-weighted postcontrast MRI demonstrating a large right cerebellar metastasis. (**b**) Post-resection stereotactic radiosurgery plan to treat the resection cavity

Conclusion

The treatment of patients presenting with brain metastases has evolved over the past few years. WBRT, once a staple therapeutic tool for the treatment of multiple metastatic lesions by decreasing the overall tumor burden, has been shown in a number of RCTs to have a limited impact on patient survival with increased frequency of associated decline in cognitive function [27]. The advent of preoperative diagnostic tools has made surgery safer and aided in preoperative planning, allowing surgeons to anticipate functional cortical and subcortical regions in the brain. The use of awake craniotomies in conjunction with direct cortical stimulation is perhaps considered the gold standard for surgical resection of metastases, especially when they appear to be in eloquent brain regions.

Even with combination therapy, resected brain metastases show high rates of recurrence, particularly for large tumors resected in piecemeal fashion. Current evidence demonstrates an en bloc approach to be safe with lower rates of local tumor recurrence and associated leptomeningeal disease. Additionally, minimally invasive procedures such as LITT and radiosurgery have further expanded the repertoire of interventions available to neurosurgeons, particularly in the recurrent post-irradiated setting. These approaches, when applicable, have allowed for both faster recovery times and the treatment of previously inaccessible lesions.

Surgical treatment of brain metastases continues to evolve. While there will always be a role for the resection of single metastases or symptomatic dominant metastases to improve symptoms and local control, surgery may also be indicated to acquire tissue and updated molecular profiling in the future. Brain metastases have been shown to be similar yet genomically distinct to their primary tumor. Targeted intervention in combination with systemic therapy may become the mainstay of treatment in patients with multiple brain metastases.

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Intraoperative Brachytherapy for Resected Brain Metastases

31

A. Gabriella Wernicke, Sean S. Mahase, and Theodore H. Schwartz

Introduction

Brain metastases, the most common intracranial neoplasms in adults [1], develop in approximately 30% of all cancer patients and are the cause of death in up to 50% of these individuals [2]. They are commonly located at the gray–white matter interface where the blood vessel caliber decreases, and their dissemination corresponds with blood flow: 80% of patients develop multiple intracranial metastases, with 80% occurring in the cerebral hemispheres, 15% in the cerebellum, and 5% in the brainstem [3]. Incidence rates are expected to rise with the emergence of increasingly effective systemic agents that, while conferring improved systemic control translating to increased survival, possess limited ability to bypass the blood–brain barrier thus making the central nervous system a sanctuary site [4]. As only 10% of patients become symptomatic from brain metastases, incidence rates are also increasing with improved surveillance [2]. Primary lung cancers account for over 50% of intracranial metastases, with breast cancers, melanoma, and colon cancers, respectively, accounting for approximately 20%, 10%, and 5% of all brain metastasis primaries [2]. Epidemiologically, these primaries are also among the most common malignancies in the United States. Conversely, small-cell lung cancers, melanoma, germ cell tumors, and choriocarcinomas demonstrate proportionally high neurotropism rates.

Symptomatic management options include corticosteroids and supportive care [5]. Chemotherapeutic agents historically demonstrated little efficacy in treating brain metastases owing to the inability to enter the central nervous system. However, the utility of targeted agents and immunotherapy in the context of multidisciplinary treatment strategies is currently an area of active investigation. Commonly utilized treatment options include whole-brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and surgical resection.

WBRT was the initial standard therapy and continues to play a pivotal role in treating brain metastases, particularly in the setting of multiple lesions, and in the presence of recurrent metastases or leptomeningeal disease. The first Radiation Therapy Oncology Group (RTOG) randomized trials established WBRT as an effective modality for patients with favorable performance status and/or well-controlled primary disease. However, these initial studies reported overall survival (OS) rates of only a few months [6]. Patchell et al.

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improved on these outcomes in a randomized trial comparing WBRT to surgical resection followed by WBRT among patients with a single brain metastasis. They demonstrated surgery followed by WBRT improved OS to 40 weeks, compared to 15 weeks with WBRT alone [7]. Patchell and colleagues subsequently randomized 95 patients who underwent surgical resection to observation or postoperative WBRT and reported no significant difference in OS among the cohorts. However, tumor recurrence was reduced from 46% in the observation group to 10% in the WBRT group, as well as a reduction in new brain metastases and death due to neurological causes in the WBRT group, thus establishing postoperative WBRT as the standard of care for brain metastases at that time [8].

SRS is a minimally invasive option for patients who are not surgical candidates; however, there are a dearth of appropriately powered randomized control trials comparing surgical resection and SRS alone for brain metastases. RTOG 9508 demonstrated that an SRS boost improves local control (LC) following WBRT with no difference in survival [9]. Conversely, several randomized trials evaluating SRS alone versus SRS with WBRT demonstrated that the latter may improve local and distant tumor control, but OS rates remained the same as using SRS alone [10–12]. Patients undergoing WBRT were also more likely to exhibit neurological or cognitive decline [13, 14]. These findings, alongside studies showing SRS may be an appropriate option for patients with multiple brain metastases [15], promotes its increasing utilization over WBRT.

Surgical resection remains the preferred initial treatment modality for patients with good performance status and a limited number intracranial lesions who require pathological confirmation, have a large (greater than 2 cm) metastasis, or who are experiencing mass effect or neurological symptoms refractory to steroids [16]. However, surgical resection without any adjuvant intracranial treatment has a 1- to 2-year LC rates of 47–59%; thus adjuvant radiotherapy is typically given in an effort to maximize LC [8, 12, 17]. Given concerns of neurocognitive decline following WBRT, the paradigm is shifting to postoperative SRS [17–19]. The relative benefits and disadvantages of giving SRS preoperatively is also under investigation, with a retrospective multi-institutional study comparing preoperative SRS to postoperative SRS showed no differences in OS and local recurrence at 2 years [20]. The only prospective trial evaluating preoperative SRS demonstrated an 85.6% 1-year LC rate without radionecrosis [21], and one trial (NCT02514915) is currently accruing.

Another appealing option to improve postoperative LC rates and obviate the need for adjuvant radiation and commute for postoperative radiation treatments entails intracavitary brachytherapy. This chapter discusses the rationale, technique, outcomes, evidence, and future directions regarding the use of intracavitary brachytherapy as an adjunct treatment to surgical treatment. We will discuss various types of brachytherapy and radioactive isotopes available for this procedure, as well as the benefits of the radioisotope Cesium-131 (Cs-131), which offers great promise as the radioisotope of choice in the future.

Considerations in Selecting an Adjuvant Radiotherapy Modality

Changes in Resection Cavity Volume

An early retrospective study of 72 patients treated with postoperative SRS, in which the resection cavity was targeted without a margin, demonstrated that LC was significantly higher among those with less conformal plans [22]. A subsequent study targeting the resection cavity with a 2 mm margin improved 1-year local failure rates from 16% to 3% without a significant increase in toxicity (3% with a 2 mm margin versus 8% without a margin) [23]. The rationale to incorporate an additional margin stemmed from more conformal plans increasing the risk of marginal miss due to difficulty contouring the post-

operative cavity. Numerous studies have explored resection cavity volume dynamics with respect to time from resection on subsequent SRS planning. In 68 metastases treated with surgical resection and postoperative SRS, Atalar et al. reported a median pre-resection tumor volume of 14.5 cm^3, and a median resection cavity volume of 10.1 cm^3, corresponding to a 29% reduction volume. Of note, MRI imaging showed shrinkage in 72% of resection cavities, but also showed increased cavity size in 26% of cases [24]. In a study comparing MRI scans obtained preoperatively, 24 hours following surgery, and 1 week prior to SRS in 43 resected brain metastases, 46.5% of cavities remained stable in size (defined as <2 cm^3 change in size), whereas 23.3% shrank by over 2 cm^3, and another 30.2% increased in size by over 2 cm^3 [25]. Thus, the resection cavity experiences significant, unpredictable changes following surgery, which may impact SRS planning. These changes may lead to inaccuracies in planning and potentially promote marginal misses or excessive irradiation of adjacent normal brain parenchyma.

Practical Considerations in Adjuvant Treatment Planning

The treatment of brain metastases is a multidisciplinary endeavor between neurosurgery, radiation oncology, and medical oncology. Each patient's baseline performance status, recovery from surgery, potential inpatient complications, primary site and systemic disease management, and social factors impact the time between resection and postoperative SRS.

The SRS planning process is inherently more technically involved than WBRT from a radiation planning perspective, which may also increase time to treatment. Accordingly, several postoperative SRS studies quote a median time from surgery to SRS of 4–5 weeks [23, 26, 27]. Additionally, there may be concern that some patients may not follow-up for their adjuvant radiotherapy, putting them at higher risk for recurrence. Preoperative SRS may provide one avenue to avoid some of these potential complications. However, some patients may present too urgently to allow time to safely perform MRI scanning, CT simulation, development of a SRS plan, and radiotherapy delivery prior to surgery. This option may also not be feasible for patient needing pathological confirmation or with large metastases.

Time to Radiotherapy

Due to a plethora of considerations discussed above, including temporal changes in resection cavity dynamics and technical and practical considerations involved in adjuvant SRS planning, there have been concerns related to the effect of adjuvant radiotherapy timing on treatment efficacy. While there is a dearth of data exploring the effect of time to adjuvant SRS on local recurrence, Seymour and colleagues reviewed patient demographics, clinical outcomes, and workflow timing, including time from MRI and CT simulation, insurance authorization, and consultation to start of SRS for intact brain metastases. They reported 6- and 12-month local freedom from progression rates of 95% and 75% for metastasis with an interval of <14 days from MRI to SRS, compared to 56% and 34% for metastases with MRI 14 days after treatment, suggesting a LC benefit in expediting treatment [28].

Radiobiological Considerations

The interval between resection and delivery of postoperative SRS may allow tumor repopulation within the cavity. Furthermore, it can be postulated that radiotherapy is more likely to produce a sustained effect if there is a smaller residual tumor volume to target. As SRS is typically administered in a single fraction, or in three fractions given over consecutive days, it is possible that cells in more radioresistant phases of the cell cycle may be spared. Postoperative SRS may also be delivered

to a relatively hypoxic resection cavity, impairing radiation efficacy. This phenomenon occurs secondary to radiation primarily acting through generating oxygen-based free radicals, which in turn induce single-strand and double-strand DNA breaks that ultimately cause cell death. Based on this reasoning, referred to as the oxygen enhancement ratio [29], preoperative SRS studies are advocating for a 20% dose reduction from the standard postoperative doses used in RTOG 9005 [30]. Furthermore, postoperative radiation might be associated with tumor cell repopulation which may take place during the postsurgical recovery and treatment planning phases.

Rationale for Perioperative Brachytherapy

Brachytherapy, entailing the implantation of a radioactive source within the tumor resection cavity at the time of surgery, has several appealing advantages over WBRT and SRS with regards to the plethora of concerns described above and in Tables 31.1 and 31.2. Perioperative brachytherapy offers an immediately available radiotherapy option that avoids tumor cell repopulation as radiotherapy treatment begins immediately intraoperatively. This treatment option does not require extensive preoperative or postoperative delays for scanning and treatment planning. Thus, the planning accuracy is not subject to changes in the resection cavity shape and size that may occur in the interval between postoperative planning MRI and delivery of SRS. Alternatively, patients who require urgent surgical resection can still receive immediate adjuvant treatment, which would not be feasible with preoperative SRS. Providing adjuvant treatment at the time of surgery removes possible delays in treatment planning due to postoperative course and recovery, concerns of patient compliance, and avoids the need to undergo the entire planning process and workflow entailed within postoperative SRS. This option is particularly appealing for patients who may have difficulty with transportation, and who may need to start systemic agents whose administration is typically avoided concurrently with radiotherapy.

SRS requires a 2 mm planning target volume expansion, increasing the volume of normal brain receiving 10–12 Gray of radiation, which has been correlated with an increased risk of radiation necrosis [31–33]. Conversely, utilizing intraoperative brachytherapy, neurosurgeons can decide upon the number of sources required to adequately cover the resected volume, thus providing a well-defined target encompassing the resection cavity and areas of microscopic disease, while enabling avoidance of deliberately extending the treatment volume into normal brain parenchyma. Several brachytherapy studies described below report 80–95% LC rates [34–39], which may be attributed to interstitial brachytherapy possessing a higher conformality index than post-op SRS [40, 41].

Brachytherapy is an alternative salvage option for recurrent metastases as repeat SRS may produce subpar outcomes in this setting [33]. Brachytherapy is also an option for larger resection cavities, given reports indicating reduced efficacy and increased risk of radionecrosis with SRS in this setting [8, 33, 42, 43]. Metastases 3 cm or greater treated with SRS generally require dose reduction to minimize risk of radionecrosis [30], resulting in subpar outcomes in this cohort [44–47]. Ebner et al. evaluated 343 patients with 754 total brain metastases treated with SRS, of which 93 had large tumors. The tumor size was 3–3.5, 3.5–4, and 4 cm or greater in 29%, 32%, and 39% of these patients. The LC of large metastases was inferior compared to smaller tumors, with 1-year LC rates of 68% versus 86%, respectively ($p < 0.001$) [48]. The potential advantage of brachytherapy of SRS in the postoperative management of large metastases may be extrapolated from the glioblastoma literature, in which resection cavities and irradiation volumes are considerably larger. In a retrospective analysis comparing SRS and interstitial brachytherapy for recurrent gliomas, Shrieve and colleagues reported similar median survivals of 10.2 months and 11.5 months among each respective cohort. However, the

Table 31.1 Neoadjuvant and adjuvant radiotherapy options for resected brain metastases

Modality	Margins	Advantages	Disadvantages
Post-op WBRT	1.5–2.0 cm "flash" anteriorly, superiorly, and posteriorly, with inferior field extended to C1 or c2	Technically easy to plan Lowers risk of distant intracranial metastases Treatment of choice for leptomeningeal disease [16] Low risk of radionecrosis Pathology available	Higher risk of neurocognitive sequela [19]
Post-op SRS	2 mm margin most commonly used [19]	Feasible for multiple lesions [15] Limited neurocognitive effects [19] Pathology available	May be difficult to define resection cavity [22–25] Requires involved planning, pre- and postoperative scans and outpatient visits [28] Delays between surgery, scanning, and radiation delivery [24, 26–28] Possible hypoxic tumor bed irradiation Risk of radionecrosis Not advantageous for irregularly shaped cavities and large lesions [66]
Pre-op SRS	No margin [21]	Easy to define target volume Delivered to well-oxygenated tumor environment Limited neurocognitive effects similar to post-op SRS	Limited adjuvant treatment options if subtotal resection follows SRS Requires involved planning, preoperative scans No pathology available at time of radiotherapy
Temporary brachytherapy	No margin	Irradiation begins immediately from time of placement Limited neurocognitive effects Delivered to well-oxygenated tumor environment Can effectively target irregularly-shaped cavities Effective for larger lesions Pathology available	Requires second surgery for implant removal [22] Patient is radioactive Dependent on technical expertise
Permanent brachytherapy	5 mm from surface [63]	Performed intraoperatively; reduces subsequent patient visits relative to postop SRS Irradiation begins immediately from time of placement Limited neurocognitive effects [67] Delivered to well-oxygenated tumor environment Can effectively target irregularly shaped cavities [66] Effective for larger lesions [39, 43] Pathology available	Patient is radioactive Potential for seed migration Dependent on technical expertise High rates of radionecrosis with I-125 [37]

brachytherapy cohort had higher radiation necrosis rates and 2-year reoperation rates (65% versus 48%) than those receiving SRS. While there were no difference in age and performance status among the cohorts, the brachytherapy group had a longer median follow-up (43 months versus 17.5 months) and a significantly larger average tumor volume (29 cc versus 10.1 cc) than the SRS group, suggesting a preference towards brachytherapy with larger cavities, as well as a question regarding what the radionecrosis rates would be if SRS were used in lesions of equal comparable size [49].

Table 31.2 Outcomes and radionecrosis rates by radiation modality in prospective trials

Modality	Study	Local control	Distant control	Overall survival	Radionecrosis	Treatment dose and volume	Time between surgery and radiation (days)
Post-op WBRT	Brown 2017 [19]	87.1% (1 year)	89.2% (1 year)	11.6 months (median)	None	30 Gy in 10 fractions 37.5 Gy in 15 fractions	Not reported
	Patchell 1990 [7]	80%	80%	10 months (median)	Not assessed	36 Gy in 12 fractions	Within 14 days of surgery
	Patchell 1998 [8]	90%	86%	12 months (median)	Not assessed	50.4 Gy in 28 fractions	Within 28 days of surgery
Post-op SRS	Brennan 2014 [26]	78% (1 year)	56% (1 year)	14.7 months	7 cavities (17.5%)	Cavity with 2 mm margin ≤ 2.0 cm: 22 Gy 2.1–3.0 cm: 18 Gy 3.1–4.0 cm: 15 Gy	Median 31 days
	Mahajan 2017 [17]	72% (1 year)	42% (1 year)	17 months (median)	None	Cavity with 1 mm margin ≤ 10 cc: 16 Gy 10.1–15 cc: 14Gy > 15 cc: 12 Gy	Within 30 days of surgery
	Soltys 2008 [22]	79% (1 year)	47% (1 year)	15.1 months (median)	3 patients (4.1%)	Cavity with 2 mm margin Dosing per RTOG 90–05 (median marginal dose 18 Gy)	Not reported
	Brown 2017 [19]	61.8% (1 year)	64.7% (1 year)	12.2 months	1.1% (1 patient)	Cavity with 2 mm margin < 4.2 cc: 20 Gy 4.2–7.9 cc: 18 Gy 8.0–14.3 cc: 17 Gy 14.4–19.9 cc: 15 Gy 20.0–29.9 cc: 14 Gy ≥ 30.0 cc: 12 Gy	Not reported
Pre-op SRS	Asher 2014 [21]	85.6% (1 year)	67.2% (overall)	60% at 1 year	None	Gross tumor with no margin Median 14Gy to 80% isodose line	Median 1 day
I-125 brachytherapy	Ruge 2011 [75]	93.3% (1 year)	54.5% (1 year)	14.8 months (median)	10% (3 patients)	Prescription dose 50 Gy at surface of target volume over 42 days	Intraoperative
Cs-131 brachytherapy	Wernicke 2014 [63]	100% (1 year); defined at recurrence within 5 mm of cavity	48.4% (1 year)	9.9 months (median)	None	Prescription dose 80Gy at 5 mm depth from resection cavity surface	Intraoperative
	Wernicke 2017 [69]	100% (1 year); defined at recurrence within 5 mm of cavity	52% (1 year)	15.1 months (median)	None	Prescription dose 80Gy at 5 mm depth from resection cavity surface	Intraoperative

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Utilizing brachytherapy may be radiobiologically advantageous compared with SRS. As radioactive implants are placed at the time of surgery, irradiation of the resection bed begins at day 0; if radiation-induced cell death exceeds proliferation, potential repopulation of residual tumor cells is minimized. Radiotherapy's therapeutic index relies on the ability of normal cells to repair sublethal damage more effectively than adjacent tumor cells. Brachytherapy exposes the resection cavity to constant irradiation, promoting accumulation of cellular damage to residual tumor cells, and increasing the probability of mitotic catastrophe, whereby cells with an abundance of DNA damage undergo apoptosis due to failure to divide. Continuous irradiation also enables eventual targeting of tumor cells undergoing redistribution from radioresistant phases to more radiosensitive phases (G2/M) [50].

As the incidence of brain metastases continues to rise, an increasingly practical consideration entails the hospital costs involved in treatment (Table 31.1). Comparative analyses suggest SRS is more cost-effective than resection alone [51, 52], as well as WBRT [53]. Wernicke et al. retrospectively reviewed treatment records of 24 patients undergoing surgery and intraoperative Cs-131 brachytherapy and 25 patients undergoing surgery and postoperative SRS with the purpose of evaluating the cost-effectiveness of each radiotherapy modality. They reported a direct hospital cost for surgery and intraoperative Cs-131 brachytherapy of $19,271, whereas surgery and postoperative SRS cost $44,219. Additionally, there was no significant difference in 1-year survival rates among brachytherapy and postoperative SRS cohorts (61% versus 49%; $p = 0.137$) [54]. Thus, intraoperative brachytherapy may be a comparably effective but more cost-effective, radiotherapy modality than SRS for patients requiring resection for brain metastases.

I-125 Brachytherapy

While several radioisotopes options exist for brachytherapy (Table 31.3), including palladium-103 (17 day half-life) and gold-198 (2.7 day half-life), historically, iodine-125 (I-125) was the most common radioactive source utilized in CNS tumors and is administered using either temporarily placed interstitial catheters or implants, or as permanent implants. I-125 possesses a half-life of 60.2 days. Temporary implants are reusable sources with an activity of 10–20 mCi per source, photon energies of 27–35 keV, and a dose rate of 40–60 cGy per hour [55]. Implanted I-125 sources possess a half-value layer of 0.025 mm of lead and are typically housed in 4 mm long by 0.8 mm diameter titanium capsules. Utilizing the higher-dose rate of temporary I-125 implants, continuous irradiation can be delivered over the next ~100 hours following resection and removed on postoperative day 4 [56]. Temporary implant dose distribution can be assessed both pre- and postoperatively. While temporary implants can be reused and enable irradiation at higher dose rates, they are a less attractive option as they must be removed, subjecting patients to a second surgery, and the ensuing preoperative planning, additional operative costs, and potential postoperative complications. Thus, permanent, low-activity implants are becoming more favored.

Table 31.3 Commonly used isotopes in brachytherapy

Isotope	Half-life	Average photon energy (MeV)	Half-value in lead (mm)	Exposure rate constant (R-cm^2/mCi-h)
Iodine-125	59.4 days [76]	0.028 [76]	0.025 [76]	1.46 [76]
Cesium-131	9.7 days [77]	0.029 [77]	0.0262 [78]	0.679 [78]
Cobalt-60	5.3 years [76]	1.17, 1.33 [76]	11.0 [76]	13.07 [76]
Iridium-192	73.8 days [76]	0.38 [76]	2.5 [76]	4.69 [76]
Palladium-103	17.0 days [76]	0.021 [76]	0.008 [76]	1.48 [76]

Permanent I-125 implants are nonreusable sources with an activity of 0.725 mCi per source and a dose rate of 11 cGy per hour [57]. The insertion of permanent radioactive sources at the time of resection exploits the precipitous but predictable drop in dose as a function of distance from the source, referred to as the inverse square law. Predicting irradiation exposure of the immediately adjacent 1 cm of normal brain parenchyma can be difficult due to production of secondary photons. However, optimizing the 1 cm distance traversed by I-125's low-energy photons enables delivery of highly conformal dose distributions to maximize targeting of residual tumor with relative sparing of surrounding normal brain parenchyma [58]. I-125 sources are placed along the walls of the resection cavity in the form of either free sources or embedded in an absorbable suture and held in place with a liquid adhesive. Unlike SRS techniques, the surgical staff is exposed to radiation during implantation and required to don lead gloves, vests, and thyroid shields. Another potential shortcoming is that seed positioning is confirmed 1–2 days following implantation, with the potential risks of inadequate dose coverage. Additionally, it is possible for the seed to migrate over time or inadequately target the cavity if it changes size or shape.

I-125 Brachytherapy Outcomes in Brain Metastases

High-Activity I-125 Brachytherapy

Bernstein and colleagues used high-activity I-125 seeds to treat 10 patients with brain metastases that recurred following initial treatment with craniotomy and WBRT. I-125 seeds (20–40 mCi) with a mean dose rate of 67.3 cGy per hour were implanted with 70 Gy prescribed to the tumor. Implant volumes ranged from 12.1 cc to 99.0 cc (mean: 44.5 cc; median: 36.4 cc). Four patients were alive 2 years following the procedure with the caveat of potential selection bias towards favorable histology and good performance status [34]. In a study of 14 patients with recurrent metastatic brain lesions (4 patients had prior surgical resections and 13 had prior WBRT) treated with temporary high-activity I-125 sources, Prados et al. reported a median survival of 20 months, with stable responses in 8 patients and radionecrosis in 2 patients [59]. Ostertag and Kreth evaluated the efficacy of interstitial high-activity I-125 in 93 patients with brain metastases ≤4 cm in diameter. Patients were either treated with interstitial brachytherapy to 60 Gy to the tumor periphery plus external beam radiotherapy to 40 Gy, or interstitial brachytherapy alone to 60 Gy. All patients with tumor recurrence or prior irradiation were treated with the latter regimen. Median survival was 17 months in the combination radiotherapy group, 15 months among those with newly diagnosed metastases treated only interstitially, and 6 months among those with recurrent metastases. Interstitial brachytherapy plus external beam radiotherapy did not prove to be superior to interstitial brachytherapy alone, and no patients developed symptomatic radionecrosis [38].

Permanent Low-Activity I-125 Brachytherapy

Schulder et al. reviewed a small series of 13 patients with large recurrent metastatic brain tumors following initial WBRT who underwent resection and permanent low-activity I-125 seed implantation. Implant dose ranged from 43 Gy to 132 Gy, with a mean dose of 83 Gy. The entire cohort had a median survival of 9 months, with durable LC achieved in 9 patients, and one case of radionecrosis [39]. In another study of 40 patients with metastases deemed too large (>2.5 cm in diameter) for SRS who underwent resection and placement of permanent I-125 seeds, Huang et al. reported a median survival of 11.3 months (12 months among patients with newly diagnosed metastases and 7.3 months in those with recurrent metastases). There were 3 local failures and 13 distant recurrences, with symptomatic necrosis developing at a median of 19.5 months in 9 patients (6 with pathological confirmation) [37]. Petr et al. evaluated the efficacy of surgical resection and permanent low-activity I-125 seeds in 72 patients with newly

diagnosed single brain metastases. At a median of 16 months, they reported a 93% LC rate, and a 23% distant failure rate, with four patients developing radionecrosis [60]. A retrospective study of two institutions' experience treating a single metastasis with gross-total resection followed by permanent low-activity I-125 implants reported a 1-year LC rate of 96%, with two patients developing symptomatic radiation necrosis requiring intervention [36]. Bogart et al. treated 15 patients with solitary brain metastases from primary non-small cell lung cancer with low dose-rate I-125, and reported a 14 month median survival with no in-site recurrences and two recurrences adjacent to the original metastases. They reported one death from a postoperative fungal infection, but no cases of symptomatic radionecrosis [35].

Raleigh et al. recently reported on the outcomes of 95 patients with 105 brain metastases who underwent resection followed by placement of permanent I-125 implants. I-125 sources were placed 6–10 mm apart and secured in place with fibrin glue. Postoperative stereotactic computerized tomography scanning for dosimetric calculations was generally performed within 24 hours of surgery, and the prescription was determined based on source activity, calibration date, and implantation date. Forty-seven percent of the lesions were new metastases and 53% were recurrent lesions, of which 40% were previously treated with SRS, 25% with prior WBRT, and 17% with a prior resection. The median metastasis volume was 13.5 cm^3 (range: 0.2–76 cm^3), a median of 28 sources were used, and the median source activity was 0.73 mCi. The median brachytherapy dose was 540 Gy at 3 mm, 263 Gy at 5 mm, and 135 Gy at 10 mm depth into brain tissue (measured outward from the resection cavity edge), which corresponded to median treatment volumes of 6.8 cm^3, 12.8 cm^3, and 33 cm^3, respectively. The median OS was 12 months, with over 22% of patients surviving beyond 2 years after intervention. The authors reported a LC rate of 90%. The median time to radionecrosis was 1 year, with 15 reported cases, of which 11 underwent prior SRS, and the remaining 4 were newly diagnosed metastases [61].

Thus, with proper technique, permanent I-125 brachytherapy may be a favorable adjuvant treatment option for selected brain metastases, including large and recurrent lesions, albeit with high risk of radiation necrosis.

Limitations and Complications with I-125 Brachytherapy

Acute side effects of interstitial brachytherapy include seizures, infection, impaired perioperative healing, hemorrhage, and other neurological sequelae, which are more common with high-activity temporary implants. Radionecrosis is also a major concern, with reported rates as high as 29% [37]. The largest criticism of permanent I-125 brachytherapy is its relatively long half-life, which subjects the patient to radiation for a prolonged period, and may potentially expose surgical staff to radiation in the case of a repeat surgery. As described above, resection cavities undergo significant dynamic changes following resection, and larger resection cavities, which were often selected for brachytherapy in the aforementioned trials, are especially subject to postsurgical changes in volume and shape [24]. Taken in context with I-125's long half-life, these changes may affect the dosimetry of the seeds, potentially decreasing tumor dose or increasing normal brain tissue exposure. As the dosimetry is dependent on seed placement and fixation to the cavity, brachytherapy is dependent on the technical expertise of the physician performing the procedure. Additionally, intracranial brachytherapy is not as common as SRS, and training in this technique is highly variable among academic hospitals.

Cesium-131 (Cs-131) Brachytherapy

Since obtaining FDA approval in 2003, Cs-131 has been utilized as radioactive permanent seed implants for treatment of prostate, head and neck, and lung malignancies. Cs-131 has a half-life of 9.69 days, a dose rate of 0.342 Gy per hour, and an average energy of 30.4 KeV. Comparative studies of radioactive seeds used in prostate

brachytherapy suggested Cs-131 has preferable dose homogeneity, required fewer seeds to provide comparable prostate coverage, and enabled superior sparing of the rectum and urethra compared to Pd-103 or I-125 [62].

Cs131 Brachytherapy Outcomes in Brain Metastases

Wernicke et al. evaluated the safety, feasibility, and efficacy of permanent intraoperative Cs-131 brachytherapy following resection in a prospective phase I/II study of 24 patients with newly diagnosed brain metastases. Cs-131stranded seeds were placed with a planned dose of 80 Gy to a 5 mm depth from the resection cavity surface. Each Cs-131 suture-stranded string contained 10 seeds (0.5 cm inter-seed spacing), were cut into shorter segments as dictated by cavity size, and permanently placed along the cavity in a tangential pattern to maintain a 7–10 mm spacing between seeds (Figs. 31.1 and 31.2). The seeds were subsequently secured with Surgicel and fibrin glue. All patients underwent a post-implant CT scan to determine dose distribution 1–2 days following the procedure. In this series, the median resected tumor volume was 10.31 cc (range: 1.77–87.11 cc), and a median of 12 seeds (range: 4–35) were implanted, with median activity per seed of 3.82 mCi (range: 3.31–4.83 mCi) and total activity of 46.91 mCi (range: 15.31–130.70 mCi). At a median follow-up of 19.3 months, the median survival was 9.9 months, with a 100% LC rate (defined as no recurrence within 5-mm from the resection cavity). There was one regional recurrence (>5 mm from the resection cavity) and a distant control rate of 48.4%. There were no reported cases of symptomatic radiation necrosis [63].

The high radionecrosis rates in the aforementioned I-125 brachytherapy trials have been attributed to a combination of I-125's long half-life, and tumor cavity shrinkage affecting radioactive seed placement, altering their dosimetry, and exposing normal brain parenchyma to excessive radiation [24, 64, 65]. In an attempt to improve on these shortcomings, Wernicke and

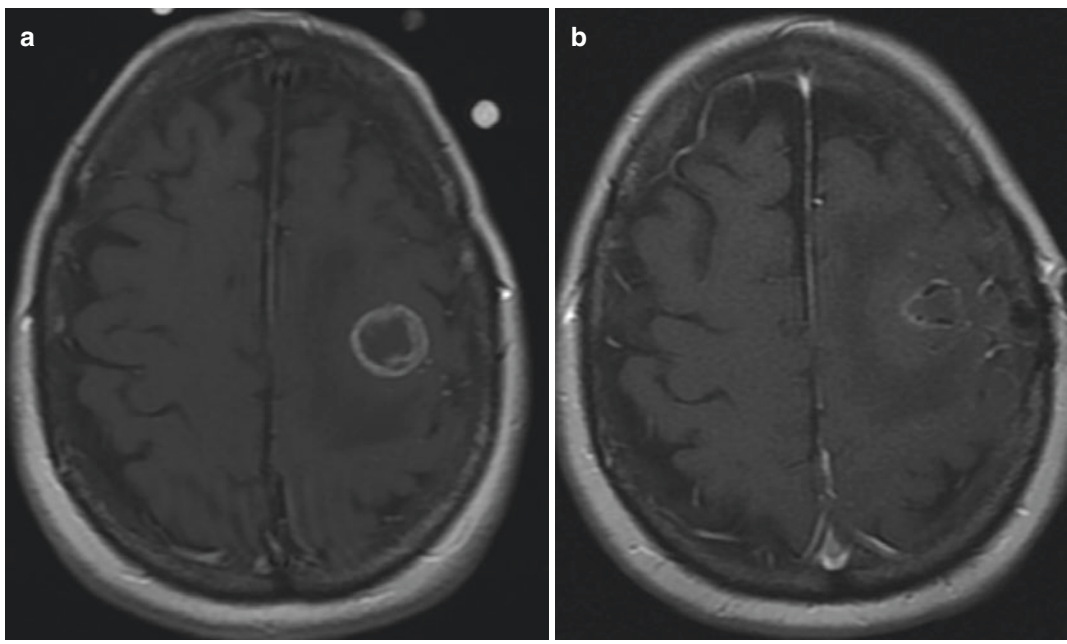

Fig. 31.1 (**a**) Preoperative and (**b**) Postoperative gadolinium enhanced MRI scans show resected single brain metastasis with the cavity lined with cesium-131 brachytherapy seeds

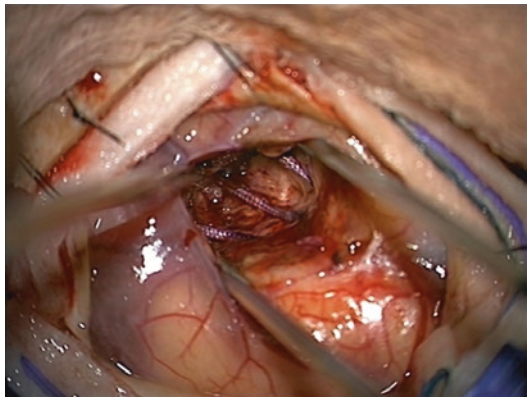

Fig. 31.2 Intraoperative photograph shows the seeds on a blue vicryl suture lining the resection cavity

colleagues prospectively evaluated the efficacy of combining the short half-life Cs-131 with a "seeds-on-a-string" technique with fibrin glue to stabilize cavity volume and minimize shrinkage. In this study, 30 patients with brain metastases (and 6 more included from the previously described phase I/II study [24]) underwent surgical resection and intraoperative Cs-131 implantation, and were compared with 30 patients who underwent postoperative SRS. Cs-131 stranded seeds were implanted approximately 1 cm apart within the cavity with a planned dose of 80 Gy prescribed to a 5 mm depth from the surface of the resection cavity. The seeds were implanted akin to "barrel staves" to utilize the string's tensile strength to maintain the resection cavity shape with the intent of preventing seed movement for at least 1 month, at which point almost 90% of the prescribed dose would be delivered. Over a median follow-up period of 110 days, resection cavities significantly shrank among those receiving Cs-131 (56.5% median volume reduction) and SRS (84.8% median volume reduction). However, the Cs-131 cohort demonstrated a nonsignificant amount of cavity shrinkage during the first month (22% volume reduction; $p = 0.06$), compared with the SRS cohort (46.7%; $p = 0.42\%$), possibly reflecting the effects of the brachytherapy "seeds-on-a-string" and fibrin glue on cavity dynamics. No patients in either group developed radiation necrosis [66]. Pham et al. prospectively evaluated the neurocognitive impact of intraoperative Cs-131 in the patients from the previously described phase I/II trial by Wernicke et al. [24]. The mini-mental status examination (MSSE) and functional assessment of cancer therapy-brain (FACT-Br) questionnaire were performed pretreatment, and at 2, 4, 6, and 12 months following treatment. The authors reported an improvement from baseline In MMSE score at 4–12 months (30 versus 29, $p = 0.017$; 30 versus 29, $p = 0.001$, respectively), and in FACT-BR score at 4 and 6 months (162 versus 143, $p = 0.004$; 164 versus 143, $p = 0.005$, respectively). They noted several limitations in this analysis, including a heterogeneous patient population, the original study not being powered to compare neurocognitive outcomes, the cohort having a high MSSE ($\geq$27) at baseline, reflecting a healthier population, and the limited follow-up time [67]. Additionally, this study does not account for neurocognitive effects relating to metastatic disease control, steroid use and systemic therapies. A summary of prospective trials evaluating neurocognitive effects of various radiation modalities is provided in Table 31.4.

Menachem et al. evaluated radiation exposure to medical personnel involved in the surgical resection and intraoperative Cs-131 implantation of 20 patients with brain tumors (16 with brain metastases). Cs-131 stranded seeds were used with a planned dose of 80 Gy to a 5 mm depth from the surface of the resection cavity. Surgeons and radiation oncologists wore dosimetry badges on the leaded aprons and rings underneath the leaded gloves, and measured radiation dose equivalent at the levels of "eye" (ocular lens), "shallow" (hands/skin), and "deep" (whole-body). The dose rate in the room was also measured following the procedure to approximate exposure to other personnel having patient contact who do not routinely wear protective equipment. Postoperatively, the median dose rate to surface, 35 cm and 100 cm distances were 0.2475 mSv per hour, 0.01 mSv per hour, and 0.001 mSv per hour, respectively. At

Table 31.4 Neurocognitive effects of various radiotherapy modalities

Modality	Study	Dose and fractionation	Assessment	Outcomes
Post-op WBRT	Brown 2017 [19]	37.5 Gy in 15 fractions or 30 Gy in 10 fractions	Cognitive-deterioration-free survival: Drop of >1 standard deviation in HVLT-R immediate recall, verbal fluency COWAT, TMT-A, TMT-B, HVLT-R delayed recall, HVLT-R recognition	Median 3 months to cognitive decline
Post-op SRS	Brown 2017 [19]	12–20 Gy in 1 fraction	Cognitive-deterioration-free survival HVLT-R immediate recall, verbal fluency COWAT, TMT-A, TMT-B, HVLT-R delayed recall, HVLT-R recognition	Median 3.7 months to cognitive decline
Pre-op SRS	No trials to date evaluating neurocognitive effects			
I-125 brachytherapy	No trials to date evaluating neurocognitive effects			
Cs-131 brachytherapy	Pham 2016 [67]	80 Gy to 5 mm depth	MMSE and FACT-BR	FACT-BR improvement at 4 and 6 months compared to pre-treatment (162 vs. 143, $P = 0.004$; 164 vs. 143, $P = 0.005$, respectively) MMSE improvement at 4 and up to 12 months compared to pre-treatment (30 vs. 29, $P = 0.017$; 30 vs. 29, $P = 0.001$, respectively)

HVLT-R Hopkins Verbal Learning Test-Revised, *COWAT* Controlled Oral Word Association Test, *TMT-A* Trail Making Test part A, *TMT-B* Trail Making Test part B, *MMSE* Mini-Mental Status Examination, *FACT-BR* Functional Assessment of Cancer Therapy-Brain

30 days following implantation, the dose rates were 0.0298 mSv per hour, 0.0012 per hour, and 0.0001 mSv per hour, respectively. Based on the National Council on Radiation Protection guidelines, the authors concluded that the dose equivalent from permanent intracranial Cs-131 brachytherapy maintains safe levels of exposure to medical personnel and family [68].

Cs-131 has also been evaluated in the setting of recurrent metastases and in treating large metastases. A retrospective review was performed on the outcomes of 13 patients with 15 brain metastases who underwent salvage resection and Cs-131 brachytherapy for recurrence following an initial radiotherapy course (10 patients had prior SRS to the lesion and 5 had prior SRS and WBRT). The median resected tumor diameter was 2.9 cm, which is significantly larger than median cavity size in many of the aforementioned postoperative SRS studies. A prescription dose of 80 Gy at 5 mm depth from the resection cavity surface was used. The median OS was 7 months, with a 1 year freedom from local progression of 83.3% and one case of asymptomatic radionecrosis [69]. Wernicke et al. prospectively evaluated the efficacy of surgical resection and Cs-131 implantation in 42 patients with 46 metastases ≥2.0 cm in diameter (median preoperative lesion diameter was 3.0 cm). One year OS was 58%, with a 1 year regional failure from progression of 89% (80% in tumors <3.0 cm), and a 52% distant failure from progression rate. Lesion size was not significantly associated with any endpoint on multivariate analysis, and there were no cases of radionecrosis [70].

I-125 Versus Cs-131 Brachytherapy

Cs-131 has several physical and radiobiological advantages over I-125 for brain brachytherapy. The intrinsically lower Cs-131 seed activity, jux-

taposed with lower dose prescriptions in the aforementioned studies, enables excellent LC rates while minimizing the incidence of radiation necrosis. Cs-131 has a higher dose rate than I-125 (0.342 Gy per hour versus 0.069 Gy per hour), translating to 90% Cs-131 dose absorption within 33 days of implantation, whereas only 32% of I-125's dose would be delivered at this juncture. Cs-131's higher mean energy (29 keV) enables adequate dosimetry with the use of fewer seeds per given volume [63]. Han et al. used modelling methods to compare the effects of resection cavity changes on I-125 and Cs-131 implant dosimetry. The model was based on a single point source. Dose distributions were estimated via TG-43 calculations, and biological effective dose calculations were compared for both radioactive isotopes. They reported that resection cavities reach their 50% reduction point at an average 3.4 months following surgery, resulting in significant differences between I-125 and Cs-131 dosimetry. In comparison to the cavity at time of implantation, I-125 exhibited a 31.8% and 30.5% increase in dose to 90% and 10% of the target volume, respectively. Conversely, Cs-131 exhibited a 1.44% and 0.64% increase in dose to 90% and 10% of the target volume, respectively, suggesting changes in resection volumes affect Cs-131 dose distribution significantly less than that of I-125 for permanent brain implants [70].

Additionally, Cs-131 has a significantly shorter half-life than I-125 (9.69 days versus 59.4 days), denoting a shorter average life of the seeds (Table. 31.3). Faster radiotherapy completion (within 1 month of implantation) may impact a patient's overall multidisciplinary management, as many patients possess extracranial metastases warranting systemic therapy that cannot be safely administered simultaneously with radiation. Furthermore, the choice of Cs-131 brachytherapy seeds potentially exposes the patient and those in their proximity to less radiation, as well as hospital staff in the event of a subsequent neurosurgical procedure than would be the case if I-125 seeds were chosen for a permanent implant following a metastasis resection.

Both are subject to the ability to achieve gross total resection of the metastasis, as well as the technical expertise of the physicians placing and securing the implants. Significant residual disease is unlikely to be controlled with brachytherapy. It must also be noted that there is a small risk of seed migration following implantation [71–73]. Seed migration may occur when resections are in close proximity to the ventricles (if opened during surgery) or when seeds migrate out of the resection cavity into the subdural/subarachnoid space [71]. If seeds are still radioactive at the time of migration, the treated cavity may be underdosed and normal tissues in distant regions will be exposed to radiation.

Despite promising results in the aforementioned studies, Cs-131 remains a less investigated isotope than I-125, which has led to less frequent routine utilization outside of clinical trials [74].

Future Directions

Trials are needed to directly compare the efficacy of I-125 to Cs-131 as well as to directly compare the efficacy of intraoperative brachytherapy to preoperative and postoperative SRS. These trials may be paradigm-changing in the setting of large metastases, recurrent disease or for patients whose individual social and medical contexts hinder access to adjuvant radiation therapies.

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32 Laser Interstitial Thermal Therapy for Brain Metastases and Radiation Necrosis

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Introduction

History

Laser interstitial thermal therapy (LITT) is a minimally invasive operative technique that delivers ablation under magnetic resonance imaging (MRI) guidance. The principle of LITT is derived from animal experiments in the 1960s describing the ablation of melanomas and sarcomas using a neodymium laser [1]. These earliest observations sparked clinical trials that demonstrated potential for the technique; however, contemporaneous limitations in laser delivery systems and technical difficulties in operation contributed to the arrest of further development as a therapeutic alternative. In 1983, almost two decades after the original animal models, Bown et al. described the factors influencing the interaction of laser light with living tissue based on tissue models and the utilities of three laser varieties: CO_2, argon, and neodymium-doped yttrium aluminum garnet (Nd:YAG) [2]. Specifically, the authors found that Nd:YAG and argon lasers had greater foci destruction potential with minimal collateral damage to surrounding tissue. These results precipitated new efforts in the development of laser ablation therapy in the subsequent decades leading to data on the effects of various light wavelengths and optic fiber probe tips on surrounding neural tissue [3, 4]. However, it was not until 1995 with the advent of magnetic resonance (MR) thermography, that the potential applications of LITT therapy were further examined as real-time imaging guidance became a reality [5]. Since that time, studies have shown promise for LITT in the management of a wide range of surgical disorders.

In the earliest stages of LITT experimentation, ablation was delivered to skin surface tumors by glass fibers, though Bown and colleagues did describe the potential benefit of flexible fiber transmission for interstitial delivery with Nd:YAG lasers [2]. However, a limiting element that prevented large-scale utilization and investigation was the poor method of estimation of the thermal damage zone, conventionally done by postoperative imaging, which made LITT too risky for use in eloquent regions [6]. The modern development of durable optic fibers for treatment delivery and stereotactic guidance has increased precision in the placement of the treatment probe [5]. In addition, MR thermometry is critical to the viability of LITT as real-time monitoring of temperature and tissue damage allows for optimization of ablation temperatures to the region of

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interest while minimizing collateral damage to nearby tissue [7]. The combination of better laser delivery systems, stereotactic techniques, and real-time MR thermometry have manifested a new era of clinical research. This chapter will describe the operative technique for LITT as well as the current evidence for the management of cerebral metastases and radiation necrosis.

LITT Mechanism

The therapeutic benefits of LITT rely on the components of high-intensity electromagnetic radiation (EMR), light power density, wavelength, exposure duration, and exposure method (surface vs. interstitial) [4]. Tissue properties, such as water and hemoglobin content, affect the absorption of laser light and contribute to the vulnerability of various lesions to LITT [8]. In addition, optical properties of various intracranial structures, such as the absorption coefficients, scattering coefficients, and anisotropy factors contribute to laser penetration [9]. The earliest experiments investigating LITT primarily utilized surface exposure, whereas modern interstitial exposure delivers LITT directly to the center of the target lesion, minimizing damage to the surrounding tissue. Thermal damage is the primary mechanism of destruction resulting in enzyme induction, coagulation necrosis, protein denaturation, and vessel sclerosis [10–12]. Histologically, edema, neuronal swelling, and cell membrane disruption can be seen and contribute to LITT-induced tissue necrosis [13]. Three tissue zones have been described surrounding the LITT probe. The first zone nearest the probe undergoes coagulation necrosis, the second zone contains some tissue necrosis as well as edema, and the third zone contains injured cells with an intact ability to undergo repair [13]. These zones are demarcated particularly well on T1-weighted magnetic resonance imaging (MRI), though the probe tract is best seen on T2-weighted images [14].

Types of Lasers and Probes

Currently, two lasers are predominately used for LITT: continuous wave Nd:YAG, first described by Bown et al., and diode lasers [2, 15]. With wavelengths within the infrared spectrum (between 1000 and 1100 nm), Nd:YAG lasers have the highest penetration potential and are indicated for highly vascularized soft tissues [16]. On the other hand, diode lasers have the ability to deliver energy more rapidly, ablating lesions in less time due to a higher water absorption coefficient [15, 17]. LITT delivery relies on optic fibers composed of either quartz or sapphire, with the terminal probe composed of a heat-resistant flexible material that does not absorb light between 200 and 2000 nm. In addition, the recent development of fluid and gas cooling systems for LITT probes have decreased probe adherence to ablated tissues, improving reliability and control [17].

Current LITT Applications

For the management of neurosurgical disorders, LITT probes are often combined with stereotactic navigation, making it suitable for the ablation of deep-seated, otherwise inaccessible, lesions. Additionally, LITT has served as an alternative for the management of radioresistant tumors and ablation for epileptogenic foci in adults and children [18, 19]. LITT has also been used for the treatment of deep-seated tumors in particular with some success [16].

Commercially Available Delivery Systems

Two systems for LITT delivery are currently commercially available: the NeuroBlate System (Monteris Medical, Inc., Winnipeg, Manitoba, Canada) and the Visualase Thermal Therapy System (Medtronic Inc., Minneapolis, MN, USA) (Table 32.1). NeuroBlate uses an Nd:YAG

laser delivered by optical fiber. The probe tips are available in 3.2 mm and 2.1 mm diameters and are cooled by a CO_2-gas system [19]. Monteris has developed the M-Vision software for real-time stereotactic guidance which allows the user to define the target region, map probe trajectory, and monitor temperature changes in the ablated tissue. Within this software suite, the extent of ablation is represented by thermal-damage-threshold (TDT) lines based on the Arrhenius rate process model [7]. Specifically, this model establishes a first-order relationship between temperature, time, and cell injury and is used to predict thermal tissue damage [20]. Accordingly, increased time or temperature will result in a greater extent of tissue ablation.

Within the M-Vision suite, the TDT lines derived from the Arrhenius equation are color-coordinated yellow, blue, and white corresponding with the previously described zonal architecture of tissue following laser hyperthermia [21]. Tissue demarcated by the white TDT line represents tissue heated to 43 °C for 60 minutes and has undergone coagulative necrosis (Fig. 32.1a). The blue line demarcates tissue that has sustained severe damage from 10 minutes at 43 °C (Fig. 32.1b). The yellow line represents transient tissue injury with 2 minutes at 43 °C while tissue beyond this margin is assumed undamaged (Fig. 32.1c). The NeuroBlate system also employs a robotic arm and side-fire probe that enables remote changes to the directionality of the ablation tip intraoperatively.

Table 32.1 Comparison between the NeuroBlate and Visualase systems

NeuroBlate	Visualase
Integrated platform	Cart-based platform
DICOM image co-registration	
3D outline of thermal therapy zone and critical structures	2D only
Dedicated head fixation	3rd party fixation
Software actuated laser rotation and depth control	Manual laser probe manipulation
Choice of 2 gas-cooled probes: directional or diffusing	Liquid-cooled, diffusing
Multi-slice/multi-plane thermal monitoring	Single-slice/ single-plane
3D display of thermal dose contours	2D display of thermal dose contours

The Visualase system employs a 980 nm diode laser instead of Nd:YAG for lesion ablation [22]. The probe tip is cooled by circulating sterile, room temperature saline in the closed system. The location of the LITT probe is superimposed upon a preoperative MRI in the Visualase software suite workstation allowing for real-time guidance and measurement of thermographic feedback. Though this system does not utilize the TDT line system favored by the NeuroBlate system, it produces unique, color-coded images to delineate thresholds of thermal damage based on the same Arrhenius model [7]. An additional feature of the Visualase system is an automatic "trip-switch" that deactivates the laser if the temperature surpasses a predesignated threshold at "safety points" set by the user based on the preoperative MRI.

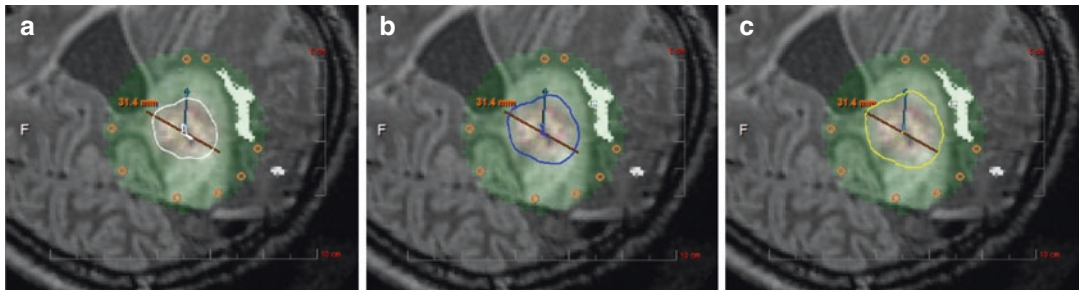

Fig. 32.1 The white thermal damage threshold (TDT) line (**a**) delineates the area of tissue ablated at 43 °C for 60 minutes, the blue TDT line (**b**) delineates the area of tissue ablated at 43 °C for 10 minutes, and the yellow TDT line (**c**) delineates the area of tissue ablated at 43 °C for 2 minutes

Operative Technique

Preoperative Preparation

Patients scheduled to undergo LITT must receive volumetric MRI sequences for procedure planning. Functional MRI (fMRI) with diffusion tensor imaging (DTI) sequences are also recommended for patients with lesions adjacent to white matter tracts. This additional analysis, particularly DTI with tractography, further defines the region of interest and allows the surgeon to plan a precise trajectory avoiding eloquent white matter tracts. The common approach to trajectory planning superimposes the potential thermal ablation zone on the preoperative MR images using a planning software. Then, a trajectory is established avoiding eloquent structures to the region of interest, taking into account the directionality of the probe tip [23]. If the volume of the region of interest is greater than 3 cm, more than one trajectory will have to be employed as the diameter of thermal ablation is 1.5 cm from the probe tip, thus influencing the size of the original incision. Alternatively, multiple probe tips may be used to ensure adequate tumor ablation.

The procedure itself can take place in an intraoperative or diagnostic MRI suite. The NeuroBlate system, in particular, is compatible with several MRI system manufacturers, including IMRIS (Winnipeg, Manitoba, Canada), Tesla Siemens (Erlangen, Germany), and GE Healthcare (Waukesha, WI, USA). Following induction of anesthesia, patients should receive 10 mg of intravenous corticosteroids and be positioned on a stabilization system. NeuroBlate utilizes the AtamA system for this purpose which employs a head immobilization ring with three to four pins, allowing supine, prone, or lateral positioning of the patient. After final arrangements are made to ensure stabilization, including sufficient reduction of risk for neuropathic and vasculopathic complications, sterile fiducials are placed on the surgical site and immobilization ring (AtamA for the NeuroBlate system) for stereotactic orientation. A preoperative MR image is performed with magnetization prepared rapid acquisition gradient-echo sequence (MP-RAGE) with the results uploaded to the supplemental software suite (e.g., M-Vision with NeuroBlate). At this stage, the lesion can be defined as well as potential trajectories for the LITT probe.

Operative Procedure: Pre-LITT

Once the patient's head is registered within the stereotactic navigation suite, superimposed upon the preoperative MP-RAGE MRI, the surgical site can be prepped and draped in sterile fashion according to hospital protocol. The interface platform can be aligned with the proposed probe trajectory to ensure an unopposed entry of the probe through the frame and the head immobilization ring. An incision is made with the number and trajectory of probes in mind (1 cm for a single probe). The interface platform can then be mounted to the skull with stereotactic guidance and anchored by screws. Alternatively, a small (5 mm) burr hole is created with a pneumatic drill and the dura opened and dilated. Then, a cannulated bolt is placed under image guidance using the VarioGuide system by Brainlab (Brainlab, Munich, Germany). Based on the planned trajectory, a 4.3 mm non-skiving drill bit is used to make a single burr hole, through which a 4 mm skull bolt is attached to the skull (Fig. 32.2a). The pre-measured laser probe is then passed through the bolt and anchored (Fig. 32.2b–d). This system has significant advantages to the previous AxiiS system and simplifies the surgical process.

The LITT software suite (e.g., M-Vision) can be used to determine the distance of the deepest margin of the lesion from the burr hole. This will allow the surgeon to select the shortest probe that can access the deepest margin of the lesion. The probe driver commander is placed into the interface platform with the probe driver follower placed into the central bore of the apparatus. The probe can now be guided through the mini-frame and burr hole following the selection of the depth stop based on lesion margin measurements. Once the laser probe is seated into the probe driver

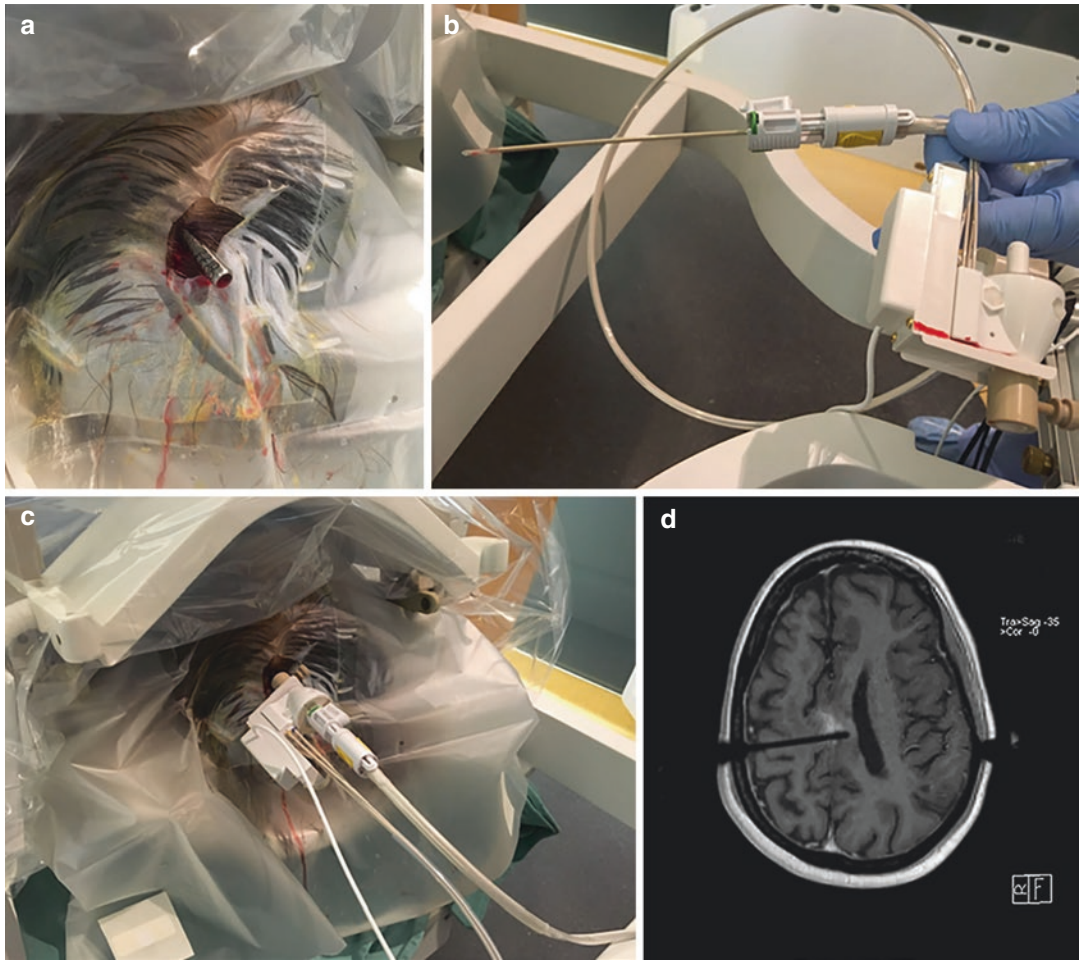

Fig. 32.2 Images of LITT procedure at M.D. Anderson Cancer Center. A cannulated bolt is placed in the patient's skull (**a**) followed by placement of the LITT probe (**b**) through the bolt. The patient is then placed in the intraoperative MRI scanner with the delivery probe in place (**c**) and a pre-ablation T1-weighted MRI is obtained confirming correct placement of the probe (**d**)

another MRI of the patient is taken to confirm the correct orientation of the probe based on the planned trajectory and to guide position readjustments if necessary.

Operative Procedure: LITT

With the probe in an acceptable location at starting depth, the MRIs are fused together and the probe coordinates superimposed over the planned trajectory created within the software suite. During treatment, the software suite will display coronal and sagittal plane images as well as three axial plane images with real-time feedback of the probe location. Once the probe is inserted to the desired depth within the lesion, corresponding to the fused MRIs, the thermography sequences can begin. Depending on the type of probe and delivery system used, the direction of laser fire may require selection at this point that will best be contained within the margins of the lesion. Eight cycles, every eight seconds, of scanning for temperature reference points must be done prior to

laser activation followed by cooling of the probe. The operator activates a switch on the software suite screen which arms the foot switch for laser activation. Total treatment time correlates with tumor size, number of trajectories, and type of laser (e.g., diode lasers have shorter ablation times) as well as tissue hydration, directionality of the probe tip, and proximity to eloquent cortex or white matter tracts [7].

Operative Procedure: Post-LITT

The protocol followed at M.D. Anderson Cancer Center calls for a final MRI before withdrawing the probe following ablation sequences along all trajectories, at which point the probe driver and interface platform are removed. The skull bolt is removed using a hex tool and the wound is irrigated followed by hemostasis, then the skin is closed with a single suture and dressed. Following arousal from anesthesia, a neurological exam is performed on the patient to determine any changes from the preoperative condition. On postoperative day one, an MRI is recommended to evaluate residual tumor volume and extent of ablation (Fig. 32.3). For uncomplicated cases, hospital stay is typically one day from the time of operation. The taper of corticosteroids can be based on the extent of postoperative edema at the surgeon's discretion.

LITT for Brain Metastases

Background

Brain metastases occur in 10–20% of adults with underlying malignancy and are estimated to be ten times more prevalent than primary intracranial tumors [24]. Conventional treatment modalities include surgical resection, whole brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS), or a combination of these. Treatment of choice should be individualized according to clinical (age, Karnofsky Performance Scale [KPS] score, primary tumor control, extracranial metastases), pathological (primary tumor histology), and radiological aspects (number of brain metastasis, functional location, deep-seated lesions, etc.) [25]. Patient preference and estimated quality of life resulting from treatment in the setting of terminal metastatic disease should also be considered; the optimal therapeutic approach must balance risks and benefits as well as patient particularities. Rapidly improving systemic therapies have prolonged the survival of cancer patients subsequently increasing the incidence of brain metastases, yet the poor penetration of the blood–brain barrier by most of these agents contributes to limited efficacy [26]. While an increasing amount of basic and clinical research has made progress in delineating the genetics, tumor microenvironment, mechanisms

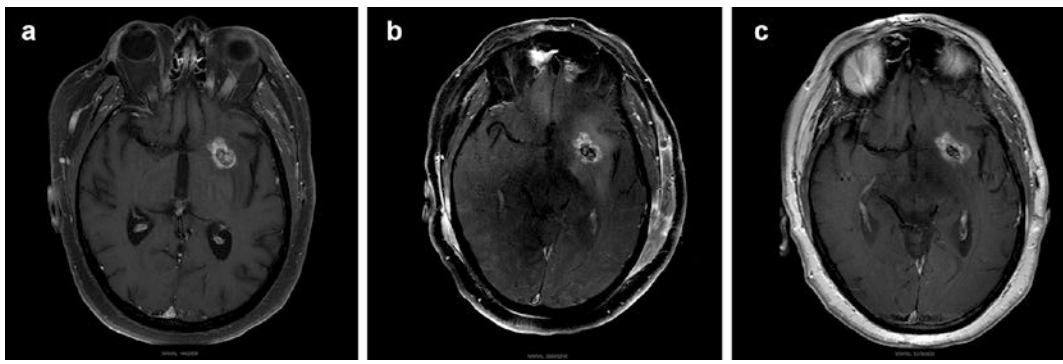

Fig. 32.3 T1-weighted post-contrast MR images showing a metastatic lesion preceding LITT (**a**), immediately after LITT (**b**), and at one-month follow-up (**c**)

of leptomeningeal spread, and effects on neurocognition, local treatment with surgical resection, SRS, WBRT, either alone or in combination remains the cornerstone of therapy for patients with brain metastases. Since the introduction of LITT, several case reports and case series have been published, describing the efficacy of this technique for the management of brain metastases (Table 32.2).

Current Evidence

In 2008, Carpentier and colleagues published pilot results of the first phase I study utilizing MR-guided LITT for the management of patients with cerebral metastases [22]. The patient cohort primarily consisted of four patients with unresectable intracranial metastases refractory to multiple treatments (chemotherapy, WBRT, and SRS). The authors utilized the Visualase system and reported positive results; all patients tolerated the procedure well and were discharged within 14 hours postoperatively. All lesions were observed to increase in volume at immediate follow-up, followed by a gradual decrease in size. No lesion recurrences occurred at any point during the 7, 15, 30, or 180-day follow-ups. The authors concluded LITT to be a safe, effective treatment for focal metastatic disease [22]. Carpentier again investigated the feasibility of the Visualase system in a cohort of seven patients, reporting similar results, with a median overall survival of 19.8 months [27].

Hawasli et al. provided additional evidence for LITT in a 2013 prospective study of 17 patients, 5 of which had cerebral metastases [28]. The authors reported an initial increase in lesion size at follow-up with subsequent steady volume decrease. The pooled analysis of LITT for primary brain tumors and metastases reduces the reliability of this data for guiding LITT for brain metastases, specifically. However, the authors concluded LITT to be a viable treatment option for cerebral metastases in selected patients. Fabiano et al. reported different findings in a series of two patients with cerebral metastases who received LITT [29]. In both patients, LITT was utilized for the management of recurrent metastases and in both cases the tumor returned and required additional resection. Although these results were suboptimal, the authors noted that failure reporting for LITT is required to properly define the utility of this procedure.

In 2016, Ali et al. reported on the first multicenter study of the treatment of LITT for post-SRS recurrent cerebral metastases in a cohort of 23 patients with 26 total lesions ranging in volume from 0.4 to 28.9 cm^3 [30]. Disease control was obtained in 17 cases while 9 lesions (35%) showed disease progression after LITT. Notably, this only occurred in lesions that received <80% ablation. The authors concluded that LITT can be considered an effective treatment when tumor ablation exceeds 80% but highlighted the importance of risk evaluation for complications that may ensue following treatment of larger lesions (defined as >20 cm^3).

In 2018, Eichberg and colleagues reported the results of a pilot study of LITT for four patients with metastatic lesions in the posterior fossa [31]. Like previous studies, lesions volumes were initially increased before gradually decreasing. The authors observed no complications and no clinical or radiographic evidence of tumor progression. They thus concluded LITT to be safe and effective for cerebellar metastases. These findings were echoed the same year by Razavi et al. in a study of eight patients who underwent LITT treatment, three of which had metastatic lesions in the posterior fossa [32].

In the largest study on the subject to date, Beechar et al. performed a volumetric analysis of recurrent lesions managed with LITT following SRS [33]. Using T1 post-contrast and T2 fluid-attenuated inversion recovery (FLAIR) MRI sequences for evaluation of edema, 50 total lesions from 36 patients were treated with LITT with a significant overall reduction in lesion size. However, 37% of lesions demonstrated an upward trend overall on follow-up MRI. The authors concluded that pre-treatment tumor volume plays a significant role in determining LITT response, with preferable responses in smaller lesions.

Table 32.2 Studies of LITT for brain metastases

Author	Year published	No. of patients	Tumor location[a]	Primary histology	Lesion diameter/volume[b] (cm/cm^3)	Outcome	Complications
Carpentier et al.	2008	4	Frontal (1) Temporal (2) Parietal (2) Occipital (1)	Breast (5) NSCLC (1)	NR	Peripheral recurrence at 3 months (3)	None
Carpentier et al.	2011	7	NR	Breast[c] NSLC[c]	Range 1–3 cm	Median OS: 19.8 months Mean PFS: 3.8 months	Probe misplacement (1) Cerebellar syndrome (1) Transient aphasia (1)
Jethwa et al.	2012	20	Parietal (2) Cerebellar (1) Frontal (1)	NR	Median 7.0 cm^3	NR	None (BM patients)
Hawasli et al.	2013	17	Insula (1) Frontal (2) Parietal (1) FP (1)	Colon (1) Melanoma (1) SCLC (2) Ovarian (1)	Mean 11.6 cm^3	Median PFS: 5.8 months Median OS: 5.8 months	Transient aphasia (3) Transient hemiparesis (3) Transient hyponatremia (2) DVT (1) Fatal meningitis (1)
Ali et al.	2016	23	Frontal (10) Parietal (4) Occipital (2) 1 lt motor strip Insular (1) BG (2) Cerebellar (1) PO (2) Thalamic (4)	Breast (6) Lung (6) Melanoma (5) Colon (2) Ovarian (1) Bladder (1) Esophagus (1) Sarcoma (1)	Median 4.9 cm^3	Recurrence (9) Local control (17)	Transient hemiparesis (3) Hydrocephalus (1) Malignant cerebral edema (1)
Beechar et al. (both CRN and BM)	2017	36	NR	NSLC (8) SCLC (2) Breast (8) Esophagus (1) SCC (1) RCC (1) Rectal (1) Sarcoma (2) Melanoma (15) Bladder (1)	Median 5.1 cm^3	↑ Lesion size transient (19) ↑ Lesion size sustained (14) ↓ Lesion size over time (31)	Motor disturbance (9) Gait disturbance (8) Visual disturbance (5) Sensory disturbance (2) Aphasia (2) Memory difficulty (1) Headache (1)

Author	Year published	No. of patients	Tumor location[a]	Primary histology	Lesion diameter/volume[b] (cm/cm^3)	Outcome	Complications
Eichberg et al.	2017	4	Cerebellar (4)	Breast (3) Ovarian (1)	Median 3.4 cm^3	Stable (4)	None
Chaunzwa et al. (both CRN and BM)	2018	30	Frontal (16) Parietal (4) Occipital (5) Temporal (3) Insular (1) BG (1)	Lung (16) Melanoma (5) Breast (3) Colon (1) Gynecological (2) RCC (1) Other (2)	Median 7.6 cm^3	Survival 6 months (15) 12 months (7) 18 months (4) 25 months (1) 30 months (1) Local control 92.6 months (92.9%) Overall (83%)	Intraoperative Hemorrhage (13%)
Ahluwalia et al.	2018	42	Frontal (41%) Parietal (29) Cerebellar (14%) Other[d] (16%)	Breast (10%) NSCSLC (50%) SCLC (5%) Melanoma (10%) Other[d] (25%)	Mean 7.1 cm^3	Survival 12 weeks (71%) 26 weeks (64.5%)	Postop Complications (5%) Intracerebral hemorrhage (5%) Weakness (5%)
Hernandez et al.	2018	45	NR	NSCLC (31) Breast (17) Colon (2) RCC (2) Melanoma (3) Testicular (2) Cervical (1) SCLC (1)	Mean 3.4 cm^3	Local control (83.1%) Recurrence (10)	Complications (25%)
Razavi et al.	2018	8	Cerebellar (3)	Colon (2) NSCLC (1)	Median 5.4 cm^3	Recurrence at 7.5 months (1) Stable (2)	CN 6 palsy (1)

NR not reported, *MI* myocardial infarction, *PE* pulmonary embolus, *FP* frontoparietal, *CC* corpus callosum, *BG* basal ganglia, *PV* periventricular, *TP* temporoparietal, *FT* frontotemporal, *NSCLC* non-small cell lung cancer, *SCLC* small cell lung cancer, *RCC* renal cell carcinoma, *SCC* squamous cell carcinoma, *Pts* patients, *OS* overall survival, *PFS* progression-free survival, *CN* cranial nerve

[a]Some patients have more than one tumor

[b]Articles vary in describing lesion diameter or volume

[c]Number not recorded

[d]Occipital lobe, temporal lobe, thalamus, and other deep nuclei

Ahluwalia et al. reported on the results of the first multicenter phase II trial of LITT for patients with radiographic progression after SRS for intracranial metastases as part of the Laser Ablation After Stereotactic Radiosurgery clinical trial (LAASR study, NCT01651078) [34]. Of 42 patients enrolled in the trial, 20 were confirmed to have a recurrence of intracranial metastases. In addition to being well powered, this study was significant in addressing the diagnostic and management conundrum of lesion recurrence following SRS and the authors reported improved short term overall and progression-free survival in patients with radiation necrosis compared to cerebral metastases treated with LITT. Ultimately, this trial provided evidence for LITT management with resultant stabilization of KPS, cognition, and quality-of-life (QOL) as well as a reduction in steroid use.

In light of the previously described diagnostic and management conundrum associated with post-SRS lesion recurrence, Hernandez et al. proposed the radiographic definition of progressive enhancing inflammatory reactions for unknown lesions following SRS based on their results of a retrospective study of 59 patients with 74 total lesions [35]. Given the demonstrated efficacy and safety reported on LITT for both conditions, the authors argue that careful discrimination between these two conditions is unnecessary as good local control was achieved for the ambiguous lesions in a majority of the patients.

Recommendations

The current body of work describing the safety and efficacy of LITT for cerebral metastases which have failed radiotherapy is still in the early stages. The case series and small clinical trials have provided pilot data to evidence the utility of this therapy while noting some associated phenomena such as the initial increase in lesion size before gradual volume reduction. Though Beechar et al. found better LITT response in smaller metastatic tumors, the results of other studies describing positive results with different lesion sizes potentially illustrate a role for this therapy in the management of metastases not amenable to SRS, namely, those >3 cm in size [33].

We stress the need for prospective collection of QOL and cognition data in future studies to provide evidence for the role of this novel therapeutic in allowing terminally ill patients to retain QOL after salvage treatment. It has been reported that when total ablation can be performed, KPS, cognitive status, and QOL can be preserved but additional prospective studies are needed to confirm these observations [34]. Complications associated with LITT are significantly less when compared to open cranial procedures and thus acceptable in this patient population but can be associated with increased length of hospital stay.

LITT for Radiation Necrosis

Background

Cerebral radiation necrosis (CRN) is a known consequence of brain tumor management, affecting between 3% and 24% of patients receiving cranial radiotherapy [14, 36]. The pathophysiology of CRN is not fully understood, although a few theories have been reported in the literature. One of the most accepted of these states that CRN is driven by vascular endothelial damage leading to coagulation necrosis and reactive gliosis in response to severe hypoxic insults by high cumulative doses of radiation [37]. This is supported by the thickening of the endothelium and lymphocytic infiltration seen on histopathology as well as the positive outcomes for CRN patients associated with bevacizumab, an inhibitor of angiogenesis [38]. A second hypothesis suggests that acute phase reactant cytokines in response to radiation therapy may drive immune-mediated damage to surrounding tissue that subsequently precipitates inflammation, gliosis, and vasogenic edema [39]. Though the exact molecular mechanism is not yet fully described, researchers and clinicians alike postulate that disruption of the blood–brain barrier ultimately defines the pathogenesis [40]. Thus, a better understanding of the molecular processes that contribute to this dis-

ease process can guide the development of more targeted therapies for treatment and prevention.

The gold standard for diagnosis of CRN is biopsy, though MRI has limited diagnostic value [41]. There are often difficulties in distinguishing between CRN and other pathologic processes on MRI, although some radiologic techniques have been described [42]. CRN can usually be managed conservatively with corticosteroids for associated edema followed by various experimental drugs if symptoms persist. Of these, bevacizumab has been reported to have some benefit, and anticoagulant/antiplatelet medications have been shown to improve outcomes in some patients based on the ability to interfere with attributable underlying vascular changes [43–48]. In addition, hyperbaric oxygen has been shown to have some efficacy in the management of these patients [49]. With conservative therapy, however, a subset of patients will either fail to improve or experience progression of CRN, requiring a more aggressive management strategy. Recently, case reports and patient series have illuminated a possible role for LITT in cases of CRN refractory to rehabilitation and pharmacotherapy (Table 32.3).

Rahmathulla and colleagues were the first to describe LITT for the management of CRN in a 2012 case report [50]. Following SRS for management of multiple brain metastases, a CRN lesion was observed in the left centrum semiovale with worsening edema refractory to high-dose glucocorticoid therapy. The authors performed LITT as the location of the lesion was not amenable to resection which resulted in a successful reduction in size at 7-week follow-up. The authors concluded that LITT is an option for patients with refractory CRN not amenable to surgical decompression [50].

One year later, Torres et al. reported on the results of six patients who underwent SRS for brain metastasis and were discovered to have lesion regrowth, later confirmed to be CRN on biopsy [51]. LITT was performed to prevent further progression of neurologic symptoms and edema. Four out of six patients treated with LITT had an improvement of neurologic symptoms. One patient died as a result of the progression of underlying malignancy and another patient required an additional craniotomy for lesion regrowth. No complications occurred during the procedure and the authors concluded that LITT is a feasible alternative for the treatment of lesion "regrowth" following SRS. It is important to note, however, that stereotactic biopsy has an intrinsic sample bias and refractory cases considered to be CRN may in fact correspond to tumor progression within this setting.

In 2014, Fabiano and colleagues reported on the case of a man who received SRS for a brain metastasis from lung adenocarcinoma. However, despite medical management, the lesion continued to progress on imaging. A decision for LITT was made based on the deep-seated location of the lesion and resulted in a marked improvement in symptoms. Despite being described as CRN, no biopsy was performed to confirm the diagnosis; though it is plausible the lesion represented tumor recurrence. Although it is unclear whether CRN was the target of LITT in this case, the positive outcome of the patient provides evidence, albeit marginal, for the management of ambiguous lesions in deep-seated loci.

The same year, Rao et al. published the results of a cohort study investigating the utility of LITT for either tumor recurrence or CRN after SRS [52]. In this retrospective cohort study, 16 patients received SRS for metastatic intracranial tumors with new onset of symptoms and MRI findings consistent with either tumor recurrence or CRN. These patients then received LITT for the management of these ambiguous recurrent lesions (either tumor recurrence and/or CRN). Of the 15 patients with reliable follow-up, two experienced lesion recurrence again at 6 and 18 weeks, respectively. Five patients died of extracranial disease progression and one died of intracranial disease progression at a different locus. The authors concluded that LITT is a well-tolerated procedure that may be effective in treating tumor recurrence and/or CRN. This study provides additional evidence for the utility of LITT in managing CRN, though it again highlights the diagnostic conundrum of these lesions following SRS.

Table 32.3 Studies of LITT for cerebral radiation necrosis

Author	Year published	No. of patients (CRN)	Tumor location[a]	Lesion diameter/ volume[b] (cm/cm^3)	Outcome	Complications
Rahmathulla et al.	2012	1	Motor cortex	2 cm or 5.4 cm^3	↓ Lesion size and edema, ↓ steroid requirement	None
Torres-Reveron et al.	2013	6	Frontal (3), Cerebellum (2), Parieto-occipital (1)	0.68–3.03 cm	↑ Lesion size at 2 weeks to 3 months, then ↓ lesion size 4.5–6 months	NR
Fabiano et al.	2014	1	Frontal	1.8 cm	↓ Volume at 10 weeks	NR
Rao et al.	2014	15	Frontal (6), Cerebellar (6), Cerebellar peduncle (1), Temporal (1), Parietal (1)	0.46–25.45 cm^3	↑ Lesion size at 24 hrs (12) ↓ lesion size at 24 hrs (2), lesion volume ≤ 10% pre-treatment at 16–44 weeks (7)	New-onset transient left-sided weakness[c] (1)
Smith et al.	2016	25	Frontal (11), Cerebellum (1) Temporal (5), Parietal (2), Thalamus (1), Occipital (1), PV (1), TP (1), FT (1), CC (3), FP (2)	NR		Transient weakness (2), permanent weakness (1), steroid complication (1)
Ahulwalia et al.	2018	19	NR	0.4–13.2 cm^3	Stabilized KPS, preserved QOL ↓ Steroid requirement	Complete hemiparesis (1), headache (1), hemineglect and weakness (1)
Rammo et al.	2018	10	Frontal (4), Temporal (2) Parietal (2), Frontal thalamic (1), Frontal medial (1)	1.62 cm^3 (mean)	↑ Lesion size at 1–2 weeks, ↓ lesion size at 6 months	Intractable seizures[d] (1), PE (1), MI (1) Transient delayed neurologic deficit (3)

NR not reported, *MI* myocardial infarction, *PE* pulmonary embolus, *FP* frontoparietal, *CC* corpus callosum, *PV* periventricular, *TP* temporoparietal, *FT* frontotemporal

[a]Some patients have more than one tumor

[b]Articles vary in describing lesion diameter or volume

[c]Patient has residual left-hand weakness

[d]Patient had preceding seizure disorder worsened by LITT

Smith and colleagues demonstrated the outcomes of LITT for biopsy-proven CRN in a cohort of 25 patients [53]. In this retrospective study, patients treated for primary and metastatic brain tumors received LITT following stereotactic needle biopsy of recurrent lesions confirming CRN. No complications occurred during the procedure and overall survival and progression-free survival were comparable to standard craniotomy and resection.

The previously discussed phase II trial published by Ahluwalia et al. in 2018 was the first study of its kind and magnitude investigating LITT for metastases and biopsy-proven radiation necrosis [34]. Of 42 patients enrolled in the trial, 19 had biopsy-confirmed CRN treated with LITT. In this study, the authors compared outcomes of LITT for CRN and cerebral metastases and found longer progression-free and overall

survival rates at 12-week follow-up for patients with CRN, although this difference was not statistically significant at 26 weeks. In this subset, LITT stabilized the KPS score, preserved QOL and cognition, and had a steroid-sparing effect. The authors concluded that LITT is a low-risk procedure for patients with few alternative options for salvage treatment that can minimize cognitive decline, stabilize QOL and functional status, and allow cessation of steroids in some cases.

Rammo et al. reported on the most recent study of LITT for CRN to date [54]. Ten patients with biopsy-proven CRN were retrospectively reviewed to assess the outcome. Four patients had neurologic deficits which resolved in three. The authors concluded LITT to be a relatively safe treatment for CRN with the added benefit of being both diagnostic and therapeutic. Like the previous study, Rammo and colleagues provide additional evidence for LITT management of biopsy-proven CRN.

Recommendations

Since the original case report described by Rahmathulla et al., LITT has been used as a salvage therapy for deep-seated lesions otherwise inaccessible by conventional resection techniques [50]. A number of small case series of patients with recurrent lesions after SRS without biopsy-proven CRN were published with good local control. These studies concluded that LITT is a safe and effective therapy for recurrence following SRS.

For patients with medically refractory CRN, LITT offers a number of advantages in comparison with traditional resection techniques. Namely, the procedure itself is less invasive than conventional craniotomy. In addition, patients can resume their chemotherapy regimens soon after LITT as there is a theoretical advantage to the disruption of the blood–brain barrier by the procedure. Although multicenter prospective studies are needed before detailed guidelines for the management of refractory CRN are developed, LITT has been shown to be an effective treatment for these patients.

Conclusion

LITT is a minimally invasive ablation technique which has recently seen a surge in research investigations and clinical applications for the treatment of radiation necrosis and cerebral metastases. The role of LITT in neurosurgical oncology is evolving and well-powered, prospective studies are needed to fully establish its potential [13, 28, 55–61]. However, LITT appears to be a safe modality in the management of lesion recurrence following SRS, irrespective of the ultimate diagnosis.

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Preventing Cranial Wound Complications in Cancer Patients

33

James C. Lee, Jimmy Xia, Rohan Ramakrishna, and David M. Otterburn

Introduction

Patients undergoing resection for intracranial neurosurgical tumors pose unique issues for the reconstructive team, and consideration needs to be given for not only the initial resection but also for possible future resections. A strong understanding of the anatomy of the overlying soft tissue is important to prevent ischemic complications. Patients undergoing re-operative cases are at higher risk for infections, wound dehiscence, and skin necrosis which all stem from decreased blood flow and tension in the scalp from prior scarring. The combination of poor nutrition, immunosuppressive agents, anti-angiogenic agents, and radiation all pose specific risks to the postoperative patient which needs to be considered during operative planning. In this chapter, we will discuss these issues and highlight how to minimize tissue ischemia with appropriate planning of incisions through assessment of scalp perfusion. We will also discuss the management of the patient in the immediate postoperative period.

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Anatomy

Anatomic Layers

The scalp consists of five anatomic layers which are often described by the mnemonic "SCALP" (Fig. 33.1). Starting from the most superficial layer to the deepest layer, the five layers consist of:

- Skin
- Connective tissue
- Galea aponeurotica
- Loose areolar tissue
- Pericranium

The skin is connected to the galea aponeurotica through a network of tight connective tissue bands, allowing the galea aponeurotica and skin to move as a single unit during surgical manipulation. This subcutaneous connective tissue layer also contains much of neurovascular structures, and dissection in this plane can result in significant bleeding. The galea aponeurotica is a fibrous layer continuous with the superficial musculoaponeurotic system (SMAS) of the face and is controlled by the frontalis muscle anteriorly and the occipitalis posteriorly. Under the galea aponeurotica is the loose areolar tissue, which allows for movement of the galea over the pericranium. The loose areolar tissue is a relatively avascular plane that allows for easy dissection

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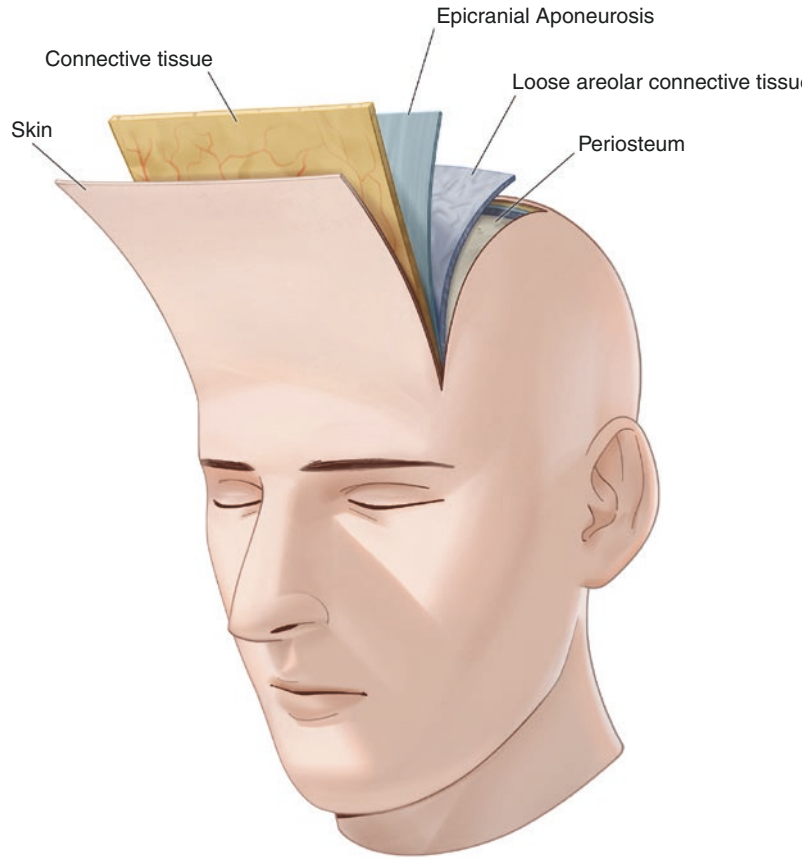

Fig. 33.1 The anatomical layers of the scalp

during surgical exposure of the pericranium with minimal bleeding. The pericranium is the periosteum of the skull that separates relatively easily from the underlying bone except at the cranial sutures. The pericranium provides nutrition to the skull and can be elevated as a flap for coverage and lining.

Innervation

Anteriorly, the scalp is innervated by the supratrochlear and supraorbital nerves, both of which are derived from the ophthalmic division of the trigeminal nerve. The supratrochlear nerve innervates the lower part of the forehead, traveling beneath the frontalis as it ascends. The supraorbital nerve originates from the supraorbital notch or foramen and terminates in medial and lateral branches. The medial branch of the supraorbital nerve enters the corrugator supercilii and frontalis muscles, while the lateral branch enters the galea aponeurotica. Posteriorly, the greater occipital nerve, originating from the C2 spinal nerve, provides innervation from the occiput to the vertex. The lesser occipital nerve originates from C2 and C3 spinal nerves and innervates the region of the scalp posterior to the ear. The auriculotemporal nerve, a branch of the mandibular division of the trigeminal nerve, innervates the tragus, the area anterior to the ear, and the posterior portion of the temple region. In the temporal scalp region, special attention should be paid to the frontal branch of the facial nerve as it passes cephalad over the zygomatic arch, running just deep to the superficial temporal fascia as it innervates the frontalis, orbicularis oculi, corrugator supercilii, and auriculares anterior and superior.

Blood Supply

Understanding the rich blood supply of the scalp is crucial to avoiding wound complications during cranial surgery. The five main paired arteries that supply the scalp come together in a rich arterial network that runs throughout the subcutaneous connective tissue layer (Fig. 33.2). From the ophthalmic branch of the internal carotid artery, the supratrochlear and supraorbital arteries arise from the superior orbital rim and supply much of the anterior scalp. The supratrochlear artery provides much of the blood supply to the midline forehead, while the supraorbital artery reaches as far up as the vertex of the scalp. Laterally, the superficial temporal artery arises from the external carotid artery and runs anterior to the ear before splitting into frontal and parietal branches. The superficial temporal artery is typically the largest of the scalp vessels, and it anastomoses with the supratrochlear and supraorbital vessels anteriorly and the posterior auricular and occipital vessels posteriorly. The occipital artery is the main blood supply of the posterior scalp, and it also arises from the external carotid artery system. It runs deep to the neck muscles posteriorly from the external carotid artery before turning cephalad from the posterior scalp up to the vertex. The posterior auricular artery, the smallest of the scalp arteries, branches off of the external carotid artery and provides bloody supply to the posterior ear and mastoid region.

The venous drainage pattern of the scalp follows veins that run with the arterial blood supply. Additionally, emissary veins on the cranium also contribute by draining blood into the dural sinuses. Lymphatic vessels also run in the subcutaneous connective tissue layer, draining into parotid, preauricular, postauricular, upper cervical, and occipital lymph node basins.

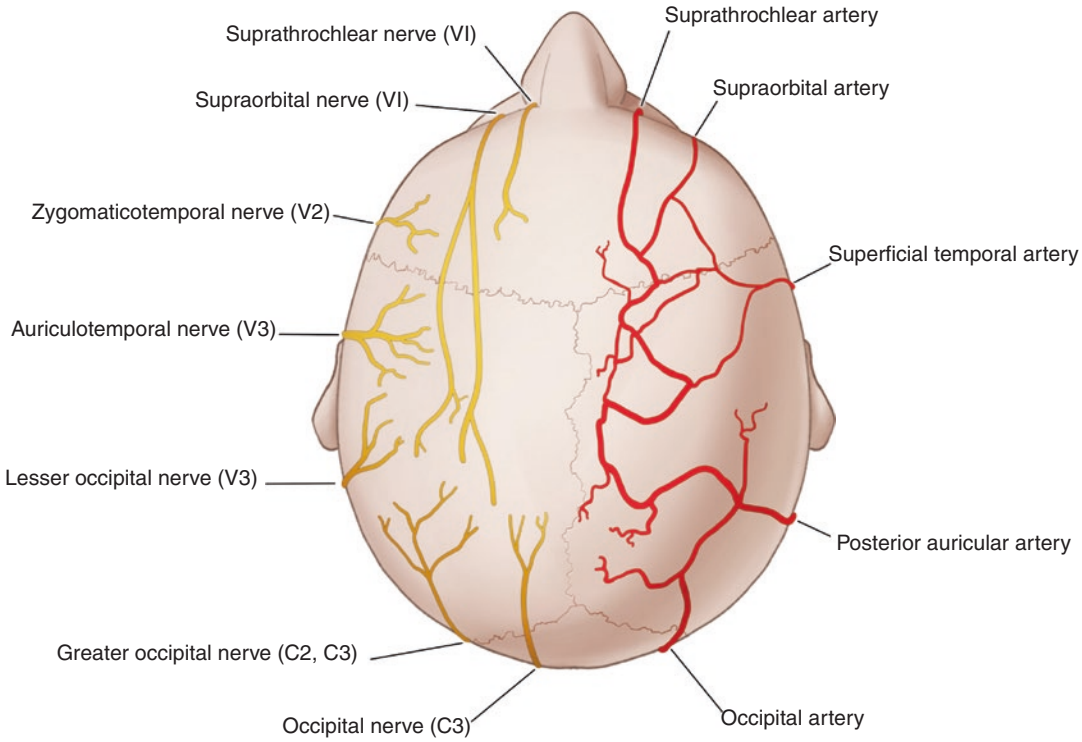

Fig. 33.2 The five main paired arteries of the scalp (right) and the neural innervation of the scalp (left)

Risk Factors for Complications

Medical History

Several patient-specific factors can put a patient at elevated risk for scalp complications postoperatively. A comprehensive preoperative history and physical is essential to note and control for these relevant factors. Factors such as smoking history and diabetes mellitus can affect the vascularity of the scalp and increase the risk of wound complications. Nicotine in smoke acts as a vasoconstrictor while also increasing platelet adhesiveness [1]. Carbon monoxide reduces oxygen transport and hydrogen cyanide impairs oxidative metabolism. These substances in cigarette smoke can lead to tissue ischemia, thrombotic microvascular occlusion, and impaired healing [1]. Similarly, diabetes mellitus contributes to poor wound healing in multiple ways, including microvascular ischemia, impaired immune function, decreased growth factor production, and reduced fibroblast proliferation.

Nutrition is also important to take into consideration, especially in cancer patients who may be cachectic or have poor oral intake. Malnutrition has been well-documented as a risk factor for poor wound healing, infectious complications, and other sources of operative morbidity and mortality. In critically ill patients or patients under stress, basal energy expenditures and caloric requirements are increased, necessitating a more aggressive approach to maintaining proper nutrition. Proper nutrition includes not only adequate intake of all macronutrients such as carbohydrates, fats, proteins, and fluids but also a sufficient supply of micronutrients [2]. These micronutrients include amino acids; vitamins A, C, D, and E; and minerals such as zinc, selenium, and iron. Vitamin C is well-known for its role in collagen polymerization and cross-linking. Vitamin A is an important cofactor in the inflammatory phase of wound healing, promoting phagocytic activity and immunologic function. Although the mechanisms of vitamin E and zinc are not as well-defined in the literature, there are data that support their importance in collagen production [2]. It is also recommended that albumin and prealbumin levels are within normal levels prior to surgical intervention, and supplemental nutrition should be provided as needed to help patients reach their nutritional goals. Enteral nutrition is preferred over parenteral nutrition, as enteral nutrition is more efficient, has fewer metabolic complications, costs less, and helps promote the growth and development of gastrointestinal mucosal tissue. When enteral nutrition is not possible, parenteral nutrition should be considered in malnourished patients. Regardless of nutritional route, all patients should be offered adequate nutritional support prior to surgical intervention in order to avoid wound complications in this high-risk population.

Perfusion

Tissue perfusion is essential to wound healing, and any conditions that may impair adequate perfusion of the scalp can increase the risk of cranial wound complications. During incision planning, previous scars should be taken into consideration, and adequate inflow from at least one of the five major blood supplies should be preserved. The vascular network of the scalp runs in the subcutaneous connective tissue layer superficial to the galea aponeurotica so great care should be taken when performing galeal scoring maneuvers. Adequate blood pressure and hemoglobin should be maintained in the perioperative period to ensure sufficient perfusion and oxygenation for wound healing. Postoperative dressings should allow for expected edema and not be tight enough to restrict blood flow to the surgical site.

Tension

Care should be taken to avoid tension over the scalp closure in order to prevent wound complications such as dehiscence, skin necrosis, and infection. Experimental studies have also demonstrated increased incidence of hypertrophic

scarring and scar widening when wounds are subjected to excessive tension during the early wound healing period [3]. Techniques to avoid tension during incision closure include wide undermining of the scalp in the loose areolar tissue layer, performing galeal scoring maneuvers, and utilizing local flaps as needed. Scalp tissue should be closed in a layered fashion with sutures in the galea aponeurotica offloading most of the tension from the cutaneous closure [4]. Tissue expansion can sometimes be used prior to oncologic resection if there is an anticipated deficit of scalp tissue and sufficient lead time prior to surgery.

Radiation

The negative effects of radiation on wound healing have been well-documented in the literature. The inflammatory phase of wound healing, characterized by the infiltration of macrophages and neutrophils, is delayed and inhibited in irradiated tissues. The formation of granulation tissue is also slowed as fibroblast activity and collagen formation are reduced. Lastly, epithelialization in irradiated tissue is delayed and the overall healing time of wounds is prolonged. The effect of external beam radiation on the scalp is characterized by early skin changes followed by chronic damage long after radiation therapy has been completed. Acute findings include skin erythema, tenderness, warmth, epidermolysis, and ulceration. These effects are often dose-dependent and reversible. Long-term effects of radiation can include tissue fibrosis, sebaceous gland dysfunction, loss of hair follicles, microvascular compromise, skin necrosis, and secondary carcinogenesis. These effects are often irreversible and result in a higher risk of delayed wound healing, infection, hardware exposure, skin necrosis, and flap failure [5].

Preoperative radiation, when indicated, should be performed at least 3–6 weeks prior to surgery in order to avoid wound complications. This is especially important when doses larger than 50 Gy are administered. Postoperative radiation therapy is often preferred to allow for a period of healing prior to initiating the negative effects of radiation therapy on wound healing [6]. Clinical studies have demonstrated lower rates of wound complications when postoperative radiotherapy is used, and this may be an important consideration when recurrence rates are similar with preoperative and postoperative radiation therapy [5, 6]. Some of these concerns can be mitigated with radiosurgical techniques either in the pre- or postoperative setting. Given the high conformality and ability to limit scalp dose, the concerns related to wound healing are minimized. In our practice, we are comfortable with either preoperative or rapid postoperative radiosurgery given the advantages conferred by this radiation technique.

Chemotherapy

Similar to radiation therapy, chemotherapy is an important component of cancer treatment but can negatively impact wound healing via several mechanisms. The effects of chemotherapeutic agents are linked to their ability to impair DNA replication, interfere with metabolic processes, and prevent cell division. While these effects disproportionately impact rapidly growing tissues such as cancer cells, they can also impact immune cells, epithelial tissue, neovascularization, and fibroblasts that are important in the wound healing process.

Alkylating agents such as cyclophosphamide at high doses have been shown to increase wound complications by impairing neovascularization during the proliferative phase of wound healing. Thiotepa and mechlorethamine have also been demonstrated to impair wound healing in animal models by inhibiting fibroblast function and collagen production. Cisplatin has also been proven in multiple animal studies to decrease wound healing by impairing fibroblast proliferation, inhibiting neovascularization, and reducing connective tissue proliferation [6].

Chemotherapeutic antibiotics such as bleomycin, doxorubicin, and mitomycin C have also

been found to have an impact on wound healing in animal models. Bleomycin inhibits the production of collagen by fibroblasts, thus decreasing wound tensile strength postoperatively. Doxorubicin also interferes with DNA transcription and has been found to decrease wound tensile strength in animal models. Mitomycin C, though most often used topically, has also been demonstrated to have a negative impact on wound healing in rat models [6].

The use of antimetabolites such as methotrexate and 5-fluorouracil at higher doses has also demonstrated some decreased wound tensile strength in animal models. The effects of azathioprine and 6-mercaptopurine on wound healing are still unclear and require further study. Similarly, plant alkaloids such as vincristine and vinblastine have shown mixed results on wound tensile strength in animal studies [6].

Anti-angiogenesis agents such as bevacizumab provide a unique challenge to the healing wound. Bevacizumab is a monoclonal antibody which targets VEGF, preventing neovascularization. It has been widely used in multiple cancers, including neurological cancers. It has a more direct effect on the healing wound than any other agent currently in use and has been shown to cause wound dehiscence, hematomas, and wound infection. As the half-life is 20 days, recommendations in the literature include waiting 6 weeks after the last therapy prior to surgical intervention [7]. Patients should be counseled that the rate of wound complications following bevacizumab therapy is considerable, particularly if the wound has been previously irradiated.

Corticosteroids, while not necessarily considered a chemotherapeutic agent, are also often used in cancer patients to alleviate pain and inflammation. Steroids are well-known for having deleterious effects on wound healing, and studies have shown increased rates of wound complications and dehiscence in patients on corticosteroid therapy in the perioperative period. The administration of vitamin A has been shown to mitigate some of the negative effects on wound healing, although further studies are needed to better define the impact of vitamin A co-administration [6].

Given the variability of chemotherapeutic agents and their effect on wound healing, it is important to keep the timing and dosing of chemotherapy in mind when considering surgical intervention. If possible, delaying the initiation of chemotherapy in surgical patients for 7–10 days may decrease the risk of wound complications in this population. Furthermore, it is important to ensure patients are not neutropenic prior to surgery. Careful consideration should be taken to control for other wound healing risk factors before surgical intervention.

Incision Planning

Careful consideration should be taken when planning cranial incisions in order to minimize the risk of postoperative wound complications. Incisions should be selected in a fashion that would allow for wide exposure of the target surgical site as well as flexibility to extend the incision for subsequent surgeries if needed. With cranial surgery, the incision choice should reflect the goals of surgery and potential for future surgeries in that patient. For example, patients with gliomas often recur within 2 cm of a previous resection cavity. As such, incisions should reflect an understanding of possible future recurrence such that the same incision can be used or easily modified in the future without causing vascular compromise to the scalp. When cranial hardware is used, we try to limit the amount of hardware directly underneath the incision. We have found this technique helps avoid delayed hardware exposure, particularly in patients with atrophic scalp tissue or those that subsequently undergo scalp irradiation.

If pre-existing surgical scars are present, an attempt should be made to incorporate those scars in the new incision to avoid leaving bridges of devascularized scalp tissue. Regardless of incision design, all remaining segments of scalp tissue once old scars and new incisions are taken

into account must be contiguous with at least one of the five main paired arteries (supratrochlear, supraorbital, superficial temporal, posterior auricular, and occipital) in order to survive. All attempts should be made to avoid acute angles between incisions as that often leads to devascularized distal segments of the scalp. New incisions can either be an extension of an old incision or take off at a 90° angle from an existing scar (Fig. 33.3).

Traditional incisions such as the coronal or bitemporal incision allow for wide access to the anterior cranial vault, forehead, and facial skeleton. The coronal incision can be reopened multiple times to allow for repeated exposure in the case of recurrent disease or complication. In the coronal approach, the anterior flap is vascularized by the supraorbital, supratrochlear, and superficial temporal arteries, while the posterior flap is supplied by the posterior auricular and occipital arteries. If access to the posterior cranium is needed, the coronal incision can be extended with a midline sagittal incision oriented perpendicular to the coronal incision.

The lateral skull base approach with the Al Kayat and Bramley modification of the preauricular incision, often referred to as the "question mark" incision, is often used to access the lateral anterior skull base and middle cranial fossa, although it can be modified to reach the posterior cranium, as well. The anterior flap is most often supplied by the superficial temporal artery although the ipsilateral supraorbital or supratrochlear arteries may contribute depending on the design of the incision. The posterior flap remains vascularized on the posterior auricular and occipital arteries. The "question mark" incision limits access to the contralateral hemisphere and posterior cranium. If exposure of the contralateral anterior cranial vault is needed, a contralateral "question mark" incision can be made with the midline scalp preserved as a bipedicle flap. If access to the posterior cranium is needed, a sagittal incision can be made perpendicular to the curve of the "question mark" and extended posteriorly, similar to Kempke's "T-bar" incision.

The midline posterior skull base approach allows access to the posterior cranium and exposure for the classical suboccipital craniotomy. In this incision, all major scalp arteries are preserved; however, blood flow across the midline is disrupted in the posterior scalp. The midline posterior scalp incision allows for much flexibility in extending the incision anteriorly as needed to gain further exposure. This incision can also be

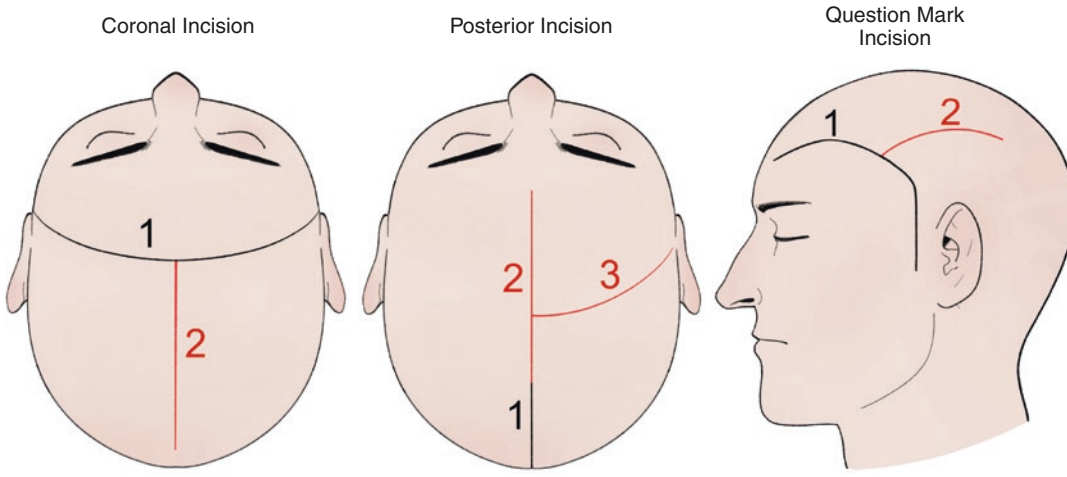

Fig. 33.3 Common neurosurgical incisions (1) and example extensions to avoid wound complications (2 and 3)

converted to a "T-bar" incision if needed. Access to the anterior cranial vault can also be achieved through separate incisions using the traditional approaches described above.

Prevention of Complications

Tissue Expansion

In patients who are high risk for postoperative cranial wound complications, several techniques can be used to maximize the chance of a successful reconstruction. When there is an existing skin deficit or resection of large portions of scalp tissue is anticipated, preoperative tissue expansion can be utilized to increase the surface area of scalp tissue available and reduce tension on the closure. Up to 50% of the scalp can be reconstructed with expanded scalp tissue, providing stable, potentially hair-bearing soft tissue coverage over cranial hardware or compromised bone. Tissue expansion, however, requires that there is adequate lead time prior to the procedure to place tissue expander devices and inflate them. Furthermore, tissue expansion requires an experienced surgeon as it can be associated with complication rates as high as 25% [8].

Laser Angiography

Intraoperatively, laser angiography can be utilized to assess the viability of scalp tissue and prevent potential wound complications. Modern laser angiography technology uses indocyanine green as a fluorescence agent to provide real-time assessment of tissue perfusion. Indocyanine green binds to plasma proteins and has a half-life of 3–5 minutes. It is administered intravenously and excreted by the liver into the bile so there is no risk for nephrotoxicity. Furthermore, indocyanine green fluorescence is viewed using a laser diode array emitting light in the near-infrared wavelength so no protective eyewear is needed and no harmful radiation is produced. Areas of scalp demonstrating poor tissue perfusion on laser angiography should be excised and replaced with well-vascularized adjacent tissue or soft tissue flaps as needed [9].

Delayed Flaps

When only a few weeks of lead time are available, flap delay is a technique that can be used to maximize the survival of anticipated scalp flaps. The delay phenomenon, also known as ischemic preconditioning, involves partially disrupting the vascular supply to a flap at the anticipated incision sites a few days or weeks prior to transfer of the flap. This allows for the opening of choke vessels in the remaining flap pedicle, propagation of collateral circulation, and increased tolerance to ischemia that can improve the survivability of the flap after transfer. This technique is useful in patients with a history of multiple cranial operations with high-risk incisions that may benefit from concomitant scalp flap reconstruction after intracranial surgery [8].

Other Therapies

Other modalities have also been described in the literature to salvage compromised scalp tissue. Hyperbaric oxygen therapy is a treatment that utilizes 100% oxygen at pressures greater than atmospheric pressure in order to raise tissue oxygenation levels. Some studies have suggested that elevated tissue oxygen levels may improve the healing and oxygen-dependent antibiosis of certain wounds such as delayed radiation injuries, burns, compromised flaps, diabetic ulcers, and soft tissue infections. The efficacy of hyperbaric oxygen therapy in salvaging ischemic scalp flaps, however, is still unproven in the literature as the evidence consists of mostly case reports [10].

Nitroglycerin ointment has also been described as a therapy to help salvage ischemic skin flaps. Topical application of nitroglycerin has been shown to increase local blood flow to the skin by acting as a vasodilator for both arteries and veins. Early studies have demonstrated benefits of 2% nitroglycerin ointment in the healing of anal fissures, pressure sores, and peripheral tissue

ischemia in neonates. In the plastic surgical literature, nitroglycerin paste has been shown to decrease mastectomy skin flap necrosis in prospective and randomized controlled trials with no increase in complication rates [11]. Although not specifically studied in ischemic scalp tissue, nitroglycerin ointment can be considered as a therapeutic option to help salvage or limit skin necrosis in compromised cranial closures [12].

Management of Complications

Scalp Reconstruction Algorithm

When cranial wound complications do occur, reconstruction is often indicated to prevent desiccation of the bone, osteomyelitis, hardware exposure, and infection of the underlying contents. An important principle of cranial wound reconstruction is that nothing replaces scalp tissue as well as scalp tissue. When possible, reconstruction should strive for a cosmetically appealing result in addition to achieving coverage by restoring normal anatomy and paying close attention to hair growth patterns and hairlines. Small deficits of scalp tissue can potentially be addressed through undermining of adjacent scalp in the loose areolar plane and performing galeal scoring techniques. When larger skin deficits are present, scalp rotation flaps or transposition flaps can be utilized to recruit tissue from areas of laxity (Fig. 33.4). When needed, large rotation flaps can be transferred to the area of concern, and skin grafting can be performed over the donor site to achieve greater coverage (Fig. 33.5). Skin graft-

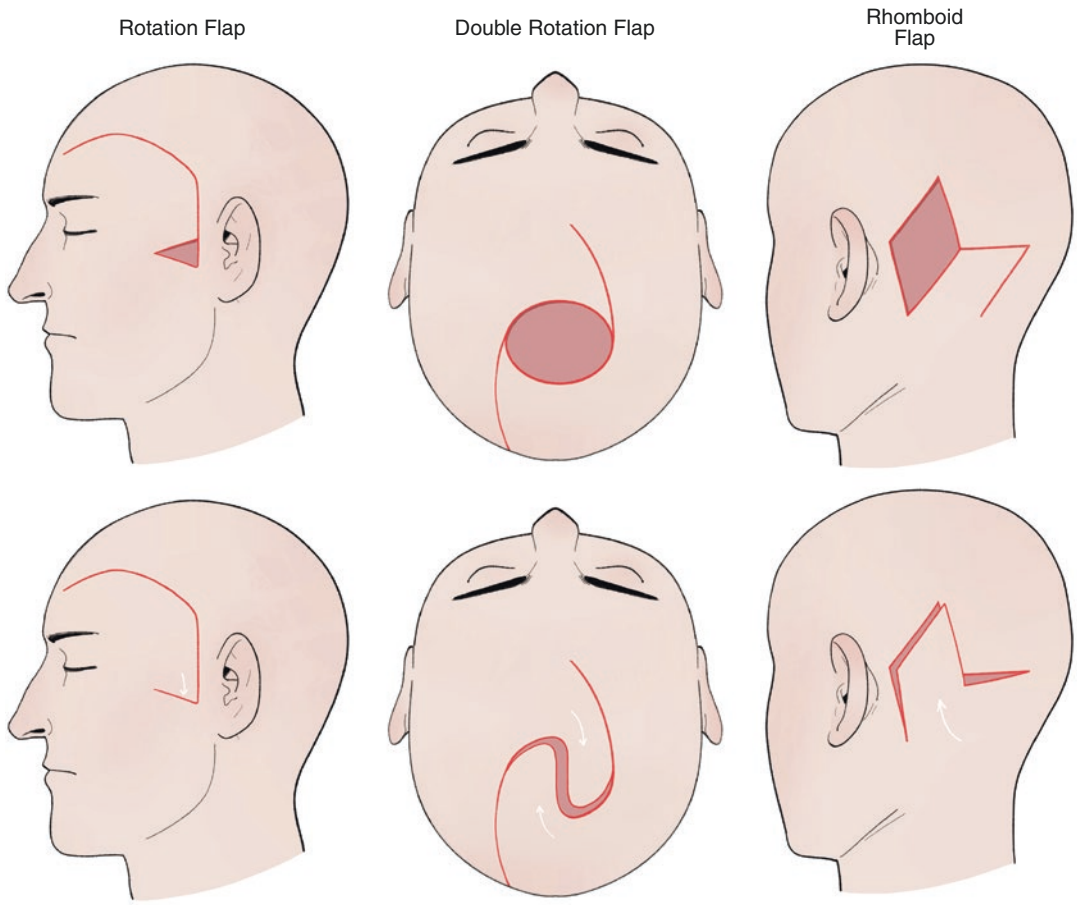

Fig. 33.4 Common local scalp flaps used to reconstruct cranial soft tissue defects

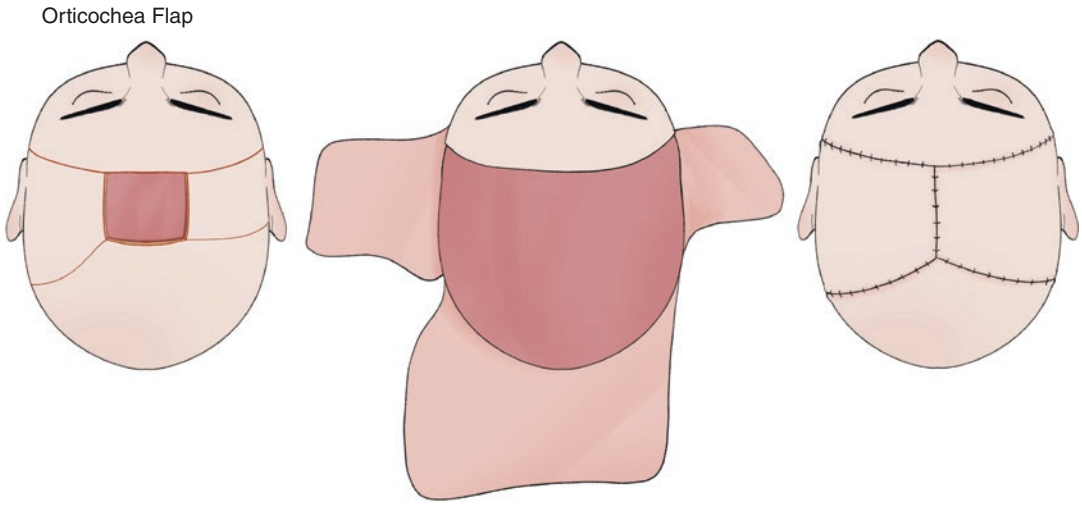

Fig. 33.5 Large scalp flaps can be designed to reconstruct bigger cranial soft tissue defects

ing can also provide permanent or temporary coverage over areas of the scalp with intact periosteum. If no periosteum is present and a pericranial flap is not available, the outer table of the cranium can be burred down to the diploic space in order to accept a skin graft. This serves as a viable option for immediate coverage of a scalp defect. In the long run, hair-bearing coverage of up to 50% of the scalp can be achieved with tissue expansion in the subgaleal plane. Tissue expansion requires staged operations with lengthy interval periods and complication rates varying from 6% to 25%. However, oftentimes the best aesthetic results can only be achieved with this technique. When even larger defects are present or if local tissue quality is poor due to radiation therapy, strong consideration should be given to free tissue transfer as a reconstructive option [8].

Cranioplasty Materials

In some circumstances, patients may require a cranioplasty either due to decompressive craniectomy, resection of cranial bone, trauma, or prior surgical complication. Cranioplasty may be performed with autologous bone graft, synthetic material, or biosynthetic material. The cranioplasty material of choice is somewhat controversial given the paucity of quality randomized, controlled trials, but some studies have suggested that the risk of postoperative infection is lower with autologous bone reconstructions [13]. Autologous bone, however, is subject to bone resorption and is not immune to infection of the devitalized bone segment. Methyl methacrylate is a popular synthetic material used in cranioplasty as it is malleable, lightweight, and radiolucent. It is often in conjunction with titanium mesh to provide enhanced structural support. Hydroxyapatite, a form of calcium phosphorus naturally present in bone tissue, is also frequently used in cranioplasty. The advantage of hydroxyapatite is its strong osteointegrative ability, minimal tissue reaction, and enhanced bone healing. Its biggest disadvantage, however, is its propensity to break under mechanical stress. As a result, hydroxyapatite is also often used in conjunction with titanium mesh reconstruction. More recently, polyetheretherketone (PEEK) has become a popular material used in cranioplasty, especially as a computer-designed implant requiring little to no intraoperative molding [14].

Timing of Cranioplasty

Regardless of material used, achieving stable soft tissue coverage over the cranioplasty implant is of utmost importance. When there is concern regarding the quality of soft tissue coverage or

potential contamination of the field, it is often best to delay the cranioplasty procedure and allow for complete healing of the surgical site before introducing devitalized or synthetic material. Various interval periods have been advocated for in the literature, but no definitive period has been proven to be superior. Most studies recommend waiting anywhere from 6 weeks to 3 months and as long as 6 months to 1 year if there is any evidence of infection. Ultimately, timing of cranioplasty is an individualized physician choice that must account for infection risk and wound healing capability.

Use of Drains

Little reliable evidence exists in the literature regarding the use of subgaleal drains to prevent cranial wound complications. Some retrospective studies have suggested that the use of scalp drains significantly reduces the seroma rate in patients undergoing craniofacial surgery. Other studies have noted subjective improvement in facial swelling and decreased length of stay with the use of subgaleal drains, but those findings have not been corroborated in the literature [15]. Most studies on drain use have not shown a statistically significant effect on infection rate, hematoma formation, transfusion requirement, or other postoperative complications [16]. Although some have questioned whether there is an association between drain use and infection risk, there is minimal supporting evidence that closed-suction drain use increases the risk of surgical site infection [17]. As a result, we recommend the judicious use of closed-suction drains in cases with an elevated risk of postoperative seroma and timely removal of drains once no longer needed. In cases where drains are aspirating the cerebrospinal fluid (CSF) because of a defect in a dural repair, it is important that these drains be removed to prevent intracranial hypotension and subsequent subdural hematomas. Should a CSF collection develop under the scalp, these can be percutaneously tapped and often they are self-limiting. In cases of recalcitrant CSF collections, lumbar drains combined with percutaneous aspiration can be used for several days which often allows dural defects to seal and thus obliterate the CSF leak. Finally, if a CSF collection persists despite these maneuvers, the patient should be evaluated for either hydrocephalus or a meningitis (possible aseptic). It is vitally important to ensure that scalp collections do not cause tension on the wound as leaks through the wound will increase the rate of postoperative infections.

Conclusion

The soft tissue concerns for patients undergoing cranial extirpative surgeries can be complex and layered. Appropriate preoperative planning, intraoperative decision-making, and postoperative care can decrease perioperative morbidity. Appropriate soft tissue coverage is necessary to allow for appropriate timing of radiation therapy and adjuvant chemotherapy. In our practice, neurosurgeons routinely involve plastic surgeons preoperatively in patients with high-risk wounds both for incisional planning and intraoperative closure. This team approach has been highly effective at preventing postoperative wound complications.

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Part V

Spinal Metastases: Foundations

Introduction to Spinal Metastases

34

Ibrahim Hussain, Brenton H. Pennicooke, and Ali A. Baaj

Introduction

The spine is the most common skeletal site for metastatic disease and up to 10% of all patients with cancer develop spinal metastases during the course of their disease [1–3]. Most tumors spread to the spine via hematogenous venous circulation; however, local invasion from close proximity tumors is also observed. In concordance with relative bone mass, the thoracic spine is the most common site for spread, followed by the lumbosacral and cervical spine, respectively. With the aging population and robust development of systemic treatment options for various cancers, the prevalence of spine metastases is likely to increase over the coming years. While the vast majority are confined to the bony elements of the spine, those with epidural extension or intradural location often require treatment to preserve neurologic status and quality of life. As with systemic treatment options, various advances in multi-modality of treatment of these tumors have accelerated over the past 20 years and resulted in excellent local control rates for the majority of patients. Nonetheless, there continues to be a void in our understanding of genetic tropism for certain primary tumors to metastasize to the spine and what mutations portend a more favorable prognosis based on available treatment options, which is an active area of research. Currently, the focus of management involves timely diagnosis, close observation, and treatment when radiographic findings or clinical symptoms become burdensome.

Categorization of Spinal Metastases

Spinal metastases can be categorized based on various parameters which have implications on management. One broad category involves primary tumor histology and more specifically if the primary pathology is of solid tumor versus hematologic malignancy. Solid tumors that most commonly metastasize to the spine are similar to their prevalence in the general population. These include breast, lung, prostate, colorectal, and renal cell [2, 4, 5] (Fig. 34.1). Other common primary tumor pathologies that commonly metastasize to the spine include thyroid, melanoma, sarcoma, gastrointestinal, and hepatocellular. These vast majority of these tumors spread to the vertebral column and through epidural extension cause mass effect on underlying neural structures. A subset of these tumors is particularly

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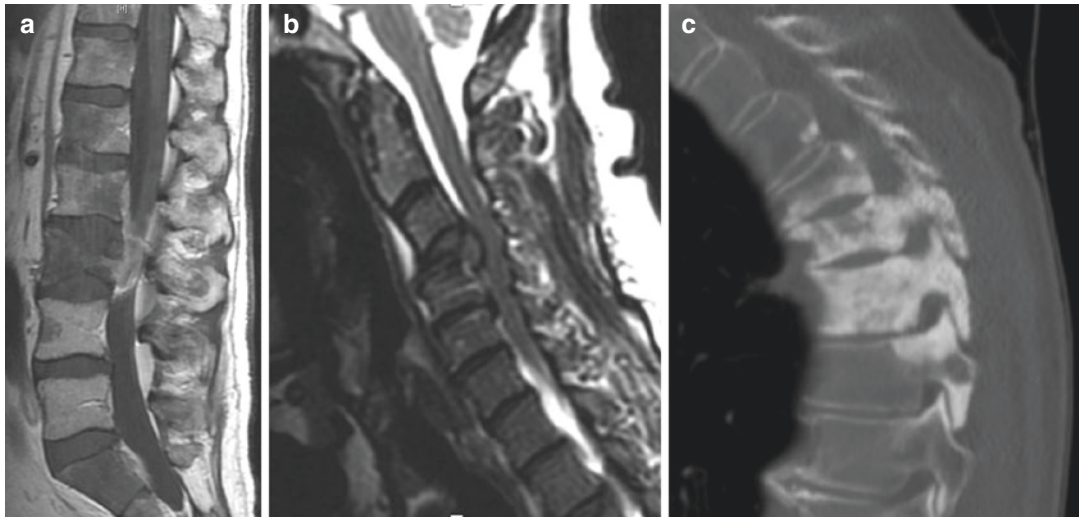

Fig. 34.1 Examples of spinal metastases. (**a**) T1-post contrast MRI demonstrating an L3 colorectal metastasis with pathological collapse and epidural extension resulting in severe cauda equine compression. (**b**) T2-weighted MRI demonstrating a C4 burst fracture due to a breast metastasis resulting in kyphotic deformity and severe cervical spinal cord compression. (**c**) CT scan of mid-thoracic prostate metastases demonstrating the blastic nature of bony involvement

notorious for being highly vascularized, such as renal cell carcinoma, thyroid carcinoma, and paragangliomas. Preoperative embolization has been shown to reduce intraoperative blood loss during resection of these tumors [6–11]. Of the hematogenous malignancies, multiple myeloma is the most common and should not to be confused with a solitary plasmacytoma which typically does not require systemic treatment [12–14]. Patients with metastatic involvement of multiple myeloma may demonstrate extensive lytic lesions and compression fractures which may benefit from vertebroplasty/kyphoplasty or percutaneous stabilization. Lymphoma and leukemia metastases similarly can involve bone and have epidural extension. Even with high-grade compressive lesions on imaging, surgical intervention is only required for acute neurologic deterioration when radiation therapy is not immediately available, for stabilization of unstable spines, or for diagnostic purposes. This is due to the face that hematologic malignancies are highly radiosensitive and respond rapidly to conventional external beam radiation [15, 16].

Another broad category which has implications on spinal metastatic management is the exact location of the tumor in relation to the central nervous system. These include epidural, intradural extramedullary, and intradural intramedullary. The latter two can further be classified with or without the presence of leptomeningeal disease. Location-wise, 98% of metastatic tumors are extradural, developing within the vertebral column itself, including the body, pedicles, facet joints, or spinous processes [17, 18]. With epidural extension, these tumors extend beyond the confines of the cortical wall and can exhibit compression of the spinal cord or cauda equina. Intradural metastatic tumors are rare. These tumors are often dural-based lesions that exert mass effect on the spinal cord. Even rarer is isolated intradural intramedullary metastases, which are reported in less than 1% of cases. Any intradural metastases can potentially be associated with leptomeningeal disease, in which there is spread of malignant cells throughout the cerebrospinal fluid that subsequently coat the brain, spinal cord, and nerve roots (Fig. 34.2). Of note, a distinct entity within leptomeningeal disease of the spine encompasses tumors referred to as drop metastases, which have spread to the spine from primary intracranial brain tumors rather than

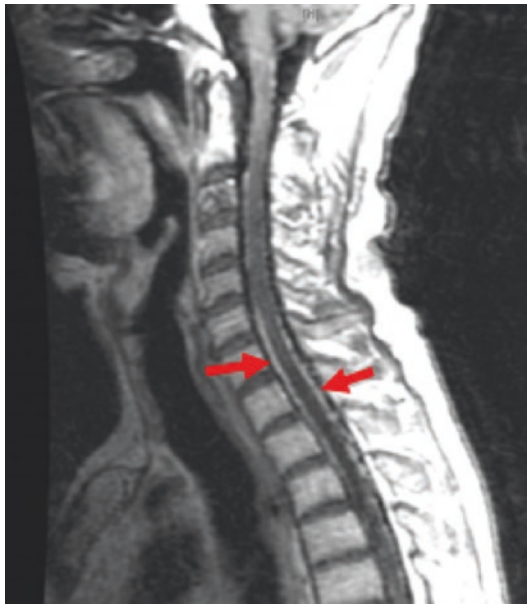

Fig. 34.2 T1-post contrast MRI demonstrating abnormal enhancement around the spinal cord in the cervicothoracic region consistent with leptomeningeal disease

extra-CNS primary cancers. Glioblastoma, medulloblastoma, ependymomas, primitive neuroectodermal tumors (PNETs), germinomas, and choroid plexus tumors are among the primary CNS tumors that can result in drop metastases [19–28]. Any form of leptomeningeal disease carries a poor prognosis, with a median survival of less than 3 months [29].

Radiographic Evaluation

A number of imaging modalities can be used in the diagnostic workup for spinal metastases. Plain radiographs have become increasingly limited for diagnostic and therapeutic planning purposes but do have a role in the assessment of load-sensitive deformities in the subaxial spine. Computed tomography (CT) and magnetic resonance imaging (MRI) are more advanced high-resolution studies and are standard in the initial evaluation of patients with known primary cancers. In fact, many spinal metastases are discovered on staging body CT scans. Plain X-rays, however, can still be useful in the symptomatic patient as an initial screen as it will highlight compression deformities and pathologic fractures as well as gross misalignment.

Computed tomography (CT) scans provide optimal assessment of the osseous structures of the spine, identifying lytic and blastic metastases and pathologic fractures. Cortical destruction can be appreciated months earlier than can be detected using X-rays, and epidural masses with displacement of the underlying thecal sac can also be identified in most cases [30]. CT imaging is also particularly useful when evaluating patients for cement augmentation procedures (e.g., vertebroplasty or kyphoplasty) to determine amenable levels as well as those undergoing surgical stabilization to determine the size and health of pedicles that may be instrumented. CT myelogram is an alternative to magnetic resonance imaging (MRI) in those patients that cannot under MRI for various reasons including non-MRI compatible implants (e.g., pacemaker, spinal cord stimulator, and intrathecal pump), those with extremely large body habitus, or those with severe claustrophobia. A lumbar puncture is performed in the lower lumbar spine caudal to the conus medullaris, and the injection of a contrast agent such as iohexol is administered. Changes in the normal cylindrical shape of the thecal sac or obstruction of contrast flow suggest epidural compression, whereas dural-based hypodensities or expansion of the spinal cord may suggest intradural and intramedullary metastases, respectively.

MRI is the gold standard for the diagnosis of spinal metastases. For patients with normal glomerular filtration rates (GFR), gadolinium-based intravenous administration increases the sensitivity of detecting these tumors and differentiating them from normal variations in bone marrow intensity. Typically, most tumors are T1 precontrast hypointense and enhance with gadolinium, though the latter is not always the case and may confound assessment when tumors are isointense to normal marrow signal. However, for intradural tumor and leptomeningeal disease, contrast enhancement is required for optimal detection. T2 sequences are useful for determining the extent of epidural cord compression. Fat

suppression sequences are also highly sensitive for diagnosing even small lesions confined to bone, such as short tau inversion recovery (STIR) sequences which demonstrate hyperintense lesion consistent with tumors. T2 and STIR sequences are also sensitive for bone edema, which can be indicative of acute pathologic fractures.

MRI-based grading schemes of epidural compression are used frequently for guiding therapy. The epidural spine cord compression, developed by Bilsky et al. [31], divides tumors into grades 0, 1A, 1B, 1C, 2, and 3. Tumors with grade 0 are confined to bone with no epidural extension. Tumors with ESCC of 1 demonstrate varying degrees of epidural extension, with thecal sac impingement without compression (1A), thecal sac deformation without spinal cord abutment (1B), and thecal sac deformation with spinal abutment but no compression (1C). ESCC grade 2 tumors compress the spinal cord or cauda equine nerve roots with preservation of CSF signal on a representative axial cut. ESCC 3 tumors have cord or cauda equina compression without visible CSF flow. ESCC grade 0 and 1 can typically managed conservatively, whereas ESCC grade 2 and 3 tumors may require more aggressive surgical consideration even in the absence of symptoms.

The role of more advanced imaging options for spinal metastases is discussed further in Chap. 38.

Clinical Evaluation

Spinal metastases can often be asymptomatic, and only discovered through imaging studies performed for other organs or symptoms. Of those patients that are symptomatic, the most common manifestation is pain, but some will present with a focal neurologic deficit or myelopathic features in the absence of pain. The NOMS framework, discussed in more detail later in this section, is a useful algorithm that takes into account the neurologic status of the patient and degree of thecal sac compression, the radiosensitivity of the primary tumor histology, the presence of mechanical pain, and the burden of systemic disease in consideration of whether a patient is a surgical candidate [16, 32, 33].

In those patients that present with pain, it is important to differentiate the exact type of pain from a treatment standpoint. Biologic pain is usually described as nighttime pain that improves during the course of the day. This is usually due to the physiologic cyclical nature of endogenous steroid production, which is highest in the morning and steadily drops over the course of the day, with lowest levels during nighttime. The effects of endogenous steroid production results in decreased inflammation, which in turn explains the improvement of pain in the morning versus nighttime for patients with spinal metastases.

Mechanical instability is distinct type of pain that specifically occurs with movement and usually a byproduct of pathologic fracture or compression deformity caused by tumor invasion [34]. Based on the location of the tumor within the canal, different symptoms may be described. In the craniocervical region, rotary head motions may exacerbate pain. In the subaxial cervical spine, neck or upper extremity radicular pain may result with neck flexion/extension/lateral bending/rotation. In the thoracic spine, lying flat with radiating band of pain around the chest or torso may occur. And in the lumbosacral spine, axial loading with maneuvers such as going from sitting to standing, ambulating, and walking stairs may result. These instances of mechanical pain are usually caused by destruction of important force-sustaining bony regions that are in close relation to exiting nerve roots which are compressed during various movement-related activities. The spinal instability neoplastic score (SINS) was developed to facilitate diagnosis of this phenomena and is comprised of six categories, five radiographic and one clinical [35–37]. Radiographic criteria include tumor location within the spinal column, intrinsic nature of bony pathology (e.g., lytic vs. blastic), segmental alignment, percent vertebral body collapse (> or <50%), and posterior element involvement. The sole clinical

component is the presence of movement-related pain. Cumulative scores range from 0 to 18, with SINS 0–6 considered stable, 7–12 indeterminate (impending instability), and 13–18 unstable. For scores of 7 or above, evaluation by a spine surgeon is recommended.

The distinction between biological and mechanical pain has critical implications for treatment. Biologic pain can usually be managed conservatively with anti-inflammatories, steroids, and radiation therapy. However, mechanical pain does not respond long term to these treatments [38]. Previous studies have shown that stabilization via kyphoplasty or instrumented fusions improves pain and functional disability faster than noninterventional therapies [39, 40].

As with all patients with spinal disease, a thorough neurological evaluation is required. This includes full sensorimotor assessment of the extremities, evaluation for long-tract signs suggestive of myelopathy (Hoffman's sign, Babinski sign, clonus, deep tendon reflexes), proprioception evaluation, and rectal tone when concern for cauda equina or cord compression. Patients can often have proximal lower extremity weakness with pain that radiates from or to the hip. It is vital to keep in mind that diffuse skeletal metastases may be present, and that the hip joint is usually not included in most spinal MRI windows. The FABER maneuver (flexion abduction external rotation) of the involved leg can demonstrate acute exacerbation of hip pain which is more suggestive of acetabular pathology than from peripheral nerve radicular issues. AP and lateral X-rays of the pelvis and femur should be strongly considered in these patients.

Treatment Options

There have been enormous strides in the treatment algorithms for patients with spinal metastases over the past 20 years (Fig. 34.3). As traditional systemic therapies, immunotherapies and other biologic agents have prolonged the life expectancy of those with metastatic disease, the incidence of central nervous system and skeletal metastases has grown. As such, it is vitally important for the CNS metastases experts to individualize care based on patient symptoms and treatment goals. Recently, radiosurgery has advanced considerably and is a good, noninvasive treatment option for patients with spinal metastases that do not require interruption of systemic therapy, even in traditionally "radioresistant" pathologies. The use of intraoperative radiation utilizing P32 plaques among other radioisotopes as well as improvements in hypofractionated regimens has also resulted in better local control rates with many primary tumor types. Advances in spinal instrumentation have been critical as well. Screw and rod titanium constructs, interbody devices, bone substitute allograft, and percutaneous systems for stabilization when open decompression is not required have all changed the way surgeons approach patients with spinal metastases. Cement augmentation through kyphoplasty/vertebroplasty and the recent development of fenestrated pedicle screws for cement augmented screws has also led to less hardware failure and the development of pseudarthrosis. Pain-related options such as spinal cord stimulation and opiate-based intrathecal pain pumps have also become excellent palliative options for those patients who cannot undergo or benefit from tumor resection or stabilization.

Conclusion

In conclusion, spinal metastases are becoming more common and treating surgeons must individualize care to provide the optimal patient outcome. Subsequent chapters will expand on the topics highlighted in this chapter including epidemiology, bone metabolism, clinical trial results, and decision-making algorithms for surgical intervention. Later chapters will delve into more details regarding treatment-specific options, which include separation surgery, radiation therapy, cement augmentation techniques, and laser therapies among others as well as the management of complications that result from these interventions.

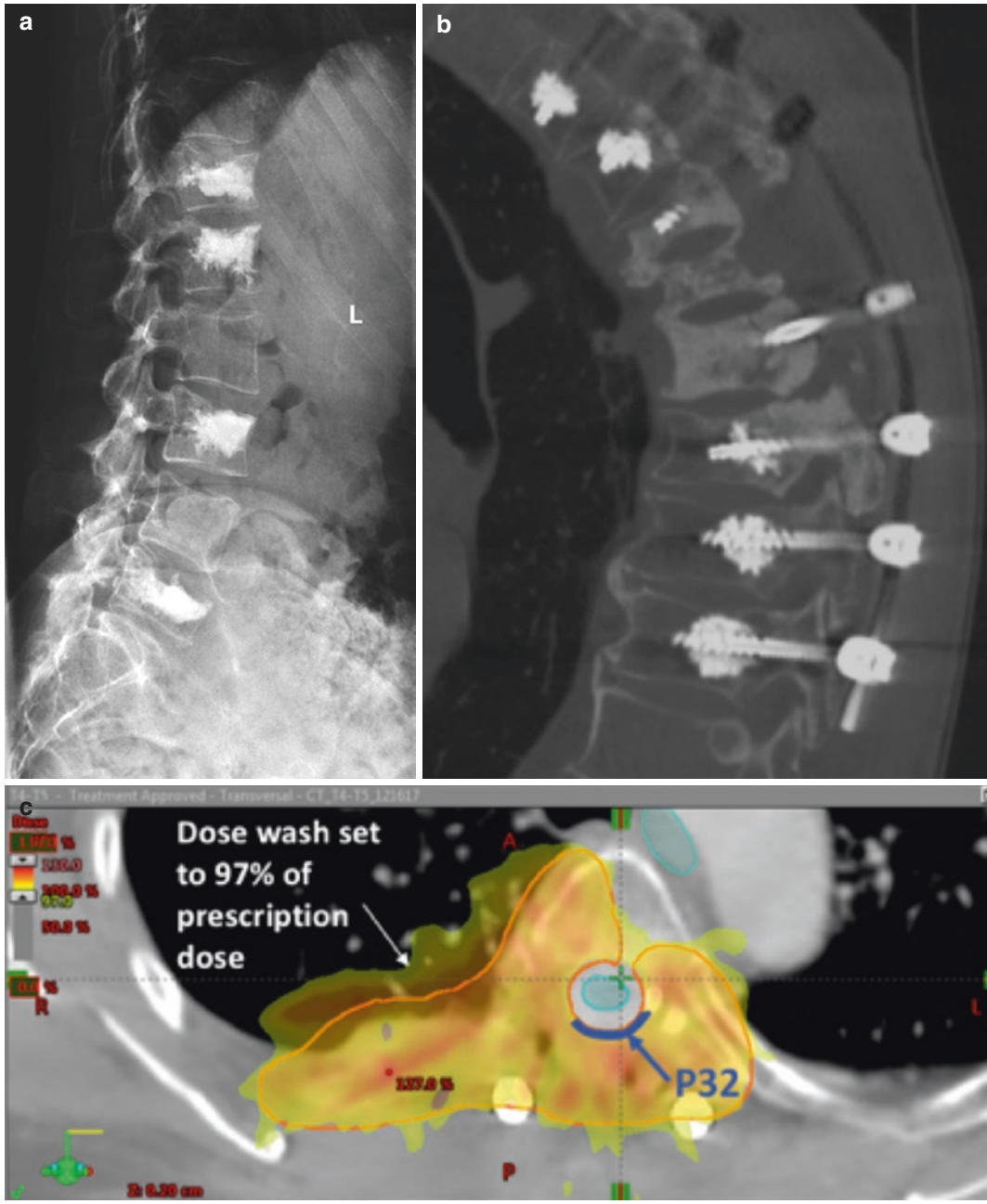

Fig. 34.3 Examples of treatment options for spinal metastases. (**a**) Later lumbar X-ray in a patient with multiple myeloma and multiple compression fractures following stabilization with multilevel kyphoplasties. (**b**) Postoperative CT scan depicting the recent development of fenestrated screws for cement augmentation during instrumented stabilization. (**c**) Adjuvant radiation planning in a patient following "separation surgery" with tumor decompression off of the spinal cord and taking into account the use of intraoperative radiation (P32 plaque) in the contouring of target volumes

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Epidemiology of Spinal Metastatic Disease

35

John Berry-Candelario, Mark H. Bilsky, Ilya Laufer, C. Rory Goodwin, and Ori Barzilai

Introduction

With the advent of new and more selective cancer therapies, the intricacies of spine metastases care have reached the forefront of medicine. Spine metastasis remains the most prevalent form of spinal neoplasia with the likelihood of further growth as these patients live longer with chronically controlled cancer. While the most common sites of metastases remain the liver and lungs, bone is next in line. Spine metastasis (SM) represents the largest proportion of this population with estimates that up to 40% of all cancer patients will have SM in their lifetime and almost 20% of patients diagnosed with SM develop symptomatic spinal cord compression [1, 2]. Postmortem studies have shown that though not always diagnosed, up to 90% of cancer patients may have microscopic evidence of SM [3, 4]. Furthermore, 70–90% of patients with breast or prostate cancer have some form of skeletal metastases. The major contributors and their incidence to spine metastases are breast cancer 19%, prostate cancer 15%, lung cancer 14%, renal cancer 12%, and multiple myeloma 6%.

Most common spinal metastases	Incidence (%)
Breast cancer	19
Prostate cancer	15
Lung cancer	14
Renal cancer	12
Multiple myeloma	6

In about 10% of patients, SM is the initial manifestation of the primary disease. In the United States, there are approximately 120,000 cases per year with 20% or 25,000 cases presenting with spinal cord compression [5]. The vast majority of these lesions occur in the vertebral body or contiguous marrow and epidural spaces, whereas 5% will present as an intradural lesion and only 1% with intramedullary metastases [6]. While all segments of the spinal column are susceptible, the thoracic spine is the most frequent site (70%), followed by the lumbosacral spine (25%), and then the cervical spine (5%). This is thought to be the function of bone mass and blood flow [6]. Patients with spinal metastasis have been reported to have a median survival of 7 months overall. Those with epidural disease spread and leptomeningeal disease may have even worse survival ranging from 3 to 6 months [7]. However, recent advances in cancer treatment point to longer overall survival and crystalizing the need for optimal care [8].

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Over the last decade, there has been an explosion in the identification of tumor-specific molecular signatures and associated targeted therapies. Combined with multidisciplinary care and targeted therapy, these aforementioned advancements have facilitated improved survival, improved progression-free survival, and in some cases even cure. In this chapter, we will explore some of the newest epidemiological data on some of the more prevalent spinal metastatic diseases with specific cancer markers and their correlates to care. We will focus our attention on the epidemiology of those cancers with the highest incidence of spine metastasis.

Pathophysiology

Cancer metastasizes to the bone through different ways of propagation, yet most frequently through hematogenous spread. In a review, Massagué illustrates with perspicacious clarity the critical steps of cancer metastasis [9]. Those basic steps commence with local invasion, extravasation, survival in circulation, intravasation, and colonization. The innate defenses against metastasis are overcome via a set of general genetic harbingers for infiltration. Among the gene classes involved are regulated transcription factors TWIST1, SNAI1, and SNAI2 that allow for invasion. Furthermore, metastatic growth is initiated by the suppression of noncoding RNAs, like miR-126. Their work hypothesizes further that beyond traits like cell motility and membrane degradation, tumor cells develop an organ-specific infiltrative advantage that mediates adhesion and penetration to organs like the bone [9]. Venous spread, primarily through Batson's plexus [6], is considered the principal process of metastases to the spinal column. This contrasts with arterial spread to other osseous sites such as the shoulder and pelvis (proximal) followed by the elbow and knee (distal). Less frequently lesions spread by contiguity and even less frequently via lymphatic spread (the role of which is not well defined) [10]. Once cancer cells have invaded the bone, they produce growth factors that stimulate osteoblastic or osteolytic activity resulting in bone remodeling. Some of them include PTHRP, IL-11, IL-6, TNF-alpha, and granulocyte-macrophage colony-stimulating factor [11, 12]. This, in turn, induces the release of other growth factors that lead to a vicious cycle of bone destruction and growth of local tumor.

Morphological changes to the bone can result in biologic pain, and often, the osteolytic process results in vertebral body or posterior element fractures, often requiring surgical stabilization.

Clinical Presentation

Regardless of the type of the primary tumor, the typical clinical presentation of spine metastasis includes either biologic bone pain (most common) or mechanical (movement-related) back pain. Mechanical back pain results from spinal instability secondary to pathologic fracture and can result in radiculopathy and myelopathy due to abnormal spinal motion. The presenting symptoms are dictated by the tumor or fracture location and rate of growth [13]. Classically, biologic pain is thought to be due to an inflammatory response to tumor expansion in the vertebral body that is worse at night when diurnal levels of cortisol are lowest which typically controls for inflammation. Pathologic fractures produce acute and subacute pain secondary to bony and sometime ligamentous destruction. Furthermore, the degree of tumor extension may produce cord or root compression resulting in neurologic sequelae including paresthesias, dysesthesias, radiculopathy, motor weakness, and/or bladder/bowel compromise. Significant spinal cord compression may lead to spinal cord edema, myelopathy, and ischemia/infarction [14] with resultant deficits in neurologic function and ambulation.

As mentioned, the most common symptom at initial presentation is pain. Motor dysfunction is the next most common presentation with between 35 and 75% of all patients. Patients typically complain of arm/leg fatigue or heaviness. This is not always accompanied by definitive weakness. Sensory complaints will lag motor findings unless there is nerve root compression. It is rare

to find bowel/bladder dysfunction in isolation based on the innervation pattern [14]. True spine-related bowel/bladder incontinence will typically be accompanied by severe back pain.

Diagnostic Evaluation

Typically, the SM patient is known to the oncology service prior to presentation. It is important to recognize that cancer patients with back pain or neurologic complaints need prompt evaluation with imaging and laboratory studies [15]. Plain X-rays remain useful particularly in evaluating instability, and full-length imaging aids in the assessment of sagittal imbalance. Computed tomography (CT) with reconstructions provides useful information of the bony elements of the spine. For example, lytic versus sclerotic changes and vertebral body collapse are well evaluated by CT scans [16]. Positron emission tomography (PET) combined with CT is also useful and can help with the assessment of treatment response. Finally, magnetic resonance imaging (MRI) is the workhorse in diagnostic evaluation with its high-resolution multi-planar imaging, clear assessment of soft tissue and osseous structures, and ability to precisely define the relationship between the tumor and surrounding neurovascular structures, bony elements, and viscera [17]. Every patient with spinal metastases should undergo a total spine MRI as occult lesions are a common occurrence and are often easily treated when promptly diagnosed [18]. Current MR technologies, such as ultrafast data acquisition and high-performance gradient systems, have made total spine examinations tolerable with considerably shortened examination times. Additional sequences such as diffusion-weighted imaging (DWI) and short tau inversion recovery (STIR) offer information about local microstructural differences and the presence of any pathological alterations. Dynamic contrast-enhanced (DCE) MRI perfusion imaging provides functional information on tumor vascularity and hemodynamics and can be used as a surrogate for determining tumor progression [19].

Prognostication and Health-Related Quality of Life

Several scoring systems such as the Tokuhashi revised score [20], the Tomita score [21], and the Bauer modified score [22, 23] have been developed to estimate expected survival in patients with spinal metastases. In the era of modern cancer care, their reliability and utility have been questioned [24, 25]. New prediction models, such as the Skeletal Oncology Research Group (SORG) nomogram [26], attempt to overcome the shortcomings of these models by identifying more prognostic factors associated with outcomes. Physicians should refrain from strictly adhering to these prediction models, and patients should be considered for surgery if reasonable systemic therapy is available.

Treatment goals for metastatic spine disease are palliative. In the past, outcomes of SM patients relied on clinician-based measures, yet recently there has been an increase in utilization of patient-reported outcome (PRO) tools as they express a direct measure of the value of care as perceived by the recipient [27]. Several generic outcome measures have been widely used for PRO reporting in the spinal oncology population, including EuroQol 5-D (EQ-5D), Oswestry Disability Index (ODI), Visual Analog Scale (VAS), and Short Form 36 (SF-36) [28]; however, none of these instruments focus on spine cancer-specific symptoms. To address this need, the Spine Oncology Study Group Outcome Questionnaire (SOSGOQ) was created and represents the only PRO instrument fully focused on the assessment of patients with spinal tumors [29, 30]. Consistent use of validated health-related quality of life (HRQoL) tools facilitates a common language in communication and reporting as we continue to evaluate patient outcomes in the current era of spine cancer therapy. An abundance of recent data demonstrate the benefit of validated PRO-based evaluations following spinal surgery for both open surgery and minimally invasive surgery, as well as for patients with oligometastatic and widespread systemic disease [31–35].

Targeted Treatment Paradigms

Early successes in identifying and targeting individual oncogenic drivers, together with the increasing feasibility of sequencing tumor genomes, have brought forth the promise of genome-driven oncology care [36]. Currently, advancement in the understanding of the genetic basis of diseases is changing the way we diagnose and treat spine cancer [37]. Genomic sequencing drives clinical management of tumors such as melanoma, sarcomas, and carcinomas of the lung, breast, thyroid, ovary, and colon [36]. These tools have been studied mostly in non-spinal tumors, yet interest on the effect they may have on spine cancer care is growing [38, 39]. Traditionally, the effect of systemic therapy on osseous metastases has been limited. A recent trial showed favorable response of osseous RCC metastases treated with cabozantinib, a small molecule tyrosine kinase inhibitor, indicating that new systemic therapy agents may offer local tumor control for osseous metastases [40]. With the ongoing expansion of precision medicine, surgeons treating cancer patients will need to increase their familiarity with the genomic and molecular oncology landscape to make informed decisions and maintain a leadership role in patient care. Although the concept of targeted therapy is similar, the results and treatment response remain cancer-specific and will be discussed separately.

Breast Cancer

Breast cancer has a strong predisposition to metastasize to bone. Despite being the second leading cause of cancer-related deaths, the median survival after metastasis diagnosis is almost 2 years. This has led providers to advocate for aggressive treatment strategies to provide palliation of pain and preservation and/or improvement of neurological function [41]. The breadth of molecular knowledge has transformed the disease course and prognosis for this patient population. Research has advanced with therapies for estrogen receptor (ER+)-positive and human epidermal growth factor receptor 2 (HER2)-positive breast cancers. Tamoxifen, an ER antagonist, has led to a marked improvement in survival [42]. Trastuzumab, a humanized monoclonal antibody, against HER2 has promising results [43].

Few studies have investigated the value of these targeted therapies in spinal cancer. A study from Johns Hopkins looked at breast cancer-specific parameters for spinal metastases and found estrogen receptor positivity to be associated with longer median survival, but metastatic tumors in the cervical spine were associated with shorter median survival [44]. Perhaps, it is due to the highly morbid symptoms associated with spinal cord compression at this level. Interestingly, the presence of visceral disease or >1 bony metastasis was not found to be prognostic [45–47].

Lung Cancer

One of the most profound and most common cancers to the spine is lung cancer. With over 1.8 million newly diagnosed cases per year, roughly 70% will have locally advanced or metastatic disease at the time of initial presentation [48–51]. The largest group is non-small cell lung cancers which can be subdivided into large cell carcinoma, adenocarcinoma, and squamous cell carcinoma. They have a median overall survival (OS) of 8–11 months when presenting with advanced disease burden [52, 53]. However, recent studies have reported improved survival with surgical intervention with RT. Weiss found over half of their patients who underwent surgical resection recovered at least 1 Frankel grade [54]. The biggest advancement in treatment involves the development of therapeutics based on molecular markers. Endothelial growth factor receptor (EGFR) mutations play a major role in NSCLC, and certain EGFR inhibitors (erlotinib and gefitinib) work through the tyrosine kinase inhibitor pathway with improved survival up to 24–36 months [55]. Their utility has been challenged by tumor resistance through the upregulation of other tyrosine kinase receptors. A literature

review evaluating survival among patients with NSCLC metastatic to the spine found that while the overall survival of patients with lung cancer metastases to the spine was 3.6–9 months, the median survival of NSCLC patients with targetable EGFR mutations was 18 months [56]. Another area of advancement has been in immunotherapy. Cytotoxic T-lymphocyte-associated protein 4 inhibitors (CTLA4, e.g., ipilimumab), anti-programmed death 1 (anti-PD1, e.g., nivolumab), and anti-programmed death ligand 1 (anti-PD-L1, e.g., BMS-936559) are three pathways that have shown moderate success with marginally improving survival [55]. These improved survival data suggest that patients with good performance scores may have extended survival in the era of targeted therapies. As such, palliation of spinal metastases-related symptoms is warranted and should be addressed early.

Prostate Cancer

Prostate cancer is the second most common cause of cancer-related deaths in men. Metastatic prostate cancer most commonly affects the spine, and the 1-year survival after SM diagnosis has been reported between 73 and 83%, with a median OS after diagnosis of spinal metastasis of 24 months [57–59]. A major advancement in therapy of prostate cancer was the discovery of androgen receptor antagonists that have greatly improved patient outcomes [57, 59]. The treatment of castration-resistant prostate cancer is proven difficult; however, several targeted therapies are available and include cabozantinib (an MET and VEGFR2 inhibitor), cetuximab (a monoclonal antibody against EGFR), gefitinib/erlotinib (small tyrosine kinase inhibitors), and ipilimumab (anti-CTLA4) [58, 60, 61]. While studies of these and other agents are ongoing, they have shown marginal improvement in clinical studies. Radiation therapy remains the mainstay of treatment for spinal metastases from prostate cancer. Fortunately, prostate cancer is considered relatively radiosensitive [62], and hence, prostate spinal metastases can be treated effectively with conventional external beam radiation or radiosurgery. The role of surgery for SM has decreased with time but remains substantial for those with progressive neurologic deficits or those with spinal instability.

Renal Cell Cancer

While renal cell carcinoma (RCC) only accounts for 2.5% of all cancers [60, 63], about 40% of bony RCC metastasis occur in the spine. At that point, the median survival is estimated at 10 months. In fact, almost one-third of patients have advanced or metastatic RCC at the time of initial diagnosis. Renal cell is known to be radioresistant to conventional EBRT; however, response rates with radiosurgery have proven promising. The advancement in the molecular and genomic knowledge of the disease has resulted in the approval of several targeted therapies for the treatment of metastatic RCC (mRCC). Some of those agents include cytokine actors (IL-2); tyrosine kinase receptor inhibitors, like sunitinib and axitinib; mTOR inhibitors (e.g., temsirolimus); and VEGF inhibitors, to name a few. With only 10% of mRCC patients living to 5 years, the advent of multitargeted therapies has resulted in PFS up to 27 months and OS to 40 months [63]. Given the recent introduction of these therapies, it is not yet clear if the 5-year survival rate has meaningfully changed. Immunotherapeutic agents such as anti-PD1, anti-PD-L1, and anti-CTLA-4 antibodies have been explored in preliminary studies with a reported 30% overall response rate and 20–25% prolonged response rate [64]. They also identified tools that could be particularly useful for prognostication of mRCC to the spine such as the initial Fuhrman grade, Tokuhashi score, and Memorial Sloan Kettering Cancer Center (MSKCC/Motzer) score.

Traditionally, surgical excision of renal cell spinal metastases was routinely performed as these tumors are resistant to conventional radiation. This is particularly challenging due to the vascularity of these lesions, and preoperative embolization is often utilized. Moreover, solitary

RCC spinal metastases were surgically removed "en bloc." The integration of spinal radiosurgery has changed the management of these tumors significantly, and currently, though still debatable, there is little role for wide or total excisions since high dose per fraction radiation provides excellent local control rates with minimal associated morbidity [65]. Despite the improved local control with SBRT and advancement in targeted therapies, surgery still plays a pivotal role in the management of mRCC spinal metastases, particularly in solitary and oligometastatic disease and for those with high-grade spinal cord compression requiring separation surgery or patients with progressive neurologic deficits.

Conclusion

This chapter provides a brief overview of the epidemiology of spinal metastasis. In the era of prolonged cancer survivors, it is likely that the magnitude of patients with spinal metastases will increase. With a better understanding of the molecular mechanisms of metastatic cancer biology, there is a broader understanding that the treatment of metastatic disease requires personalization and a multidisciplinary effort. While we chose to focus on advancements in the more common spine metastatic cancer types, these developments are proving true for cancer in general.

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Bone Metabolism in Cancer

36

Tilman D. Rachner, Lorenz C. Hofbauer, and Andy Göbel

Introduction

Basics of Bone Physiology

In adult bone, a physiological level of bone remodeling is required to maintain long-term structural quality and strength. The activity of bone-forming osteoblasts and bone-resorbing osteoclasts is coupled, and under healthy conditions, the level of bone formation and resorption is balanced, resulting in a stable bone mass. The coupling process is mediated by direct cell contacts, ligand-receptor interactions, and a variety of soluble factors. In addition, mechanical force and microcracks are key drivers of bone remodeling where the old or damaged bone matrix is resorbed and replaced by newly formed tissue [1]. The bone remodeling process is responsible for the renewal of 5–10% of bone of the mature skeleton each year [2]. Stretching and compression of the bone tissue during locomotion or microcracks are detected by osteocytes, which are terminally differentiated osteoblasts and fulfill a sensing function of mechanical forces and metabolic signals in the bone microenvironment. A balanced remodeling is a hallmark of healthy bone. However, under phases of increased strain or stress, bone adapts to the changing requirements by increasing bone formation. Vice versa, if there is a reduction in physical strain, for example, due to temporary immobilization after surgical procedures, bone adapts by reducing its mass and architecture [3].

Locally and systemically, bone metabolism is regulated by numerous hormones, cytokines, as well as physical factors [1, 2]. The most prominent hormones, which regulate bone acquisition as well as the differentiation and lifespan of bone cells, are sex hormones. Estrogens suppress bone resorption by inducing osteoclast apoptosis and inhibiting osteoclastogenesis. On the other hand, they diminish the apoptosis of osteoblasts and support the differentiation and maturation of osteoblast precursor cells [4]. The decline of systemic estrogen in women after menopause is a primary cause of postmenopausal osteoporosis characterized by an impaired bone mass and increased risk of developing fragility fractures [5]. Testosterone can be converted to estrogen by aromatization and also mediates bone-protective effects [2]. Further important hormones with divergent effects on bone cells and remodeling are thyroid and parathyroid hormones, growth hormone, and corticosteroids [2, 6, 7].

In addition to hormones and physical factors, multifaceted interactions of bone and immune cells have been identified. For example, inflammatory cytokines like tumor necrosis factor alpha

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(TNFα) or interleukins (IL)-1 and IL-6 directly activate osteoclastogenesis and osteoclastic bone resorption [8]. These mechanisms are key contributors to bone damage and loss in rheumatoid arthritis, an inflammatory joint disease [9].

Pathophysiology of Bone Metastases

Bone is a site of metastasis in several human malignancies including breast, lung, and prostate cancer [10]. The metastatic process underlying the occurrence of bone lesions is complex, requiring a tight interaction of cancer cells and cells from the bone microenvironment. The predisposition of certain cells to metastasize to bone has been well recognized for over a century. Stephen Paget was first to describe the "seed and soil" hypothesis in 1889 [11]. This hypothesis is based on the assumption that growth factors and cytokines stored within the bone provide a growth-promoting microenvironment for cancer cells. The vicious cycle of bone metastases provides a simplified explanation for the process of local bone destruction and increased tumor growth in the bone, where cancer cells that have successfully migrated to the bone secrete factors that directly and indirectly promote bone resorption by increasing osteoclast activity and inhibiting osteoblasts [12]. The increased bone resorption in turn results in an increased release of growth factors stored in the bone matrix, which promotes the local proliferation of the tumor cells [13].

Bone metastases can be differentiated according to their radiographic morphology into sclerotic or lytic lesions. While prostate cancer-derived bone lesions are often sclerotic, breast cancer bone metastases are typically osteolytic. While the bone quality is inferior in both cases, patients with predominantly osteolytic lesions are at a higher risk of fractures [14]. In osteolytic bone lesions (Fig. 36.1), the RANKL/RANK/osteoprotegerin (OPG) system is a major contributor to the progression of disease. Receptor activator of nuclear factor kappa-B ligand (RANKL) binds to its receptor RANK which is expressed on osteoclasts and osteoclast precursors. Osteoprotegerin (OPG) is a decoy receptor for RANKL. Physiologically, the ratio of RANKL and OPG determines the level of osteoclast activity. In malignant bone disease, a local increase in RANKL and lower OPG levels result in an imbalanced ratio promoting osteoclast activity [15].

Tumor cells not only stimulate osteoclastogenesis but also impair the differentiation and activation of bone-forming osteoblasts. The maturation of these cells is dependent on multiple pathways, of which the Wnt pathway is the most important. Wnt ligands mediate a complex cascade of signaling processes within osteoblast precursor cells which lead to the activation of key genes of osteoblastogenesis. These steps are strongly suppressed by cancer-derived inhibitors of the Wnt pathway. One of the most prominent examples in this regard is Dickkopf-1, which can be found in osteolytic bone metastases [16].

Prevalence of Bone Metastases

In general, up to 30% of patients with breast cancer will develop metastatic disease [17]. Bone metastases are a common late-stage complication of prevalent malignancies like prostate or breast cancer. But also other cancer entities like renal, lung, or thyroid have a high tendency to metastasize to bone. The incidence of bone metastases in advanced stages of the disease is highly dependent on the primary tumor type. The highest risk of developing bone metastases can be found in patients with prostate cancer with a 5-year incidence of 24.5%, followed by lung (12.4%), renal (8.4%), and breast (6%) cancers [18].

General Treatment Approach to Bone Metastases

To achieve an optimal outcome, bone metastases require a multidisciplinary treatment approach consisting of surgeons, radiologists, oncologists, as well as doctors specializing in pain and nuclear medicine as well as osteology. Following the diagnosis of bone metastases, an individual treat-

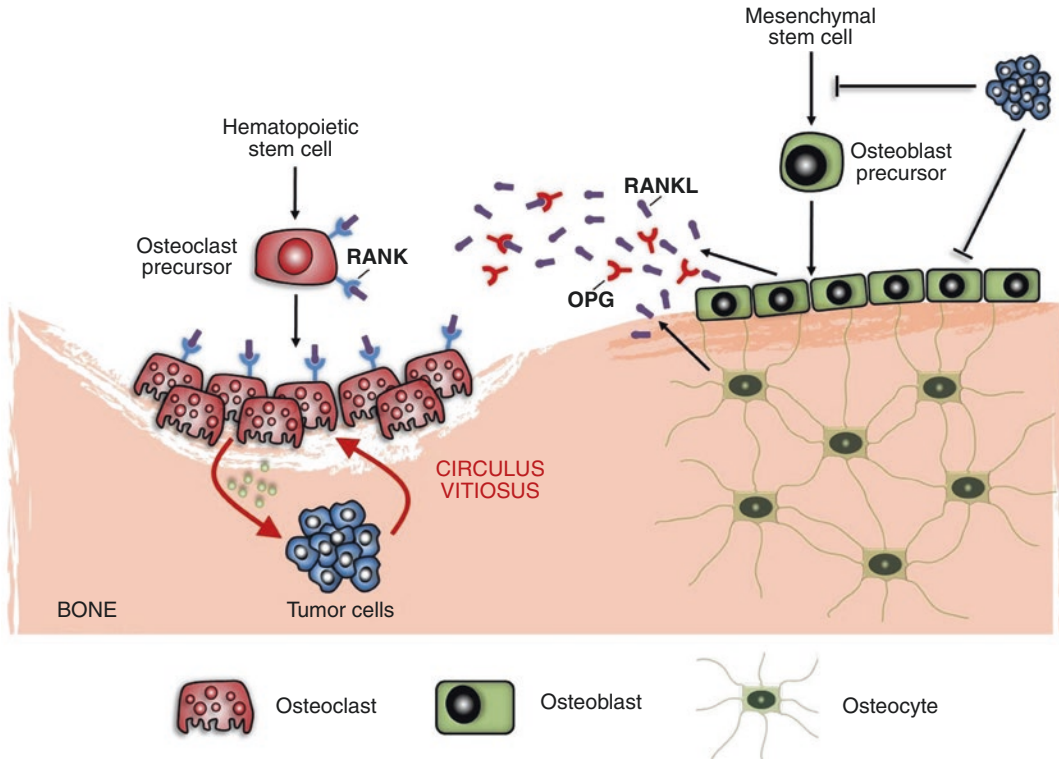

Fig. 36.1 Effects of osteolytic tumor cells on bone remodeling. The balanced remodeling of the bone is ensured by the tightly controlled actions of three main cell types: osteoblasts, osteoclasts, and osteocytes. Osteoblasts originate from mesenchymal stem cells and osteoblast precursors. They are responsible for the de novo formation of bone matrix. Bone-resorbing osteoclasts derive from hematopoietic stem cells and osteoclast precursors. Apart from other factors, osteoclastic differentiation is mainly dependent on the receptor activator of nuclear factor kappa-B ligand (RANKL) which is produced by osteoblasts and binds the receptor RANK on osteoclast precursors and mature osteoclasts. The action of RANKL is limited by its natural antagonist osteoprotegerin (OPG), which is also produced by osteoblasts. Osteocytes are terminally differentiated osteoblasts which are embedded in the bone matrix and serve as mechanosensors and support osteoclastic differentiation by the production of RANKL. In the presence of osteolytic tumor cells, osteoclastic bone resorption is increased by tumor cell-secreted factors that favor the production of RANKL, while OPG production is diminished. Growth factors and calcium stored within the bone matrix which are released by resorption in turn support tumor cell growth within the bone (*circulus vitiosus*). In addition, osteoblastogenesis and osteoblastic functions are inhibited by tumor cell-derived factors

ment strategy should be provided to each patient in an interdisciplinary tumor conference. Aspects to consider when proposing a treatment scheme are the localization, extent, and operability of the lesion. In addition, age, general health, and concurrent medical conditions need also to be considered. Bone metastases are still generally considered palliative, but increasingly curative approaches for single lesions in otherwise healthy patients are considered. While the initial decisions on operative or radiotherapy procedures are required, pharmacological treatment should be offered to all patients. Pharmacological treatment options for bone metastases will be extensively discussed in the following paragraphs.

Pharmacological Approach to Treating Patients with Bone Metastases

Pharmacological approaches to treat bone metastases generally consist of a potent antiresorptive therapy. Of note, antiresorptive therapy is

recommended independent of cancer entity or morphologic appearance of the bone lesion. Two main classes of antiresorptive drugs are currently approved to treat bone metastases, namely, bisphosphonates and denosumab (Fig. 36.2).

Bisphosphonates

Bisphosphonates are a class of antiresorptive drugs that are widely used to treat benign and malignant bone conditions. Since their initial discovery in the 1960s, several generations of bisphosphonates have evolved with increasing bone affinity and antiresorptive potency.

All bisphosphonates share a P-C-P structure (two phosphate groups with a carbon atom), which makes them very stable and robust. Pharmacokinetic properties are largely determined by additional side groups. Aminobisphosphonates are named after a nitrogen atom included in the side group and are more potent than traditional bisphosphonates. These exert their antiresorptive properties by inhibiting the mevalonate pathway [19]. Several bisphosphonates are now approved for the treatment of bone metastases and/or myeloma. Of these, zoledronic acid, which is also considered the most potent bisphosphonate, has been most extensively investigated in clinical trials [20].

Breast Cancer

Several randomized trials have compared the use of bisphosphonates to placebo in preventing

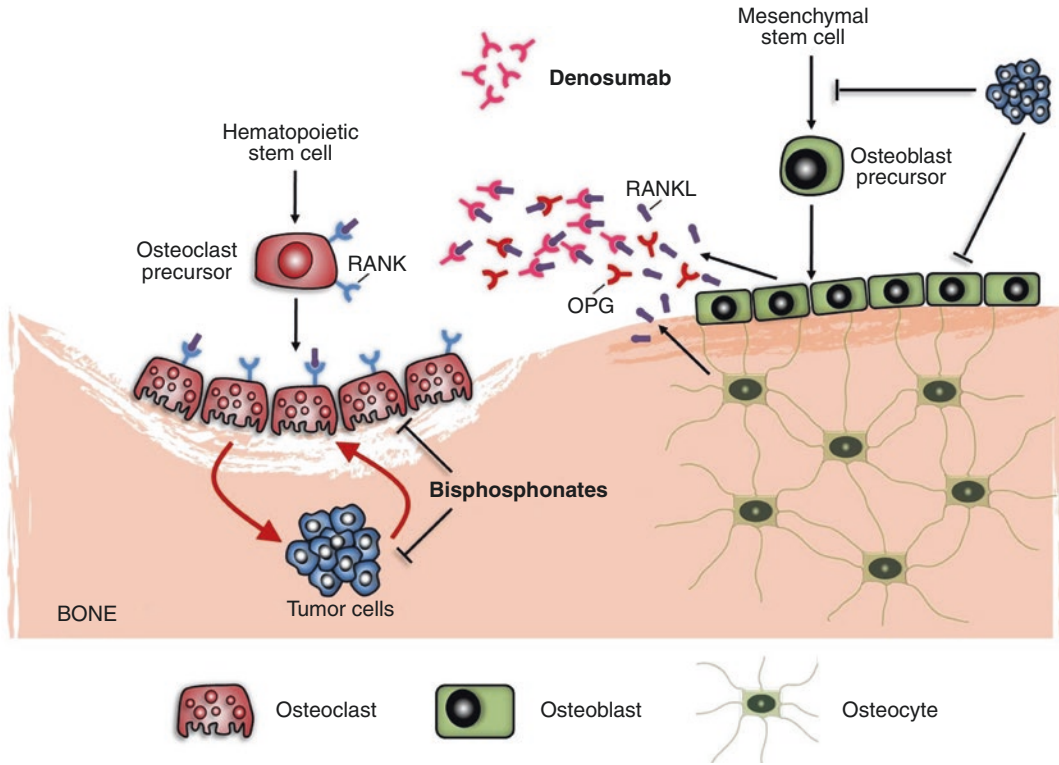

Fig. 36.2 Denosumab and bisphosphonates as antiresorptive therapies in osteolytic bone metastases. Denosumab is a neutralizing monoclonal antibody against receptor activator of nuclear factor kappa-B ligand (RANKL). It reduces the binding of RANKL to RANK on osteoclast precursors and mature osteoclasts, thereby reducing osteoclastogenesis and bone resorption. (Amino) bisphosphonates are inhibitors of the mevalonate pathway and inducers of apoptosis in bone-resorbing osteoclasts. In addition, they exert direct antitumor effects on osteolytic tumor cells

skeletal-related events (SREs) in patients with breast cancer. A reduction or significant delay of SREs has been confirmed for clodronate, pamidronate, ibandronate, and zoledronic acid (summarized in [21]). Meta-analyses have confirmed the benefit of bisphosphonates in reducing the risk for fractures, surgery, and hypercalcemia, but not for spinal compression [22]. Importantly, effects were time-dependent, and treatment had to be performed for at least 6 months to see positive effects on skeletal morbidity outcomes [22]. Fewer trials were conducted to directly compare different bisphosphonates. In a comparative trial, intravenous pamidronate (90 mg, monthly) appeared more effective than oral clodronate in controlling bone symptoms and suppressing bone resorption [23]. In breast cancer patients, zoledronic acid was shown to be superior to pamidronate in reducing the rate of SREs in patients who had at least one osteolytic lesion (48% vs. 58%) and significantly reduced the time to first SRE ($p = 0.013$) [24].

A Cochrane analysis came to the conclusion that bisphosphonates reduce the risk of SREs in women with breast cancer and clinically evident bone metastases [25]. In addition, a more recent meta-analysis concludes that bisphosphonates provided an overall survival benefit independent of bone metastases (HR 0.91, 95% CI 0.83–0.99; $p = 0.04$). However, subgroup analysis by menopausal status showed a survival benefit from bisphosphonates in postmenopausal women only (HR 0.77, 95% CI 0.66–0.90; $p = 0.001$) but no survival benefit for premenopausal women (HR 1.03, 95% CI 0.86–1.22; $p = 0.78$) [26].

An important aspect in breast cancer patients with hormone receptor-positive tumors is the negative impact that adjuvant cancer therapies may exert on bone health [27]. In postmenopausal women, aromatase inhibitors are currently used to achieve maximal suppression of residual estrogen levels. While effective in reducing the risk of disease relapse, aromatase inhibitors cause a rapid decline in bone mass and increase fracture risk. Several studies have investigated the adjuvant use of antiresorptive agents in this setting [28].

The adjuvant use of bisphosphonates in breast cancer has only yielded positive results in postmenopausal women or those that had menopause induced by GnRH analogues like goserelin. A recent meta-analysis supported the anticancer effect of bisphosphonates, with a decrease in the incidence of bone recurrence by 34% and breast cancer-specific mortality by 17% [29]. Based on these findings, the use of an antiresorptive therapy should be considered in all postmenopausal women with early breast cancer. Adjuvant bisphosphonates in women with early BC are now recommended (joint position statement of the IOF, CABS, ECTS, IEG, ESCEO IMS, and SIOG) [27].

Prostate

Trials investigating bisphosphonates in metastatic prostate cancer are scarcer than in breast cancer. In a study of 643 men with metastatic prostate cancer, zoledronic acid significantly reduced the risk of at least one SRE by 11% (39% vs. 49%, $p = 0.028$) while reducing the overall risk of skeletal complications by 36% after 24 months [30]. In another trial, the effect of a single infusion of ibandronate (6 mg) was compared against single-dose radiotherapy with regard to bone pain. At 4–12 weeks, the pain response was not statistically different, with comparable reductions in pain score in both groups [31].

Myeloma

As a systemic hematological disease derived from the bone marrow, the pathogenesis of multiple myeloma is distinctly different from solid tumors. However, osteolytic lesions are a hallmark of multiple myeloma [32]. Several larger studies have investigated the use of different bisphosphonates in patients with multiple myeloma.

Clodronate represents the only non-aminobisphosphonate approved for the treatment of lytic bone lesions derived from myeloma. Clinical trials in the 1990s using clodronate were the first to confirm a reduction in SREs [33, 34]. These trials did not show a general survival

benefit for clodronate, although subset analyses revealed that among the subgroup with no skeletal fractures at presentation, survival was significantly improved (59 vs. 37 months, $p = 0.006$) [35]. While oral pamidronate (300 mg/daily) failed to reduce SREs [36], intravenous pamidronate significantly reduced the rate of skeletal events compared to placebo (24% vs. 41%, $p < 0.001$). Survival in a subgroup of patients with more advanced disease was significantly longer (median survival 21 vs. 14 months, $p = 0.041$) [37]. Several trials have investigated zoledronic acid in multiple myeloma. Compared to pamidronate, zoledronic acid was at least comparable in reducing the rate of SREs [38]. Compared to clodronate, zoledronic acid reduced the risk of SREs by 26%. Importantly, zoledronic acid reduced the rate of SREs in patients with and without detectable bone lesions [39]. Furthermore, zoledronic acid in addition to standard therapy reduced the risk of death by 16% ($p = 0.012$) and prolonged median overall survival by 5.5 months from 44.5 to 50.0 months [39]. Meta-analyses of different bisphosphonates showed no overall survival benefit for individual agents, but zoledronic acid was superior to placebo (and etidronate) in improving survival [40]. Based on their clear efficacy in reducing SREs, it is recommended to consider bisphosphonates in all myeloma patients [41].

Safety of Bisphosphonates

Bisphosphonates are generally considered as safe and well-tolerated drugs. When discussing adverse events, it is important to distinguish between events that occur in the lower doses used for the treatment of osteoporosis and those that occur in patients treated with higher doses for bone metastases. Following parental application, some patients may experience an acute-phase reaction with flu-like symptoms. Acute-phase reactions are described in up to one-third of patients and are caused by the activation and proliferation of gamma-delta-T-cells [42]. Self-limiting symptoms generally resolve within 1–2 days and occur predominantly after the first infusion. Bisphosphonates increase the risk of renal complications and hypocalcemia. To reduce the risk of these complications, regular assessment of renal function as well as adequate calcium supplementation is recommended. Osteonecrosis of the jaw (ONJ) is a recognized complication of bisphosphonate therapy. While the prevalence in the osteoporosis setting is very low, about 1–5% of patients treated for bone metastases may develop ONJ [43]. To decrease the risk of ONJ, dental assessment prior to the initiation of therapy and good dental hygiene in addition to perioperative antibiotics are recommended.

Denosumab

Denosumab is a monoclonal antibody against RANKL. Denosumab is approved for the treatment of osteoporosis (60 mg every 6 months) and for the treatment of bone metastases secondary to solid cancers and myeloma (120 mg every 4 weeks). Following successful phase 2 trials, denosumab was investigated in three large phase 3 trials which led to the initial approval of denosumab for the treatment of solid tumors.

Denosumab was assessed in a head-to-head trial against zoledronic acid in patients with prostate cancer. In 1904 men with metastatic prostate cancer, denosumab was superior to zoledronic acid in delaying the time to first and subsequent SREs. The time to first SRE was delayed by 3.6 months (17.1 vs. 20.7 months; HR: 0.82, 95%CI 0.71–0.95; $p = 0.008$ for superiority) in the denosumab arm. Denosumab significantly reduced the risk of first and subsequent SREs by 18% compared to zoledronic acid ($p = 0.001$ for superiority) [44]. Overall survival was similar in the two treatment arms. In a separate breast cancer trial, 2046 patients were randomized to receive denosumab or zoledronic acid. Denosumab was superior to zoledronic acid in delaying time to first on-study SRE (HR 0.82; 95%CI 0.71–0.95; $p = 0.01$ superiority) and time to first and subsequent (multiple) on-study SREs ($p = 0.001$). Overall survival and disease progression were similar between groups [45].

In a third trial, denosumab was compared to zoledronic acid in the treatment of bone metasta-

ses in patients with advanced solid cancer other than breast and prostate cancer and myeloma. Denosumab was non-inferior to zoledronic acid in preventing or delaying first on-study SRE (HR 0.84; 95% CI, 0.71–0.98; $p = 0.0007$). No superiority for denosumab could be shown in this trial, and a post hoc analysis revealed a potential negative effect for the myeloma subgroup [46].

Notably, exploratory analyses of this trial revealed a significant survival benefit for patients with lung cancer (non-small cell lung cancer and small cell lung cancer) treated with denosumab. Denosumab was associated with improved median overall survival versus ZA in 811 patients with any lung cancer (8.9 vs. 7.7 months; hazard ratio [HR] 0.80) and in 702 patients with NSCLC (9.5 vs. 8.0 months; HR 0.78) ($p = 0.01$, each comparison). Further analysis of NSCLC by histological type showed a median survival of 8.6 months for denosumab versus 6.4 months for ZA in patients with squamous cell carcinoma (HR 0.68; $p = 0.035$). Based on these results, a subsequent myeloma trial was initiated. In this trial, 1718 patients were randomized to receive subcutaneous denosumab 120 mg plus intravenous placebo every 4 weeks or intravenous zoledronic acid 4 mg plus subcutaneous placebo every 4 weeks. The primary endpoint, non-inferiority of denosumab to zoledronic acid for time to first skeletal-related event was achieved (HR 0.98, 95% CI 0.85–1.14; non-inferiority $p = 0{\cdot}01$). Notably, renal toxicity was reported in less (10%) patients in the denosumab group compared to 17% in the zoledronic acid group [47].

Optimizing Bone Health in Patients with Cancer at High Risk of Developing Bone Metastases

In patients with nonmetastatic prostate cancer, the adjuvant use of denosumab (120 mg monthly) delayed the occurrence of bone metastases by a median of 4.2 months (HR 0.085, 95%CI 0.71–0.98, $p = 0.032$) [48]. While overall survival did not differ between denosumab and placebo, the rate of ONJ was significantly increased by denosumab (5% vs. 0%). Two trials have investigated denosumab in the adjuvant treatment of breast cancer. The ABCSG-18 trial compared the effects of denosumab or placebo on fracture incidence in 3425 postmenopausal breast cancer patients on aromatase inhibitor therapy. Denosumab significantly reduced the risk of any clinical fracture (HR 0.50; 95% CI 0.39–0.65; $p < 0.0001$). Interestingly, the reduction in fracture rate was seen in both patients with and without baseline T-scores below −1 as well as age above and below 65 [49]. Recently, data from the D-Care trial (NCT01077154), which aimed to establish the ability of denosumab to prevent the occurrence of bone metastases in BC patients with a high risk of developing metastatic bone disease, were presented. In this trial, RANKL inhibition with denosumab failed to reduce the rate of bone metastases [50].

Summary

The pathophysiology of bone metastases is complex and treatment requires an interdisciplinary approach. Antiresorptive therapy is an essential aspect of providing optimal treatment. Bisphosphonates and denosumab have proven efficacy in reducing the occurrence of SREs and improving life quality by targeting the bone-resorbing osteoclast. Future research will need to identify how metastatic cells home to bone and engraft with the aim of identifying both preventative and therapeutic strategies.

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37 Systemic Therapies for Patients with Metastatic Spinal Disease

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Epidemiology

The spine can be considered to be composed of the spinal cord of the central nervous system (CNS) and the bony vertebral column. Spinal metastases occur in 30–90% of patients with malignant tumors of advanced stage. Of those, 20% ultimately result in symptomatic compression of the spinal cord [1, 2]. The most common location of spinal metastatic disease is the thoracic spine (70%), followed by the lumbar (20%) and cervical (10%) spine [1, 2].

Oncologic Parameters Affecting Treatment

The management of spinal metastases with systemic therapy is essentially palliative, focusing on symptomatic relief, preserving neurological function, and restoring or maintaining the stability of the spine [2, 3]. Beyond the acuity and severity of the presenting symptoms, several other clinical characteristics are involved in determining the most appropriate therapeutic management, including the patient's age and performance status, the extent of metastatic disease, and the primary tumor type [2, 3].

In general, the comprehensive assessment of these parameters requires the involvement of multiple different specialties, including surgery (neurosurgery, orthopedic surgery), radiation oncology, medical oncology, interventional radiology, pain and rehabilitation medicine, and others. To ensure the optimal use of treatment in the right patient at the right time, a framework of decision points on four sentinel aspects of the disease was developed, also known as NOMS (neurologic, oncologic, mechanical instability, systemic disease) [1]. The role of the initial oncologic assessment within the NOMS framework is to determine the likelihood of response to radiation and systemic therapy [1]. According to the established algorithm, radiosensitive tumors may be effectively addressed by external beam radiation therapy (EBRT) or stereotactic radiosurgery (SRS), whereas radioresistant or previously radiated tumors usually necessitate a surgical approach first, particularly in the presence of cord compression and/or myelopathy [1, 4].

Systemic anticancer therapies include classic chemotherapeutic agents, targeted therapies, and immunotherapy which promotes the activity of a patient's native immune system against their tumor (at present most commonly represented by programmed death-1 (PD-1) or programmed death-ligand 1 (PD-L1) immune checkpoint inhibitors). Despite recent advances, systemic

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therapy is not yet clearly integrated into the NOMS framework. This apparent discrepancy may be due to multiple reasons. First, chemotherapy is generally considered to be more effective for visceral than for osseous disease [1]. Intriguingly, several chemotherapeutic drugs may actually negatively affect bone health by acting through different mechanisms, including inhibition of osteoblasts (doxorubicin, cyclophosphamide), stimulation of osteoclasts (cyclosporine), reduction of vitamin D levels (5FU, leucovorin), phosphate wasting through the kidneys (ifosfamide), hypomagnesemia (platinum agents), and ovarian suppression-induced menopause [5]. Additionally, there are only limited, premature data on the effect of newer systemic therapies on bone metastases.

Impact of Systemic Anticancer Therapies on Spinal Metastatic Disease

Systemic therapies have transformed the natural course of several types of cancers. These agents are used to treat solid tumor metastases including sites in the spinal cord and vertebral column. However, the cord- and bone-specific effects of these drugs on the outcomes of metastatic tumors are yet to be fully determined. This is particularly true for metastases to the spinal cord, where local therapies such as radiation and surgery currently have a more significant role.

Chemotherapy

Chemotherapeutic agents are usually effective in treating chemosensitive tumors with or without spinal cord or osseous metastases, such as small cell lung cancer (SCLC), Ewing's sarcoma, and neuroblastoma [3]. However, their role is limited in chemoresistant malignancies. The most common primary tumors that demonstrate bone tropism are breast, prostate, and lung cancers [6].

Breast cancer is sensitive to several chemotherapeutic agents, including anthracyclines and taxanes, which comprise the backbone of many regimens [7]. In the advanced setting, which is most relevant for the development and progression of bone disease, including spinal metastases, taxane-based regimens or capecitabine are the most commonly used agents whenever visceral disease is also present and a rapid tumor regression is needed [8]. Other approved chemotherapy drugs include gemcitabine, vinorelbine, eribulin, pemetrexed, and platinum agents [8]. Despite the fact that several trials have reported on the activity of these agents (single or combined), there is a paucity of contemporary studies on bone-specific effects of chemotherapy in metastatic breast cancer. Older cumulative data from 12 trials supported a tendency for soft tissue lesions to have a higher response rate (55–60%) compared to visceral and bone metastases (31–44%) [9]. In the era of targeted therapies, including HER-2-directed therapies, anti-hormonal agents, and cell cycle inhibitors (discussed separately in "Vertebral Metastases and Targeted Therapy" section), patient selection is becoming key in order to improve site-specific and overall antitumor responses.

Prostate cancer (PC) is also responsive to chemotherapy, particularly to taxanes. Docetaxel is an established treatment for both castration-resistant prostate cancer (CRPC) and high-volume hormone-sensitive prostate cancer (HSPC) [10, 11]. In updated results from the CHAARTED trial, HSPC patients with high-volume disease (defined as presence of visceral metastases and/or ≥ four bone metastases with at least one outside of the vertebral column and pelvis) had a significant survival benefit from treatment with docetaxel plus androgen deprivation therapy (ADT) compared with ADT alone. However, those with low-volume disease did not have an overall survival (OS) benefit with the addition of docetaxel, providing evidence for the activity of the drug in osseous disease [11]. Cabazitaxel is approved for the treatment of metastatic CRPC after progression on docetaxel [12]. Because the majority of patients studied in trials with these drugs had osseous metastases, characterizing the effect of chemotherapy on markers of bone metabolism became a relevant endpoint. In a prospective randomized study of docetaxel/

estramustine versus the bisphosphonate zoledronic acid (discussed in "EGFR-Directed Therapies" section), no significant difference was found in median change of any measured bone turnover markers in patients given zoledronic acid when compared to chemotherapy, including interleukin-6 (IL-6), urinary deoxypyridinoline to serum creatinine ratio (DpD), tartrate-resistant acid phosphatase (TRAPC), bone-specific alkaline phosphatase (BAP), intact osteocalcin (OCN), osteoprotegerin (OPG), and ligand for receptor activator of nuclear-factor κB (RANKL) [13]. This suggests that docetaxel may lead to a similar degree of bone turnover as zoledronic acid in CRPC bone metastases. Additionally, there was a significant reduction of IL-6 levels by 35% in prostate-specific antigen (PSA) responders compared to non-responders, suggesting that IL-6 could serve as a surrogate for clinical response of bone metastases to docetaxel-based chemotherapy [13]. Within the same context, CaBone is an ongoing single-arm phase II study of cabazitaxel in metastatic CRPC patients with bone-only metastases assessing bone progression-free survival as the primary endpoint as well as several bone-specific secondary endpoints, including time to skeletal-related event (SRE), time to bone pain progression, bone pain response, and bone turnover markers (ALP, bone ALP, LDH, serum CTx, iPTH, and 1,25 (OH)2D3) [14].

Newly diagnosed, metastatic non-small cell lung cancers (NSCLC) with bone metastases and no targetable driver mutations (such as in EGFR or ALK), and low (<50%) expression of PD-L1, are commonly treated with platinum-based chemotherapy doublets. The standard of care was to use these regimens alone, until the most recent phase III trials which showed improved outcomes by combining platinum-based chemotherapy with the checkpoint inhibitor pembrolizumab, regardless of PD-L1 expression on tumors [15, 16]. Although data on specific effects of chemotherapy on bone metastases from NSCLC are limited or not reported, patients with bone metastases who receive chemotherapy have a more favorable prognosis (11.4 vs. 7.5 months median overall survival) [17].

Table 37.1 Examples of chemotherapy agents with CNS penetration

Drug	Tumor type used for
Temozolomide	Glioma, melanoma, breast cancer, SCLC
Ifosfamide	Ewing sarcoma, lymphoma
Pemetrexed	NSCLC
Topotecan	SCLC
Methotrexate	ALL
Capecitabine	Breast cancer

In patients with cancer metastatic to the CNS, of which the spinal cord is a component, a number of chemotherapy drugs have activity by virtue of their ability to penetrate into this part of the body (Table 37.1). Nevertheless, this does not often translate into an increase in overall survival as chemotherapeutics usually lack sufficient concentrations for adequate duration to cause a significant antitumor effect [18]. Additionally, with few exceptions (e.g., high-dose methotrexate for prevention of acute lymphoblastic leukemia (ALL) CNS relapse), the use of CSF drug concentrations as a surrogate for brain and/or tumor penetration is not informative due to the complexity of the CSF barriers and drug kinetics. It will be critical for future studies to determine a more precise assessment of CNS extent of disease and to optimize systemic and/or intrathecal dosing to improve the likelihood of prolonging survival in this setting.

Vertebral Metastases and Targeted Therapy

Hormonal Therapy

Aromatase Inhibitors

Aromatase inhibitors (AIs) play an important role in the treatment of postmenopausal women with estrogen or progesterone receptor-positive breast carcinoma, both in the adjuvant and metastatic settings. However, natural bone loss is accelerated due to AI-induced estrogen depletion. Additionally, there is an inherent difficulty in evaluation of response of osseous metastases with current imaging modalities (bone scan, CT,

MRI) [19]. The % change in the maximum standardized uptake value (SUVmax) on PET/CT at 8 weeks compared to baseline, either with [18F] fluorodeoxyglucose (FDG) or [18F]-fluoride (NaF), appears to be the most promising metric as a predictor of clinical progression-free survival (PFS) by week 24; however, validating studies are warranted [20]. Interlesional response heterogeneity, flare phenomena, and non-FDG avid osseous metastases, which may occur in up to 40% of cases, are remaining challenges that need to be overcome [21, 22].

Androgen-Directed Therapies

Luteinizing hormone-releasing hormone (LHRH) agonists and antagonists are an essential component of ADT for advanced PC. In most patients, ADT results in regression of metastases and in serum prostate-specific antigen (PSA) response. For skeletal metastases, the total area of hot spots on bone scan (<3 vs. ≥3 lumbar vertebral bodies) combined with the percentage of the total scan (<75% vs. ≥75% or superscan) has been used to calculate a score, termed the Soloway score. The latter was prognostic of early ADT failure, defined as death from metastatic prostate cancer within 12 months after the start of ADT [23]. At present, the most widely used imaging marker of bone response is included in the Prostate Cancer Clinical Trials Working Group 3 criteria [24]. Progression of osseous metastatic disease by these criteria requires at least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2 + 2 rule). In contrast, changes in intensity of uptake alone do not constitute either progression or regression [24].

Similar to endocrine therapies for breast cancer, the benefits of ADT in bone metastatic PC come at the cost of secondary osteoporosis, which has a variable prevalence across different studies (9–53%) but highlights the importance of preventative and early diagnostic approaches (calcium/vitamin D supplementation, exercise, bone densitometry) as part of the standard care of these patients [24].

Abiraterone acetate (AA) is an androgen biosynthesis inhibitor with strong activity against PC in both castration-sensitive and resistant settings. A post hoc analysis of the landmark COU-AA-301 phase III trial compared the time to first occurrence of skeletal-related events, spinal cord compression, palliative radiation to bone, or bone surgery in metastatic CRPC patients who received AA plus prednisone vs. prednisone alone [25]. AA plus prednisone resulted in faster and more pronounced alleviation of skeletal pain and prolonged time to occurrence of first skeletal-related event compared to prednisone alone (25 vs. 20 months) [25]. The PREVAIL study was another key study that resulted in the approval of the androgen receptor inhibitor enzalutamide for metastatic CRPC [26]. When focusing on bone-specific endpoints, enzalutamide significantly delayed the occurrence of first SRE and self-reported pain in chemotherapy-naive men with metastatic CRPC [26]. Overall, both abiraterone and enzalutamide have demonstrated the ability to delay bone progression resulting in improvements in bone-related endpoints in patients with metastatic CRPC [27]. This benefit correlates at the molecular level with pretreatment tumor nuclear AR overexpression (>75%) and CYP17 expression (>10%) [28].

HER2-Directed Therapies

Bone metastases are equally common in all breast cancer subtypes, including HER2-positive disease [29]. There is indirect evidence to support a positive role for anti-HER2 monoclonal antibodies (trastuzumab) or small molecule inhibitors (lapatinib) in the outcome of these patients. Presence of bone metastases is associated with long-term survival in patients with metastatic breast cancer who receive anti-HER2 treatment [30].

EGFR-Directed Therapies

The pattern of metastases at diagnosis is associated with the tumor molecular status in certain cancers [31]. In NSCLC, more than half (54%) of stage IV patients with EGFR mutations (specifically exon 19 deletions and exon 21 L858R

mutations) have bone metastases [30]. Additionally, the presence of mutations in oncogenes including EGFR, ALK, MET, and ROS1 in NSCLC patients with spinal metastases is associated with increased overall survival [32]. Targeting these alterations may be beneficial for prevention of skeletal-related events. Indeed, in a retrospective analysis of NSCLC patients with bone metastases, EGFR mutation status was predictive of treatment efficacy with an EGFR tyrosine kinase inhibitor (TKI) [33]. The addition of bisphosphonates (discussed in "Bone-targeted Therapies" section) to EGFR TKIs can further enhance their antitumor effect in patients with EGFR-mutated NSCLC and bone metastases, supported by a longer PFS compared to patients only receiving EGFR TKIs [34]. Continuation of the EGFR TKIs beyond skeletal progression of pre-existing lesions in such patients, combined with adequate local treatment, results in long post-skeletal metastasis progression survival, which is more evidence of the activity of anti-EGFR therapy in this setting [35].

Anti-angiogenic Therapies

The paradigm of angiogenesis-driven tumors is renal cell carcinoma (RCC). Despite the fact that the presence of bone metastases is an adverse prognostic factor in metastatic RCC patients, the use of vascular endothelial growth factor (VEGF) pathway inhibitors (sunitinib, pazopanib, axitinib, cabozantinib, lenvatinib, sorafenib) in the TKI era has significantly improved the median OS compared to historical controls or other systemic therapies in the pre-TKI era [36]. Notably, concurrent use of VEGF pathway-targeting TKIs with bisphosphonates (discussed in "Bone-Targeted Therapies" section) in metastatic RCC patients with bone metastases can further prolong median PFS and OS [37].

Less is known about the potential priming role of antiangiogenic therapy in bone-related outcomes of patients with other tumor types. The monoclonal anti-VEGF antibody bevacizumab (Bev) enhances the activity of first-line platinum-based chemotherapy against bone metastases from NSCLC. This was evidenced by prolongation of bone-specific time-to-progression and reduction in the frequency of SREs in Bev-treated patients compared to non-Bev-treated patients [38]. In patients with bone-predominant metastatic breast cancer, the level of soluble VEGF receptor 2 (VEGFR2) was prognostic of OS in those treated with the combination of the VEGF receptor targeting agent vandetanib and endocrine therapy with fulvestrant [39].

An interesting observation in patients with vertebral metastases of different primaries (breast, lung, kidney) undergoing palliative radiotherapy (RT) is that concomitant use of bevacizumab is tolerable. Thus, patients already receiving bevacizumab as part of their systemic antitumor treatment should not be excluded from emergency RT if indicated [40].

Bone-Targeted Therapies

The third-generation bisphosphonate zoledronic acid (ZA) and the monoclonal antibody against the receptor activator of nuclear factor kappa-B ligand (RANKL) are the two most widely used systemic agents for targeting bone metastases in several different cancers. Mechanistically, they impair osteoclast-mediated bone resorption and reduce tumor-associated osteolysis [41]. Numerous studies have demonstrated a statistically significant reduction in the rate of pathologic fractures, pain and analgesic consumption, and improvement in the quality of life with these agents compared to placebo [42].

In a pivotal trial comparing ZA with the second-generation bisphosphonate pamidronate in patients with metastatic breast cancer or myeloma, fewer patients treated with the former required RT (19 vs. 24%) [42]. An additional 25% reduction in the mean % of annual SREs and skeletal morbidity was seen with ZA, compared to that achieved by pamidronate [43]. The optimal dosing of ZA was studied in a randomized, open-label clinical trial comparing administration every 4 weeks with every 12 weeks in patients with bone metastases due to breast cancer, prostate cancer, or multiple myeloma [44].

This study suggested that a longer interval may be an acceptable treatment option since the risk of skeletal events was not increased over 2 years compared to the conventional dosing [44].

Despite ZA treatment, more than one third of patients with bone metastases will still develop SREs [42]. The discovery of the osteoprotegerin (OPG)–RANKL–RANK pathway led to the development of denosumab, which is a recombinant RANKL antagonist [45]. Several clinical studies examined the effects of this drug in patients with bone metastases from different primaries and compared denosumab with ZA. Across numerous randomized comparisons and post hoc analyses, denosumab appears to be more effective in the prevention or delay of SREs and in pain control compared to ZA. In metastatic breast cancer, denosumab delayed the time to first on-study SRE by 18% when compared with ZA and further reduced the risk of subsequent SREs by 23% [46]. Denosumab was also superior to ZA in delaying skeletal events in metastatic CRPC patients (20.7 vs. 17.1 months) [47]. In another phase III trial comparing these two bone-targeted therapies in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma, denosumab outperformed ZA in prevention of skeletal complications, including risk of radiation to bone, worsening of pain, and frequency of a shift from no/weak opioid analgesic use to strong opioids [48]. In general, no significant differences in PFS or OS were observed between ZA and denosumab across different primaries. One exception was NSCLC, whereby an OS benefit was demonstrated in the entire cohort (8.9 vs. 7.7 months) and in the subgroup of patients with squamous cell carcinoma (8.6 vs. 6.4 months) [49].

Another bone-targeted modality is Radium-223 (Ra223), which exerts an antitumor effect via alpha particle emitting radiation. Ra223 is administered intravenously, has a high affinity for the bone matrix by virtue of its chemical properties, and was studied in the phase III ALSYMPCA trial in CRPC patients with bone metastases. Treatment with Ra223 resulted not only in delay of time to first SRE but also in OS benefit compared with placebo (14 vs. 11.2 months) [50].

Vertebral Metastases and Immunotherapy

While the use of immune checkpoint inhibitors, particularly PD-1 and PD-L1 antagonists, has been established in different cancer types, little is known about these new agents and their efficacy in treating metastatic spine lesions. Recent studies in tumor/bone mouse models suggest an osteoclast-independent role of CD8+ T cells in the negative regulation of bone metastases [51]. Thus, the immune microenvironment of tumors has emerged as a putative regulator of bone metastasis. These findings coupled with clinical observations on favorable outcomes of patients with bone and/or bone marrow involvement (e.g., in melanoma) treated with PD-1/PD-L1 inhibitors support a potential synergistic activity of PD-1/PD-L1 inhibitors and bisphosphonates or denosumab [52]. Another strategy that supports the activity of immunotherapy agents in the treatment of osseous metastatic disease involves combination with concurrent RT. Not only is it safe and tolerable, but it can also result in a decrease in the tumor growth rate of bone lesions [53].

CNS Metastases and Targeted Therapies/Immunotherapy

The treatment of spinal metastatic disease with CNS involvement using systemic therapies is challenging. However, promising prospective data on the safety and efficacy of targeted therapies and immunotherapy in these patients are beginning to emerge [54] (Table 37.2). One explanation for this is that newer targeted agents have better CNS penetration. In the absence of validated response criteria specific for CNS metastases, it is sometimes difficult to fully assess and compare the CNS-specific activity of these systemic therapies.

Table 37.2 Examples of targeted therapies and immunotherapies with CNS penetration

Drug	Target	Tumor type used for
Gefitinib, erlotinib, osimertinib	EGFR	NSCLC
Ceritinib, alectinib, brigatinib	ALK	NSCLC
Lapatinib, trastuzumab, T-DM1	HER2	Breast cancer
Vemurafenib, dabrafenib	BRAF	Melanoma
Sunitinib, pazopanib	VEGF pathway	RCC
Dasatinib	BCR-ABL	Chronic myeloid leukemia, ALL
Rituximab	CD20	Non-Hodgkin's lymphoma
Ipilimumab	CTLA4 (immunotherapy)	Melanoma
Nivolumab, pembrolizumab	PD-1 (immunotherapy)	Melanoma, NSCLC

Supportive Care

Corticosteroids

Corticosteroids are the mainstay of pharmacological therapy for pain associated with vertebral metastases and for the acute neurological deterioration that often accompanies metastatic epidural spinal cord compression (MESCC). Corticosteroids decrease tumor-associated inflammation (analgesia effect), decrease spinal cord edema (thereby improving short-term neurological function), and may be directly oncolytic in certain malignancies, including lymphoma, multiple myeloma, and breast cancer [55]. Experimental animal models have confirmed the clinical observations that those treated with dexamethasone improved motor function faster than in untreated controls. Currently, there is no optimal dosing regimen for corticosteroids used with MESCC, and no consensus data is available to recommend high-dose steroids (96 mg/day) versus low-dose steroids (16 mg/day) [53]. For instance, comparison of initial doses of 10 mg IV bolus versus 100 mg IV bolus showed no outcome differences regarding pain, ambulation, or bladder function [56].

Analgesia

Metastatic bone pain results in decreased quality of life, function, and mood. Symptomatic relief with use of pain medications until other anticancer local or systemic interventions are introduced or take effect is essential. Analgesics are usually administered in a ladder approach, starting with non-opioid agents (e.g., nonsteroidal anti-inflammatory drugs and paracetamol) [57]. For mild-to-moderate breakthrough pain, opioids such as codeine and tramadol are recommended. For severe breakthrough pain, opioids such as morphine, oxycodone, hydromorphone, and transdermal fentanyl should be started, slowly titrated, and rotated to ensure adequate analgesia while minimizing the risk for overdose [57]. Adjuvant analgesics can be added depending on the type of pain, including gabapentin or pregabalin for neuropathic pain. Corticosteroids are also active in inflammatory pain, and bisphosphonates can reduce bone pain [57].

Conclusions

Spinal metastases are an important source of morbidity and mortality in advanced cancer patients. Improvement of existing multidisciplinary assessment models and algorithms is essential to improve spine-specific and general outcomes (PFS, OS). Systemic antitumor therapies alone are generally reserved for asymptomatic or minimally symptomatic spinal metastases and in situations where considered therapies have good CNS and bone penetration. Combination approaches, such as the paradigm of TKIs or checkpoint inhibitors with radiation, hold promise for addressing patients presenting with subacute symptoms and signs. Clinical and molecular

biomarkers of bone and spinal cord response to systemic therapies are urgently needed. As the number of new systemic therapies increases with better molecular characterization of tumors, assessing their specific impact on patients with spinal metastases should be further elucidated and integrated into revised comprehensive treatment models.

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The Role of Advanced Imaging in Spinal Metastases

38

Sasan Karimi, Nicholas S. Cho, Kyung K. Peck, and Andrei I. Holodny

General Overview of Conventional Methods

The spine is the most common site for skeletal metastases. With spinal metastases being present in up to 70% of cancer patients at autopsy [1], the need for detecting spinal metastases and assessing their treatment response remains a priority when treating patients with cancer. The evaluation for spinal metastases is largely performed using conventional imaging methods including bone scan, computed tomography (CT), and magnetic resonance imaging (MRI).

Positron emission tomography (PET) has been combined with CT technology and recently with MRI to optimize localization, diagnostic accuracy, treatment planning, and follow-up by combining the imaging modalities.

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Conventional Magnetic Resonance Imaging

MRI has been commonly utilized for spinal cancer because it is the only modality that can directly image the bone marrow with high spatial resolution. In particular, T1-weighted, T2-weighted, and short tau inversion recovery (STIR) MRI sequences have been commonly employed for detecting spinal metastases [2]. T1-weighted spin-echo sequences are successful in detecting spinal metastases as hypointense lesions compared to healthy bone marrow and vertebral discs [3]. T1-weighted post-contrast sequences can further improve tumor detection because spinal metastases often show increased enhancement after contrast injection [4]. T2-weighted spin-echo sequences can also detect spinal metastases because of their high water content, and they often present with a ring of bright T2 enhancement, often referred to as a halo sign [5]. Finally, STIR MRI is able to suppress the signal from fat through a 180° inversion pulse, and it sums the contrast effects of T1 and T2 to improve tumor detection [6].

However, these traditional MRI methods also have their limitations in the management of spinal metastases. For example, there is a risk of false-negative results if a lesion is too small or early in its progression to cause a significant alteration in local cell composition, which may yield no observable difference in MR signal

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intensities on the resulting image [2, 7]. The surrounding location of the lesion itself may also pose challenges in its diagnosis. Some metastatic tumors exhibit similar T1 and T2 signal intensities as healthy hematopoietic bone marrow, which is found abundantly in the axial skeleton among young patients. These methods also have a risk of false-positive results in diagnostically challenging spinal lesions. Lesions involving infarction, edema, fibrosis, infection, or compression fractures as well as vertebral hemangiomas, the most common type of benign spinal tumors, have been known to resemble malignancies on conventional imaging [7, 8]. Another drawback of these methods is their difficulty in assessing the treatment response of spinal metastases. Tumor progression is defined as an increase in the size of the lesion, but with traditional MRI, evaluation of positive treatment response is limited to simply observing stability of the lesion size after treatment [9–11].

Dynamic Contrast-Enhanced Magnetic Resonance Imaging

Background

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is an emerging imaging method for spinal tumors [12]. DCE-MRI can provide a direct, quantitative measurement of the tumor microvasculature, making this technique very valuable for assessing spinal metastases.

Despite their varying histology, spinal metastases are well-known to secrete proangiogenic growth factors upon their localization in the spine [13]. The resulting aberrant neoangiogenesis leads to the development of highly fragile and permeable blood vessels in the tumor microenvironment, which can be characterized by DCE-MRI. This T1-weighted perfusion MRI technique noninvasively assesses the vascular microenvironment and the hemodynamic information of the tumor through quantitative parameters such as plasma volume (V_p), which is related to the number of blood vessels in the tumor, and the permeability constant (K^{trans}), which is a measure of vasculature leakiness [12] in addition to semi-quantitative parameters including area under the curve of contrast uptake. DCE-MRI is already established as an imaging method for brain tumors [14, 15] and has been recently used for diagnostic imaging and treatment monitoring in patients with spinal metastasis.

Imaging Protocol

Gd-DTPA Contrast Agent

The DCE-MRI perfusion measurements are obtained using the injected contrast agent Gd-DTPA (gadolinium diethylenetriaminepentaacetic acid), which provides higher physiological and tissue contrast compared to endogenous contrast techniques such as arterial spin labeling (ASL). Gd- DTPA has already been utilized in other imaging modalities for assessing tumors, for increased blood vessel permeability in tumors can be detected by 2D static imaging of contrast agent accumulation in a time window following administration. For example, T1-weighted post-contrast sequences have shown increased enhancement of lesions after the injection of Gd-DTPA compared to images taken prior to injection [4]. Another technique is dynamic susceptibility contrast perfusion MRI (DSC MRI), which has been used in the brain to assess tumor diagnosis and progression by measuring the relative cerebral blood volume (rCBV) between tumors and healthy tissue [16, 17]. However, limitations of this technique include that the perfusion measurements are context-variant, the images have poor spatial resolution, and the analysis is relative and user-dependent.

Pharmacokinetic Two-Compartment Model

During DCE-MRI, the patient is injected with Gd-DTPA and scanned periodically for several minutes before, during, and after the contrast agent accumulates in the microenvironment of the region of interest (ROI). Analysis of dynamic data can be used to study tissue

perfusion and vascular permeability. Voxel-wise tracer kinetic analysis is accomplished by applying a pharmacokinetic two-compartment model by Tofts et al. where the two compartments are (1) the intravascular space (blood plasma) and (2) the extracellular extravascular space (EES) [18].

Pharmacokinetic modeling of contrast agent uptake is applied to the measured signal intensity changes (ΔSI) over time, allowing for the quantitative estimation of vascular characteristics (Fig. 38.1): V_p estimates tumor vascularity through the blood vessel compartment, and K^{trans} estimates vessel permeability through the volume transfer constant per minute from the blood vessel to the EES.

Quantitative analysis includes detection of the arterial input function (AIF) from the aorta within the imaging volume. Appropriate shape of the AIF curve is usually confirmed based on pixels with a large change in signal intensity, with a rapid change immediately after bolus injection, and with an early peak in intensity. Further semi-quantitative analysis can be conducted by placing ROIs and analyzing the averaged time-intensity curves (TIC) of the changing MR signal intensity during contrast accumulation.

Three measurements from these TICs include (1) area under curve (AUC), (2) wash-in enhancement slope ($[signal_{max} - signal_{base}]/time_{rise}$), and (3) peak enhancement signal percentage change ($[signal_{max} - signal_{base}]/signal_{base} \times 100\%$) [19, 20]. Chen et al. have also established a qualitative classification of five general types of TIC morphologies: (1) Type A (nearly flat), (2) Type B (slowly rising contrast enhancement), (3) Type C (rapid wash-in followed by a plateau), (4) Type D (rapid wash-in followed by a wash-out), and (5) Type E (rapid wash-in followed by a second slowly rising contrast enhancement) [20].

MR Acquisition

The 3D T1-weighted spoiled gradient recalled echo (SPGR) sequence is the most widely used method for DCE-MRI data acquisition. 3D acquisition can be used to improve the image resolution and coverage. Post-contrast images are acquired every 4–5 s to provide sufficient data to model the contrast concentration-time-intensity curve. Low flip angles between 15 and 25° can be used to improve the measurement of signal change due to contrast injection. Short repetition time and short echo time should also be used to improve the scan time and to remove the T2∗ effect of contrast, respectively. Recently, a new 3D volume acquisition, called Differential Subsampling with Cartesian Ordering (DISCO), has been demonstrated with an effective temporal resolution of 3–4 s while preserving spatial resolution [21].

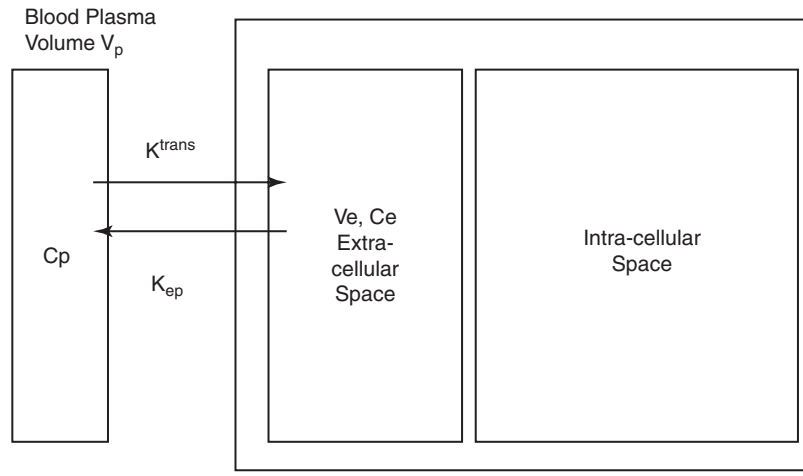

Fig. 38.1 A schematic illustration showing the pharmacokinetic two-compartment model. The tissue is presented as two compartments: the vascular plasma space and the extracellular extravascular space. C_p concentration of contrast agent in plasma space, V_e extracellular volume, V_p plasma volume, K^{trans} and K_{ep} volume transfer constants between V_p and EES

Diagnostic Imaging Using DCE-MRI

Determining Healthy Bone Marrow and Tumor Vascularity

Several DCE-MRI studies have shown highly promising results for the diagnosis of spinal metastases with this method. Khadem et al. retrospectively analyzed 26 patients with spinal metastases using DCE-MRI and conventional MRI, and DCE-MRI was able to differentiate spinal metastases from normal bone marrow through general TIC morphologies alone [19]. While healthy controls exhibited little to no contrast enhancement (Type A TIC [20]), spinal metastases exhibited contrast enhancement above the baseline [19].

DCE-MRI can also differentiate new spinal metastases from previously treated metastases despite their similar appearance on conventional MRI (Fig. 38.2a). New metastases are easily visualized on DCE-MRI through enhancement on phase-derived and V_p heat maps (Fig. 38.2b, c), and previously treated metastases exhibit flat TIC morphologies like normal bone marrow (Type A TIC [20], Fig. 38.2d).

Moreover, DCE-MRI can differentiate between hypervascular and hypovascular metastases, while conventional MRI cannot. Khadem et al. found that conventional MR signal intensity percentage changes between pre- and post-Gd-DTPA injection for T1-weighted images were not significantly different between hypervascular and hypovascular spinal metastases. Nevertheless, DCE-MRI was able to semiquantitatively distinguish these two groups, for hypervascular metastases were found to have higher average wash-in enhancement slope ($p < 0.01$) and higher average peak enhancement signal percentage change ($p < 0.01$) compared to hypovascular metastases.

A follow-up study by Saha et al. analyzed 20 patients with hypervascular renal spinal metastases and 20 patients with hypovascular prostate spinal metastases, and DCE-MRI was able to also quantitatively distinguish these two groups. Hypervascular metastases had higher V_p ($p < 0.001$) and K^{trans} values ($p < 0.01$) compared to hypovascular metastases, which was in line with the expected higher degree of neoangiogenesis in hypervascular metastases. V_p was also considered the best discriminator between the two groups, with hypervascular lesions having values 1.8× higher than hypovascular lesions. V_p was followed by peak enhancement signal percentage change as the second-best discriminator, which was 1.64× higher in hypervascular lesions than in hypovascular lesions [22]. Finally, DCE-MRI has been deemed as an effective, noninvasive surrogate to catheter spinal angiography, the current "gold standard" for assessing tumor vascularity despite its invasiveness and high cost [23]. This has implications for surgery because DCE-MRI can noninvasively determine hypervascularity so that catheter spinal angiography need only be employed for preoperative tumor embolization to reduce intraoperative blood loss [22]. DCE-MRI can assess biomarkers for antiangiogenetic treatment.

Malignant and Benign Vertebral Compression Fractures

Vertebral compression fractures are a common and growing concern in our aging patient population. In elderly patients, compression fractures are usually benign as a result of osteoporosis [24]. However, elderly cancer patients are prone to developing malignant compression fractures as a result of osteolytic spinal metastases that can decrease bone density and structural integrity. Common treatment regimens such as chemotherapy, radiation therapy, hormone therapy, and steroids can also affect bone density and lead to compression fractures [25]. Diagnosis is further complicated by malignant and benign fractures having similar appearances in conventional MRI [26].

DCE-MRI can differentiate between these two types of fractures through multiple perfusion metrics. Arevalo-Perez et al. found that malignant fractures had higher V_p, K^{trans}, wash-in slope, peak enhancement, and AUC compared to benign fractures ($p < 0.01$) [27]. DCE-MRI also had sensitivity within benign fractures to distinguish between acute (edema present) and chronic fractures (no edema present), with acute fractures having higher values of the aforementioned.

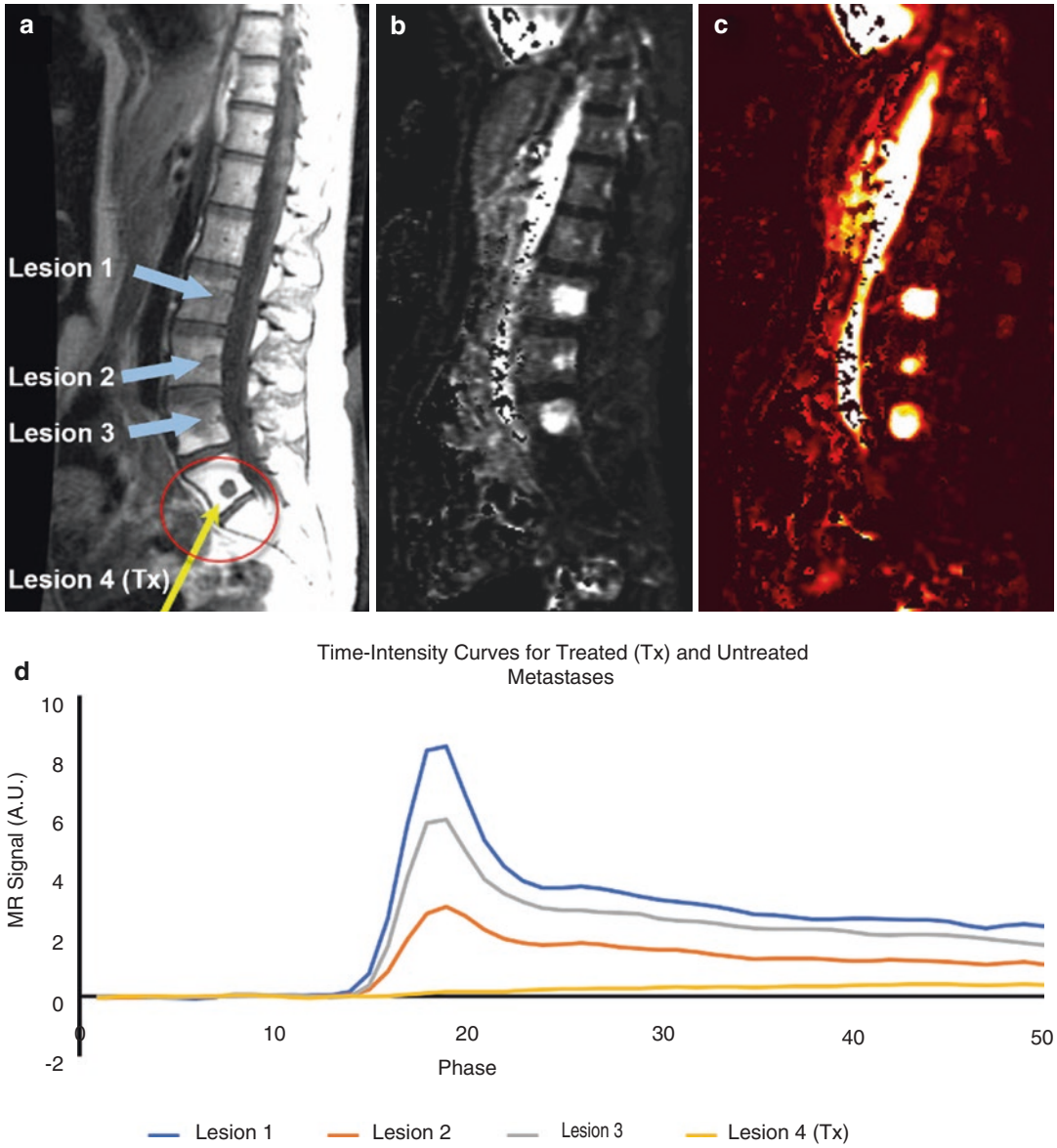

Fig. 38.2 Evaluating untreated (lesions 1–3) and treated (lesion 4) metastases using DCE-MRI. Conventional MRI shows little difference between the two lesion types (**a**). On DCE-MRI, untreated metastases appear hyperintense on the phase-derived (**b**) and V_p (**c**) heat maps and exhibit a rapid wash-in followed by a wash-out Type D TIC (**d**). (Tx = treated; A.U. = arbitrary unit)

Atypical Hemangiomas

Atypical hemangiomas are common benign tumors that often resemble spinal metastases and other malignant lesions in conventional MRI due to their high vascularity and low-fat composition [8]. DCE-MRI can quantitatively differentiate spinal metastases from atypical vertebral hemangiomas. Morales et al. found that spinal metastases had higher V_p values ($p < 0.01$) and higher K^{trans} values ($p < 0.01$) than atypical

vertebral hemangiomas. From a qualitative analysis of the TICs, spinal metastases also had higher signal intensities and a curve morphology of rapid wash-in followed by a wash-out (Type D TIC [20]), while atypical vertebral hemangiomas generally had a curve morphology of slow wash-in followed by a plateau (closest to Type C TIC [20]). Interestingly, four cases of atypical hemangiomas presented Type D TIC morphologies similar to spinal metastases, underscoring their challenging diagnosis [28].

Monitoring Radiation Therapy Treatment Response Using DCE-MRI

Radiation Therapy for Spinal Metastases

DCE-MRI also has the valuable capability to quantitatively monitor radiation therapy treatment response in spinal metastases (Fig. 38.3). As seen earlier in this chapter, spinal metastases are known for their high perfusion metrics, particularly in V_p. However, radiation therapy induces changes in the tumor microvasculature that reduce blood flow through fibrosis, thrombosis, and apoptosis [29]. DCE-MRI can detect these changes through decreased V_p values in less than 1 hour after high-dose image-guided radiation therapy, and Lis et al. reported an average drop of 65.2% ($p < 0.05$) compared to pretreatment with no significant change in this value to the first clinical follow-up [30]. Decreased V_p after radiation therapy has also been found to be the best predictor of positive treatment response within only 6 months of treatment, which is about half the time needed to establish stable tumor size in conventional MRI [31]. Moreover, qualitative TIC analysis of successfully treated tumors has shown a rapid wash-in followed by a second slowly rising contrast enhancement (Type E TIC [20]), while unsuccessfully treated tumors retained their rapid wash-in followed by wash-out (Type D TIC [20]) morphology [31]. DCE-MRI can also indicate local recurrence of spinal metastases through an increase in V_p and K^{trans} values about 6 months earlier than conventional MRI [32].

Application in Chordomas

Chordoma is a rare type of spinal tumor, accounting for only 1–4% of bone cancers. However, they are known for being very aggressive tumors that are also prone to recurrence. Moreover, they are diagnostically challenging using conventional imaging and predominately clinically silent before exhibiting rapid progression and becoming highly resistant to treatment [33]. Assessing treatment efficacy remains difficult as well because chordomas generally do not change in appearance in conventional imaging during positive response to therapy.

DCE-MRI has demonstrated potential clinical utility in the treatment of chordomas. This method has been successful in differentiating chordoma from giant cell tumors [34], and their TICs exhibit a distinct rapid wash-in followed by a second slowly rising contrast enhancement morphology [35] (Type E TIC [20]). Also, decreased V_p, K^{trans}, and MR signal intensities have been found to be more sensitive than conventional imaging in determining positive treatment response after radiation therapy [35].

Limitations of DCE-MRI

DCE-MRI also has several limitations. Application of the pharmacokinetic two-compartment model requires accurate measurement of the AIF. However, the low temporal resolution of DCE- MRI because of its high spatial resolution, field-of-view, and signal-to-noise ratio may be insufficient in reliably capturing the AIF. As a result, insufficient sampling of the AIF can affect its time course and cause saturation effects during initial wash-in of the contrast agent [30].

Quantitative analysis using the pharmacokinetic model also relies on a set of model assumptions, which may not uphold for all tumor or tissue types [22]. Also, the physiological basis of semiquantitative parameters such as peak enhancement and AUC as well as of the mechanisms that lead to perfusion differences before and after radiation therapy remains unknown [22, 30].

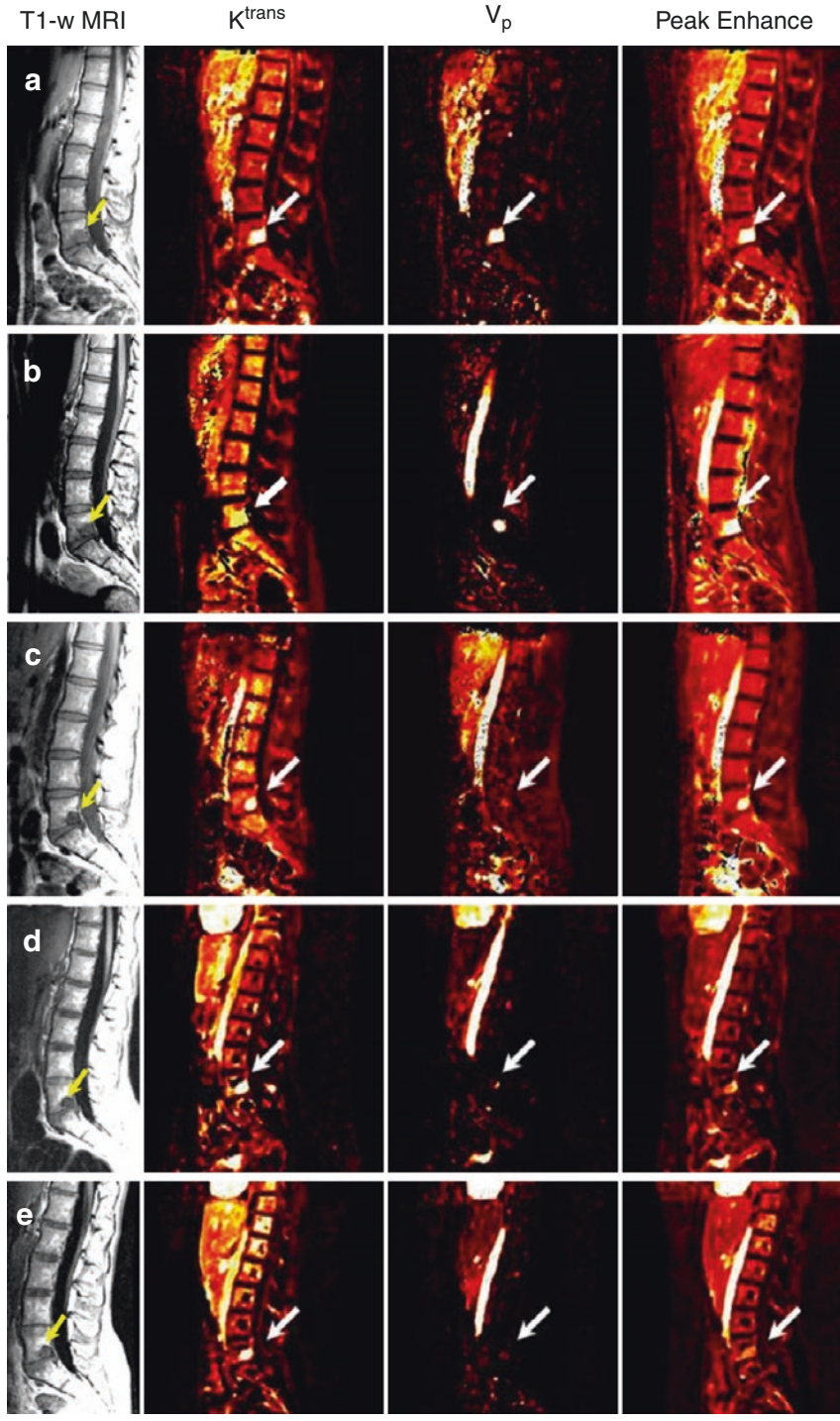

Fig. 38.3 Monitoring treatment response at baseline (**a**), 3 weeks (**b**), 13 weeks (**c**), 15 weeks (**d**), and 16 weeks (**e**) using conventional MRI (first column to the left) and DCE-MRI (second–fourth columns to the left) of successfully treated metastasis. The arrows indicate the lesion on each of the MRI scans. The lesion appears stable in conventional MRI, but there are dramatic changes seen on the perfusion maps, particularly in the decreased plasma volume (V_p) indicating positive treatment response. (T1-w = T1-weighted; V_p = plasma volume)

Unlike T2∗-based DSC perfusion which is acquired within a minute range, DCE-MRI requires a certain amount of scanning time to allow sampling the wash-out phase which is used to estimate the Ve parameter. Despite its limitations, DCE-MRI has already demonstrated great potential in the management of spinal metastases given its recent advent as described above. Future studies involving larger sample populations and more different types of pathologies can provide further insights into the clinical applications of this emerging and promising method.

Diffusion-Weighted Imaging

Background

Diffusion-weighted imaging (DWI) has commonly been used for imaging stroke patients, but it is now finding a new role in assessing tumors as well. DWI is an advanced method of MRI that is sensitive to free water diffusion, or the random Brownian motion of water molecules. Within tissue microstructure, diffusion can be impacted by hindered diffusion and restricted diffusion. In hindered diffusion, water molecules are impeded extracellularly by cells and other obstacles in the extracellular matrix. In restricted diffusion, water molecules are impeded intracellularly by cellular compartments such as the cell membrane [36].

Tumors are known for their high cellularity, which results in increased restricted diffusion. This behavior can be detected in DWI from the original DWI image, but it is more commonly assessed by converting the image into its apparent diffusion coefficient (ADC) map, which is a quantitative measure related to the amount of diffusion in a voxel. ADC is negatively correlated with cellularity [37], so tumors exhibit decreased ADC values and appear hypointense on ADC maps.

Imaging Protocol

MR Acquisition

DWI scans are typically acquired using a T2-weighted single-shot echo-planar imaging protocol with an additional application of diffusion-sensitive gradients at multiple "b-values". The b-value determines the strength of the diffusion-weighting, with higher b-values having greater sensitivity to diffusion properties but lower b-values having higher SNR [38]. Scan times are relatively quick in DWI, and this method does not utilize an intravenous contrast agent as in perfusion MRI, making this technique safe for pregnant patients and those with allergies or poor renal function.

Diagnostic Imaging Using DWI

Quantitative assessment of DWI using ADC is a reliable method for diagnosing spinal lesions. A meta-analysis conducted by Suh et al. has found that ADC can differentiate between benign and malignant vertebral bone marrow lesions with 89% sensitivity and 87% specificity as well as differentiate between benign and malignant compression fractures with 92% sensitivity and 91% specificity [39]. Multiple studies have shown that spinal metastases have lower ADC values than healthy bone marrow and that malignant neoplastic compression fractures have lower ADC values than benign osteoporotic compression fractures [40–42]. Similarly, spinal metastases were also found to have lower ADC values than both typical and atypical vertebral hemangiomas [43]. However, Pozzi et al. showed that DWI is unsuccessful in differentiating between spinal metastases and malignant primary spinal tumors [41].

Monitoring Treatment Response Using DWI

DWI has been successful in determining positive treatment response for spinal metastases. Radiation therapy causes necrosis of tumor cells, which decreases tumor cellularity and increases extracellular volume fractions that can lead to more free water diffusion [44]. This has been used to explain how ADC values increased in successfully treated spinal metastases and continued to decrease in unsuccessfully treated cases as early as 1 month after radiation therapy [44, 45], despite no significant changes in signal intensities being observed in conventional MRI [45].

DWI has also shown promise in assessing positive treatment response for androgen withdrawal therapy, where Resichauer et al. found significantly higher ADC values in successfully treated metastases in the pelvis at 1, 2, and 3 months posttreatment [46].

Limitations of DWI

Despite its clinical utility, DWI has several limitations. For example, determining a strict cutoff ADC value for different diagnoses is not practical because ADC values are dependent on the field strength of the MRI scanner and the b-value of the diffusion-sensitive gradients [47].

DWI is not suitable for assessing sclerotic lesions because of their low water content, which can lead to false-negative results [48, 49]. It has also been suggested that infections, blood products, and abscess formations can lead to false-positive results due to their decreased ADC values [50]. Castillo et al. also found that DWI did not offer any advantage over conventional non-contrast T1-weighted MRI in detecting spinal metastases, likely due to the T2 shine-through effect in DWI [51]. Treatment can lead to heterogenous ADC increases and decreases in tumors that can significantly impact mean ADC analysis for assessing treatment response as well [52].

Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) is another diffusion MRI technique that can evaluate the integrity of white matter tracts and provide more sensitive information about spinal cord alterations, such as those originating from inflammation, trauma, neurodegenerative diseases, and intramedullary tumors [53]. Diffusion tensor imaging utilizes a single-shot echo-planar imaging sequence, and it has been widely used to investigate the brain.

There has been a recent implementation of DTI for the management of spinal tumors. For example, DTI can be used for pre-surgical planning to delineate tumor boundaries for spinal cord surgery [54]. DTI can also assess the integrity of the spinal cord after radiation therapy, such as evaluating for radiation-induced myelopathy [55]. This has led to DTI being employed to monitor the spinal cord during radiation therapy for spinal metastases.

However, its use for spinal cord imaging is still challenging due to its low spatial resolution and the small size of the spinal cord, which results in low SNR. Moreover, this technique is sensitive to susceptibility and flow artifacts in the spine that can lead to distortion [54]. Recently, a new DTI method using a restricted small field-of-view (FOV) is recognized as a promising way to acquire images of regions' thin structures like the spinal cord [56]. It consists of reducing the FOV in the phase- or frequency-encoding direction to shorten the echo-planar readout train and to attenuate susceptibility- and motion-related artifacts.

Dual-Energy Computed Tomography

Continual improvement in computed tomography (CT) technology has allowed for high-quality imaging of the spine. CT offers exquisite detail of the bony cortex and can provide answers to most clinical questions, especially for evaluating fractures. It is also ideal for evaluating the integrity of spinal hardware. The use of intrathecal contrast as in CT myelography can further increase its utility as it improves visualization of the spinal cord and the subarachnoid space. It is also routinely used at many tertiary institutions as the modality of choice for radiation treatment planning and simulation as it provides very high spatial resolution [57].

One of the more recent innovations in CT technology is dual-energy CT (DECT). DECT is essentially simultaneous imaging at two different energies. DECT takes advantage of that fact that substances exhibit varying imaging characteristics at different X-ray energies. That information can then be used to extract various information about tissue composition such as differentiating between soft tissue and vertebra, cystic lesions,

and crystals. It can also be used to provide virtual unenhanced and perfusion images. With regard to spinal imaging, DECT can be used to decrease artifact in patients with metallic hardware which in turn allows for better visualization of structures near the hardware like grafts and more importantly the spinal canal [58].

Conclusion

Conventional imaging techniques have been valuable for the management of spinal metastases, but their imaging limitations have posed difficulties in diagnosis and treatment monitoring. The development of advanced imaging techniques, particularly in dynamic perfusion MRI, diffusion MRI, and dual-energy CT, offers promising solutions for imaging spinal metastases. Increased development and clinical implementation of these techniques will be important to further improve clinical care for spinal metastases patients.

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39 Decision-Making Algorithms for Surgical Treatment of Spine Metastatic Disease

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History of Treating Spinal Epidural Disease

In the 1980s, epidural spinal cord compression (ESCC) treatment consisted of a combination of corticosteroids and radiotherapy [1] after a study showed that performing a laminectomy alone or in combination with radiation resulted in no benefit and possible harm when compared to radiation alone. With the advancement of surgical instrumentation techniques, a wide circumferential decompression and posterior instrumentation with or without an anterior column reconstruction became the optimal treatment for patients with ESCC. This modality of treatment was validated by Patchell et al. in 1990 who performed a randomized, multi-institutional, non-blinded trial, in which patients with spinal cord compression caused by metastatic cancer were randomly assigned to either wide surgical decompression and appropriate reconstruction followed by radiotherapy ($n = 50$) or radiotherapy alone ($n = 51$) [2]. This study showed that patients in the surgical group were able to walk after treatment (84% vs. 57%, odds ratio 6.2, $p = 0.001$), retained the ability to walk longer (median 122 days vs. 13 days, $p = 0.003$), regained the ability to walk if they were unable to do so at the time of randomization (62% vs. 19%, $p = 0.01$), and had longer survival times (median 126 days vs. 100 days, $p = 0.033$), when compared to the radiation alone group.

Framework for Surgical Decision-Making

NOMS (Neurologic, Oncologic, Mechanical, Systemic) Criteria

Assessing the patient's symptoms, tumor burden, life expectancy, the degree of neural element compression, and comorbidities is essential for offering surgery to patients with epidural spinal cord or cauda equina compression. The goal of any surgical intervention for patients with spine metastases is palliative with the intent to preserve or restore neurologic function, improve pain, treat mechanical instability, improve quality of life, and provide durable tumor control. The NOMS criteria, as seen in Table 39.1, is a decision framework that selects those patients most likely to benefit from surgical decompression and instrumentation [3, 4].

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Table 39.1 NOMS decision framework

Neurologic	Oncologic	Mechanical	Systemic	Decision
Low-grade epidural spinal cord compression with no myelopathy	Radiosensitive Radiosensitive Radioresistant Radioresistant	Stable Unstable Stable Unstable		Conventional external beam radiation (cERT) Stabilization followed by cERT Stereotactic radiosurgery (SRS) Stabilization followed by SRS
High-grade epidural spinal cord compression with or without myelopathy	Radiosensitive Radiosensitive Radioresistant Radioresistant Radioresistant Radioresistant	Stable Unstable Stable Stable Unstable Unstable	Able to tolerate surgery Unable to tolerate surgery Able to tolerate surgery Unable to tolerate surgery	

Data from Laufer et al. [4]

Neurologic Status

The neurologic assessment of a patient with spinal metastases with or without CEC or ESCC involves the assessment of myelopathy, mechanical pain, weakness, and radiculopathy on a neurologic exam or patient history. Additionally, the neurologic assessment involves the evaluation of the radiographic degree of ESCC or CEC.

Pain

Pain is typically the presenting symptom in virtually all patients (90–95%) with metastasis to their spine [5, 6]. Given the prevalence of pain as the presenting symptom, it is important to differentiate the quality, form, and distribution of the pain the patient is experiencing. Though many patients complain of local back pain, particular types of back pain are indicative of compression of the neural elements.

Mechanical pain is one classification of pain, which is characterized by pain that is exacerbated by axial loading such as standing from a seated or laying down position or lightly pressing on the top of the patients head during a physical examination. This mechanical pain is typically due to the destruction of the vertebral body or the posterior bony elements, which results in compression of exiting nerve roots in their neuroforamina with normal physiologic movement. Patients with mechanical pain are usually able to find particular positions that alleviate their pain, such as lying down if the spinal metastasis is in the lumbar spine or sleeping in an upright position if the spinal metastasis is in the thoracic spine. However, once these patients move into a particular position, they have an instant exacerbation of their pain. Mechanical pain is typically a sharp, shooting pain that follows the dermatomal distribution of the nerve root that is being compressed in the neuroforamina with movement.

The second classification of pain is referred pain, which occurs at a location that is distant from the metastasis and midline point tenderness on palpation. Both referred pain and point tenderness on palpation do not radiate and are indications of subclinical spinal instability. Referred pain to the sacroiliac joints and iliac crest can occur with upper lumbar metastatic lesions. Referred pain can also occur in the interscapular region from a cervical metastatic lesion.

The third classification of pain is biologic pain, which is caused by invasion and irritation of the periosteum and its innervation by the metastatic disease. Biologic pain is often worsened while lying supine, possibly due to increased flow through vertebral veins, and during the early morning, due to cortisol levels being at their lowest. However, this pain typically improves over the course of the day as cortisol levels and its corresponding anti-inflammatory effect rise.

Motor Weakness and Myelopathy

Motor weakness and/or myelopathy are clinical manifestations of neural element compression, which may require surgical decompression for treatment. Aside from highly radiosensitive tumors that have a robust response to radiation therapy, patients with motor weakness and/or

myelopathy require an expedited surgical decompression to ensure the preservation of function [2].

Epidural compression in the lumbar spine or the cauda equina results in lower motor neuron symptoms. If the compression is severe, the patient will have a cauda equina syndrome, which is characterized by low back pain with radiation into the perineum and legs, saddle anesthesia, hyporeflexia, legs weakness, and bladder/bowel dysfunction, which is typically a late finding unless the lesion is at the conus medullaris.

Epidural compression in cervical or thoracic spine results in upper motor neuron symptoms and myelopathy. Upper motor neuron symptoms include neck pain with radiation into the arms and hands, loss of hand dexterity characterized by an inability to button shirts or write, difficulty walking/wide-based gait, hyperreflexia, and progressive arm/hand weakness. Additionally, if there is focal compression of exiting nerve roots in the cervical or lumbar spine, these patients can have specific weakness of the muscle group innervated by that nerve root.

Numbness/Tingling

Numbness/tingling as a manifestation of neuropathy and nerve root irritation along a dermatomal distribution are typically well tolerated by the patient. However, the presence of this clinical finding is an indicator that particular nerve roots are being compressed or irritated by the spinal metastasis. Therefore, though numbness/tingling in isolation is not an absolute indication for spinal decompression for the preservation of function, it may indicate impending spinal instability or worsening function should the offending metastasis not be treated promptly.

Imaging

In patients who have new-onset or progressive back or neck pain with a cancer history, a contrast-enhanced MRI scan must be obtained for a full clinical assessment and to guide further management. The contrast-enhanced MRI is the gold standard for detecting and evaluating metastatic epidural compression, with a sensitivity of 98.5% and a specificity of 98.9% in detecting lesions. The amount of compression may also influence if surgical intervention is required. The Bilsky epidural disease grading system is a grading scale that is helpful in delineating high-grade ESCC, which may require surgical decompression versus low-grade ESCC, which may require simply radiotherapy for disease control [7]. The grading system assigns a grade 0 for no epidural disease present; grade 1a for epidural disease impinging on the thecal sac but no deformation; grade 1b for epidural disease deforming the thecal sac but not contacting the spinal cord; grade 1c for epidural disease deforming the thecal sac and contacting the spinal cord; grade 2 for epidural disease with spinal cord compression with CSF visible; and grade 3 for epidural disease with spinal cord compression with no visible CSF. High-grade ESCC is used to describe compression that is a grade 2 or 3, as this amount of cord compression typically requires surgical intervention for adequate and expeditious decompression of the spinal cord.

In addition to an MRI, a computed tomographic (CT) scan is helpful to obtain for assessing bony destruction in cases where instability is suspected. A CT scan can also guide the extent of instrumentation needed to stabilize a patient, as some tumors are lytic while others are sclerotic, though in both cases bone will be suboptimal. Lastly, in cases for which an MRI is contraindicated or previous hardware will complicate imaging assessment, a CT myelography can be used to image any spinal cord compression.

Oncologic Assessment

This subcategory of the NOMS criteria assesses the likelihood of local tumor control with radiation and chemotherapy alone versus surgical decompression followed by radiation and chemotherapy. Tumors such as lymphoma, multiple myeloma, and plasmacytoma are highly radiosensitive, and bulky metastasis is effectively controlled or eliminated by chemotherapy without the need for surgical decompression.

However, tumors that are classically radioresistant, such as renal cell carcinoma, non-small cell lung carcinoma (NSCLC), thyroid, melanoma, and hepatocellular carcinoma, require higher radiation doses to treat these tumors effectively [8, 9]. A common radiation dose used for conventional external beam radiation is 30 Gy in 10 fractions [8–10]. With conventional radiation, the spinal cord is within the radiation field; thus, the dose of radiation is limited due to potential toxicity and radiation injury [11]. Recently, stereotactic radiosurgery, which is defined as >10 Gy per fraction in typically <5 fractions [12–20], can be used to effectively treat radioresistant tumors after surgery to circumferentially decompress the thecal sac and allow for contouring around the spinal cord.

For patients who do not have an established cancer diagnosis and do not have an acute neurologic compromise, a percutaneous biopsy may be warranted to assess if the offending tumor is radiosensitive. Nevertheless, patients with radiosensitive tumors may require decompression and stabilization, if they demonstrate mechanical stability (to be discussed below). Of note, although the Patchell study was overwhelmingly positive in favor of the surgical group, it excluded patients with radiosensitive tumors (e.g., lymphoma and multiple myeloma), multiple (noncontiguous) areas of spinal cord compression, or total paraplegia for longer than 48 hours [2]. Additionally, it excluded patients with <3 months of expected survival time due to tumor burden. Thus, a comprehensive framework for assessing patients with these attributes is needed to decide which patients benefit from surgical decompression and instrumentation.

Mechanical

The mechanical assessment of spinal instability due to tumor invasion and resulting pathologic fractures are the strongest indicator for surgical intervention. Spinal instability due to a neoplastic process differs from traumatic injuries in the pattern of bony and soft tissue involvement, as well as in bone quality. A tool used to classify spinal instability specifically in the oncology population is the Spine Instability Neoplastic Score (SINS) created by the Spine Oncology Study Group (SOSG). SOSG, an international group of 30 spinal oncologists, defines spine instability as "a loss of spinal integrity as a result of a neoplastic process that is associated with movement-related pain, symptomatic or progressive deformity, and/or neural compromise under physiological loads" [21, 22]. The SINS score, as seen in Table 39.2, is composed of six subcategories, including mechanical pain, spinal alignment, spine location, bone lesion quality, spinal alignment, and posterolateral involvement of spinal elements. After each subcategory is scored, the total summation is used to guide surgeons to instrument patients with higher scores, who likely have spinal instability. The SINS ranges are as follows: total scores of

Table 39.2 Spinal Instability Neoplastic Score (SINS)

Score		
Location	Junctional Mobile Spine Semirigid Rigid	3 2 1 0
Pain	Yes Occasional pain but not mechanical Pain-free lesion	3 1 0
Bone lesion	Lytic Mixed (lytic/blastic) Blastic	2 1 0
Radiographic spinal alignment	Subluxation/ translation present De novo deformity (kyphosis/scoliosis) Normal alignment	4 2 0
Vertebral body collapse	> 50% collapse < 50% collapse No collapse with >50% body involved None of the above	3 2 1 0
Posterolateral involvement of spinal elements	Bilateral Unilateral None of the above	3 1 0
Total score	Stable Indeterminate Unstable	0–6 7–12 13–18

Data from Fisher et al. [22]

0–6 indicate spinal "stability," scores of 7–12 indicate "indeterminate (possibly impending) instability," and scores of 13–18 indicate spinal "instability." Thus, the authors recommend instrumentation of patients who have a SINS >13 but allow the treating surgeon discretion on instrumenting patients with SINS between 7 and 12 [21, 22].

Though SINS is a relatively granular tool for grading spinal instability and the need for surgical stabilization, typically the strongest motivator to decompress and instrument a patient is a drastic increase in their pain and decrease in their functional status. The primary role for surgery in patients with metastatic disease is palliative with a goal to prevent the patient from becoming increasingly immobile and unable to complete activities of daily living if their pain or neurologic compromise is not adequately treated. Immobility results in increased risk of deep venous thrombosis/pulmonary embolisms, atelectasis resulting in pneumonia, muscle atrophy, and emotional distress. All of these factors ultimately reduce the patient's likelihood of survival. Thus, our group weighs the patients' change in functional status as the strongest relative indicator for surgical decompression and instrumentation.

Systemic

The systemic assessment involves the evaluation of the patient's burden of disease and the overall patient's survival. It allows the surgeon and oncology team to assess the patient as a whole, considering the patient's medical comorbidities, the number of systemic tumor metastases, and their baseline functional status [12, 23, 24]. These factors indicate the ability of a patient to tolerate a proposed procedure, inform the risk-benefit ratio of treatment, and characterize the likelihood of survival outside of the perioperative period. A high likelihood of death within the perioperative period and high systemic metastatic disease burden are relative contraindications for surgical intervention.

Conclusion

There has been a significant advancement in radiation therapy and chemotherapy in the treatment of metastatic disease; however, surgery has evolved as a major treatment option for patients with spinal metastases. Surgical decompression is particularly useful in treating patients with high-grade ESCC and CEC, and instrumentation is useful for treating spinal instability. The use of NOMS framework provides a treatment algorithm that facilitates coordination between a multidisciplinary team to offer safe, reliable, and reproducible treatment for patients with metastatic spinal disease.

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Part VI

Surgical Treatment of Spinal Metastases

Biomechanics of Spinal Fixation in Metastatic Disease

40

Allen L. Ho and Atman M. Desai

Introduction

Spinal bony metastases are the most common neoplasms encountered in the spine. They have a slight male predominance, peak between the ages 40 and 60, and occur most frequently in the thoracolumbar spine. Typical clinical presentation includes a combination of symptoms arising from mechanical pain, radiculopathy, instability, and neurologic deficits. Treatment of spinal metastases is typically multimodal with options including surgery, radiation therapy, and systemic chemo- or immune-therapy.

When surgically treating spinal metastases, surgical goals typically include tissue diagnosis and reduction of oncological burden, decompression of neural elements, and restoration of spinal stability and spinal alignment. Mechanical instability of the spine secondary to metastatic disease can cause significant pain, neurological deficit, spinal deformity, and disability. Such instability can arise from the osteolytic nature of the metastatic lesions themselves – pathological fractures – or may be iatrogenic in origin as a result of tumor resection. Spinal fixation with instrumentation is necessary in both of these scenarios to treat or prevent the symptoms of spinal instability.

Complications following surgical resection and stabilization of spinal metastasis are significant, ranging from 10% to 52% [1–5]. However, a randomized controlled trial published by Patchell et al. in 2005 demonstrated the superiority of decompression with instrumented stabilization where patients had evidence of spinal instability, followed by external beam radiation therapy over external beam radiation therapy alone for symptomatic patients with spinal metastasis causing spinal cord compression. Patients undergoing surgery had significant improvements in ambulation, bowel and bladder function, and overall survival [6]. This has led to the wide adoption of surgical decompression and stabilization for symptomatic spinal metastasis. In parallel, over the past two decades, the development of stereotactic radiosurgery (SRS) has led to the newer paradigm of combined judicious use of surgical and radiosurgical approaches. This strategy, commonly referred to as "separation surgery," typically utilizes surgery for rapid treatment of epidural cord compression and spinal instability followed by SRS to contain the bulk of nonepidural metastatic disease. Similar outcomes of symptom improvement and tumor control can be achieved while minimizing surgical morbidity with this approach [7].

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Diagnosis and Decision-Making

Modern decision-making in the treatment of spinal metastasis needs to incorporate all possible treatment modalities and approaches. The most comprehensive framework for decision-making is the NOMS decision framework that consists of four fundamental components [8]:

- *N* – Neurologic: includes presence of myelopathy, functional radiculopathy, and the degree of epidural cord compression appreciated on imaging
- *O* – Oncologic: includes ability to achieve local, dural control and, thus, reflects the radio/chemosensitivity of tumor type
- *M* – Mechanical: assesses the degree of instability or the spine's ability to withstand physiologic loads without pain, deformity, or neurologic deficit
- *S* – Systemic" assesses both the degree of systemic tumor burden and systemic medical disease and comorbidities

The vertebral body is the most common location for seeding of spinal metastasis. As the primary axial-load bearing structure in the spine, bony replacement and destruction of the vertebral body by metastatic lesions lead to instability and compression fracture. The most important predictors of instability from vertebral body metastasis include the cross-sectional area of remaining tumor-free vertebral body, tumor size, and bone mineral density [9, 10]. Mechanical back pain is the most common presenting symptom for spinal instability related to metastatic disease. While biologic back pain related to periosteal stretching from the tumor itself is mainly nocturnal or early morning pain that improves throughout the day, patients with mechanical back pain have pain that worsens with movement and is localized to the level of involvement. The Spinal Instability Neoplastic Score (SINS) was devised to help surgeons as well as radiation and medical oncologists predict the degree of spinal instability based on six components: location, pain, bone lesion, radiographic spinal alignment, vertebral body collapse, and posterolateral element involvement. Tumor location in more mobile segments of the spine such as the cervical spine receives more points than those in stable segments such as the thoracic spine and sacrum. Mechanical pain receives more points than local biologic pain from periosteal stretching. Any subluxation, translation, or vertebral body collapse greater than 50% can lead to instability. Finally, evaluation of posterior element involvement, including bilateral pedicle, facet, or costovertebral joints, will receive more points. The score ranges from 0 to 18 points, with 0–6 classified as stable, 7–12 as potentially unstable, and 13–18 as unstable [11, 12] (Table 40.1).

Table 40.1 Spinal instability neoplastic score (SINS) scoring

Element of SINS		Score
Location		
	Junctional (occiput–C2, C7–T2, T11–L1, L5–S1)	3
	Mobile spine (C3–C6, L2–L4)	2
	Semirigid (T3–T10)	1
	Rigid (S2–S5)	0
Pain relief with recumbency and/or pain with movement/loading of the spine		
	Yes	3
	No (occasional pain but not mechanical)	1
	Pain-free lesion	0
Bone lesions		
	Lytic	2
	Mixed (lytic/blastic)	1
	Blastic	0
Radiographic spinal alignment		
	Subluxation/translation present	4
	De novo deformity (kyphosis/scoliosis)	2
	Normal alignment	0
Vertebral body collapse		
	>50% collapse	3
	<50% collapse	2
	No collapse with >50% of body involved	1
	None of the above	0
Posterolateral involvement of the spinal elements (facet, pedicle, or CV joint fracture or replacement with tumor)		
	Bilateral	3
	Unilateral	1
	None of the above	0

From Fisher et al. [91]. Reprinted with permission from Wolters Kluwer Health, Inc.

Biomechanics of Surgical Stabilization

In the past, decompressive laminectomy was the standard procedure to address neurologic compression from symptomatic spinal metastasis. However, this approach fails to address pathologic fractures and may paradoxically increase instability by removing posterior elements of the spinal column. Therefore, aggressive surgical decompression with spinal stabilization has become the main surgical approach [13, 14] and remains the most effective technique for reducing pain and improving quality of life (QOL) in patients with symptomatic spinal metastasis [15]. These lesions most commonly arise anterior to the spinal cord in the vertebral body and progress posteriorly to cause compression of the spinal cord and/or exiting nerve roots. These lesions are easily accessed via an anterior approach in the cervical spine. Anterior decompression followed by anterior fixation and supplemented with posterior instrumentation (with additional decompression if necessary) is generally the most common strategy for subaxial cervical lesions. Anterior approaches in the thoracic spine are more challenging, especially in the upper thoracic spine (T1–T4) due to the anatomic relationship to the sternum that may necessitate a sternotomy or thoracotomy [16]. Similarly, because of the anatomic location of the aortic arch and great vessels in relation to thoracic levels T5 through T10, a right-sided thoracotomy is recommended for anterolateral approaches to the spine unless the target lesion is exclusively on the left side of the spine [17, 18]. Because of the difficulty of pure anterior approaches, development of posterior-only approaches to the ventral thoracic spine (transpedicular, costotransversectomy, and lateral extracavitary) is increasingly utilized [19]. However, these posterior approaches often involve division of nerve roots and segmental vessels that can increase risk of ischemic injury to the spinal cord. Animal studies have shown that interruption of bilateral segmental arteries of four or more consecutive level risked ischemic spinal cord damage [20]. The remaining thoracolumbar junction is typically accessed via a posterior-only or combined 360-degree approach with a thoracotomy or retroperitoneal approach. Lumbar levels are access via retroperitoneal, transabdominal, or posterior transpedicular approaches. Finally, sacral lesions may require most complex posterior approaches or even anterior approaches through the pelvis.

Given the degree of vertebral body resection required for complete or meaningful resection of symptomatic and/or compressive spinal metastasis, many cervical and generally all thoracolumbar resections of spinal metastases will be inherently destabilizing and require careful consideration of reconstruction strategies. The large gap created by spondylectomies creates a challenge of arthrodesis, and a robust construct design is essential to withstand the mechanical stresses on the spinal column until arthrodesis can be achieved. Recreation and augmented support of all three columns of the spine is imperative [21]. Anterior column reconstruction is most commonly performed with utilization of carbon fiber or titanium expandable cages or polymethylmethacrylate (PMMA) [22–24]. Posterior spinal stabilization can help ensure posterolateral arthrodesis and is performed with standard screw and rod fixation [25, 26]. Most of these patients will need additional postoperative treatment with adjuvant radiation therapy and imaging surveillance for recurrence. Thus, careful implant selection to minimize interference with therapy and imaging artifact is also important.

Interbody Grafts

Although autograft bone remains the gold standard construct material for arthrodesis, most ventral constructs for reconstruction of vertebral body removed from metastatic lesion resection are now a combination of synthetic and allograft material [27]. Long-term solid bony fusion may not be necessary if life expectancy is less than 18 months, and autogenous donor sites may also have tumor involvement. Moreover, in patients with metastatic disease, bone autograft carries significant short-term donor-site morbidity [28]. Postoperative local irradiation and chemotherapy

can also interfere with bone remodeling and fusion [29, 30]. Local bone autograft can be plentiful, especially in posterior and posterolateral exposures of the spine that include significant bony decompression. Without incurring the morbidity of iliac crest harvest, local bone can be just as effective in achieving short-segment lumbar fusion [31, 32]. Cadaveric fibular allograft is preferred to autologous iliac crest since it avoids complications associated with iliac crest harvest. Additionally, it can be tailored to any length and provides a central packing channel for local autologous bone graft or other cancellous bone substitute to enhance fusion. However, it carries a higher modulus of elasticity which confers a significant risk for "pistoning" or subsidence. Though allograft fibula is slower to incorporate than autologous iliac crest [33], there has been no significant difference in pseudoarthrosis rates between the two identified [34, 35].

Interbody cages provide anterior column stabilization with synthetic materials such as stainless steel or titanium. Titanium alloys provide a high tensile strength while retaining a reasonable degree of malleability and biocompatibility. They also have less imaging artifact compared to stainless steel. Titanium mesh cages allow for easy selection for cage length and can be filled with autologous graft material. Although the modulus of elasticity is more rigid than vertebral bone with some risk of subsidence, clinically significant subsidence causing deformity or pseudoarthrosis is rare [36]. Expandable titanium cages allow for deployment of full cage lengths after placement in the vertebral body cavity. This allows for ease of placement with a smaller profile implant that is especially advantages in posterior and posterolateral approaches to the ventral spinal column where the working corridor is smaller than the resection cavity. Expansion of the ventral graft in situ allows for additional simple distraction fixation to resist axial loads and well as correct any cervical deformity be restoring natural lordosis [37].

Other synthetic materials, such as polyetheretherketone (PEEK) and carbon fiber cages, are also increasing utilized. PEEK is a semicrystalline polyaromatic polymer with similar elasticity to bone, which decreases its risk of subsidence in comparison to titanium. PEEK is also radiolucent and also has magnetic resonance imaging (MRI) compatibility without artifact. Both PEEK and carbon fiber improve visualization on postoperative imaging without artifact, and while PEEK has a more favorable modulus of elasticity compared to carbon fiber, carbon fiber is more osteoinductive and may allow for an increased degree of cellular integration that can help support fusion [38–40]. Finally, osteoconductive bone substitutes can be either mixed with a localized autograft bone or crushed cancellous allograft bone to form a packing material for interbody implants and as a substrate to facilitate dorsal bony fusion. Demineralized bone matrix (DBM) is the most common of these substitutes that supplies potent bone morphogenetic proteins (BMPs) to the fusion bed on a collagenous conductive substrate. High-dose recombinant human BMPs, primarily rhBMP-2, can be quite effective in promoting bony fusion but are contraindicated in tumor surgery given the oncogenic properties of these agents. The most common hardware complication encountered with graft placement is a result of dislodging at either the proximal or distal ends where the graft sits against adjacent spinal segments. Placing the graft under compression serves the dual purpose of stabilizing the graft in the interbody space and promoting fusion by ensuring a stable contact surface for bony ingrowth to occur [41].

Pedicle Screws

Pedicle screws apply force to the spine by fixed moment arm cantilever beam fixation. The pedicle screw represents the fixation point that supports the cantilever, either a rod or plate that rigidly buttresses the spine, thereby resisting axial loads. With fixed pedicle screw and rod/plate constructs, there is no load sharing with the anterior column, and the bulk of the stress is borne by the screw/rod or screw/plate junction which can lead to failure [42]. Dynamic, or non-fixed, pedicle screw fixation systems allow for some toggling of the screws and constitute a

nonfixed moment arm cantilever beam fixation. There is some axial-load transfer onto the anterior column, which decreases stress at the screw rod/plate junction. However, the toggling of the screw leads to increased failure via screw pullout. Thus, fixed moment arm systems are more effective at resisting sagittal translation and especially useful for deformity correction. Different screw modifications have been devised to combat the problem of screw pullout. Screw strength is directly proportional to the cube of the core or minor screw diameter. Screw pullout strength is directly proportional to the volume of bone between screw threads. This is determined by the screw thread depth (outside diameter) and pitch (distance from one thread to another). Increasing the pitch and thread depth will increase the pullout strength by increasing the bone volume between screw threads. The angulation or shape of the thread affects the bone volume and pullout strength. Varying the core (minor) diameter to increase screw depth along the distal end but increasing diameter to increase screw strength where they are most like to fail (conical shaped screws) near the tulip head can be another strategy for increasing pullout strength. Undertapping of pedicle trajectories or utilization of self-tapping screws can also increase the pullout resistance of a screw. Axial loading can lead to screw failure due to the parallelogram-like translational motion created. Directing screw trajectories medially ("toeing in") and utilization of transverse connectors can help limit this motion and prevent screw pullout with axial loading [43]. Trajectories aligned along cortical bone surfaces have also shown to have superior pullout strength, given implantation of screw threads within more rigid cortical bone versus cancellous bone within the vertebral body [44, 45].

Bone quality plays an important role in pedicle screw pullout. Patients with spinal metastases are particularly vulnerable to poor bone quality as they may have tumor at multiple levels affecting bone quality or simply have concurrent osteopenia or osteoporosis. Though pedicle screws are superior to hooks and sublaminar wires when bone mineral density is normal, instrumentation failure with pedicle screws in patients with osteoporosis remains relatively common. A longer construct can supply more points of fixation and distribute the load over more segments in osteoporotic patients, decreasing the pullout load at any specific screw site. Consideration may be given to the judicious use of cement augmentation of pedicle screws. An intact cortical surface must exist prior to injection of PMMA into a pedicle screw track to prevent leakage. Pedicle screws must then be rapidly inserted after injection of PMMA. Alternatively, newer fenestrated screws allow for direct injection of PMMA down the hollow bore of these screws to extrude out of the shaft at fenestration points. PMMA may increase the pullout strength of pedicle screws up to threefold in osteoporotic vertebrae [46, 47].

Biomechanics of Cervical Fixation

Occipitocervical Fixation

Occipitocervical fixation is typically required when there is destruction of one or both occipital condyles. This may be from osteolytic tumor or a far lateral approach to the foramen magnum. This approach is generally taken to improve visualization to the ventral or ventrolateral craniocervical junction [48]. Generally, up to 70% resection of one occipital condyle (resection up to the hypoglossal canal) is well-tolerated without the need for fusion. Any further resection increases the likelihood of occipitocervical instability. Fixation is achieved most commonly with occipital plating. Several indications have been identified for fusion in these cases: identification of a painful head tilt, instability on flexion–extension radiographs, or complete resection of the occipital condyle [49].

Cervical Spine Fixation

More complete resections of metastatic lesions of the cervical spine generally require either

partial or complete corpectomy, causing ventral instability. Cervical constructs need to be designed to correct this instability while providing a necessary substrate for osseous fusion. The main modes of application for this purpose include simple distraction and cantilever beam fixation. Interbody grafts create simple distraction fixation by applying a distraction force ventrally to resist axial loads and kyphosis. In this way, these grafts reconstitute the ventral load-bearing column of the cervical spine. There is also some stability imparted in flexion, extension, axial rotation, and lateral bending movements [50]. However, some sort of fixation, either via ventral plating or posterior instrumentation, is necessary to provide full stability, given the degree of vertebral body removal necessary to resect most symptomatic metastatic lesions. The principle of cantilever beam fixation is achieved with ventral cervical plating systems with locking screws as well as rigid posterior lateral mass/rod instrumentation. The fixed movement arm of these cantilever beam devices allows for axial-load sharing across the construct. Ventral plate and screw constructs provide immediate internal stability, recreate the ventral tension band, and provide stabilization and resistance to abnormal motion, especially flexion and extension [51]. They should be applied to the completely intact vertebral bodies above and below the level(s) of interest, spanning the entirety of the interbody graft. Plating systems that utilize nonlocking, variable angle screws are more dynamic implants that allow graft exposure to more continuous axial loading that may facilitate bone fusion. Generally, though bicortical screw placement achieves greater pull-out strength, the added complexity and risk of placing these screws in the cervical spine have made unicortical screw placement the standard for cervical plate fixation.

Dorsal cervical stabilization following cervical metastasis resection is most commonly achieved with lateral mass-based instrumentation. Dorsal decompression of the spinal cord can be advantageous in cases of circumferential epidural spinal cord compression, and posterior stabilization is necessary if there is excessive lesional or iatrogenic disruption of posterior elements [27]. It can also be helpful in preventing postlaminectomy kyphosis [52]. Especially with multilevel corpectomy, there is evidence to suggest increased fusion rates and less kyphosis with the addition of posterior instrumentation [53, 54]. Generally, tumors that invade both ventral and dorsal neural elements and cause kyphotic deformity are good candidates for a combined approach [55]. Lateral mass screw and rod constructs generally behave as nonfixed moment arm cantilever beam fixators, while also providing some dorsal tension-band fixation. These devices restore stiffness to the cervical spine in flexion, extension, and torsion [56]. Lateral mass screws provide superior flexion/extension stability and torsion resistance compared to wiring constructs [57–59]. Lateral mass fixation can be achieved from C1 to T1 (Fig. 40.1), but modern systems allow for integration with various fixation techniques across the occipitocervical and cervicothoracic junctions. Similar to ventral plating, posterior screw instrumentation should be placed only in normal stable bone free of metastatic disease. Adequate spinal alignment must be achieved before instrumentation because lateral mass screws are not optimized for adjustments in spinal alignment. The normal 3.5-mm diameter lateral mass screws utilized are not large enough to correct kyphotic deformity or reduce significant translation or subluxation. Cancellous screws provide better purchase than those with cortical threads. Though not mandatory, safe bicortical fixation can be achieved with 14- to 16-mm screws. Rescue screw placement with slightly larger diameter screws can improve bony purchase in patients with osteoporotic bone. However, larger screws run the risk of fracturing the lateral mass [60]. Alternatively, a small amount of polymethyl methacrylate (PMMA) may also be infused into the hole prior to screw placement. Finally, cervical transfacet screws can also serve as salvage fixation [61]. In addition to traditional dorsal periosteal decortication and placement of bone graft to encourage arthrodesis, placement of interfacet grafts can help encourage fusion

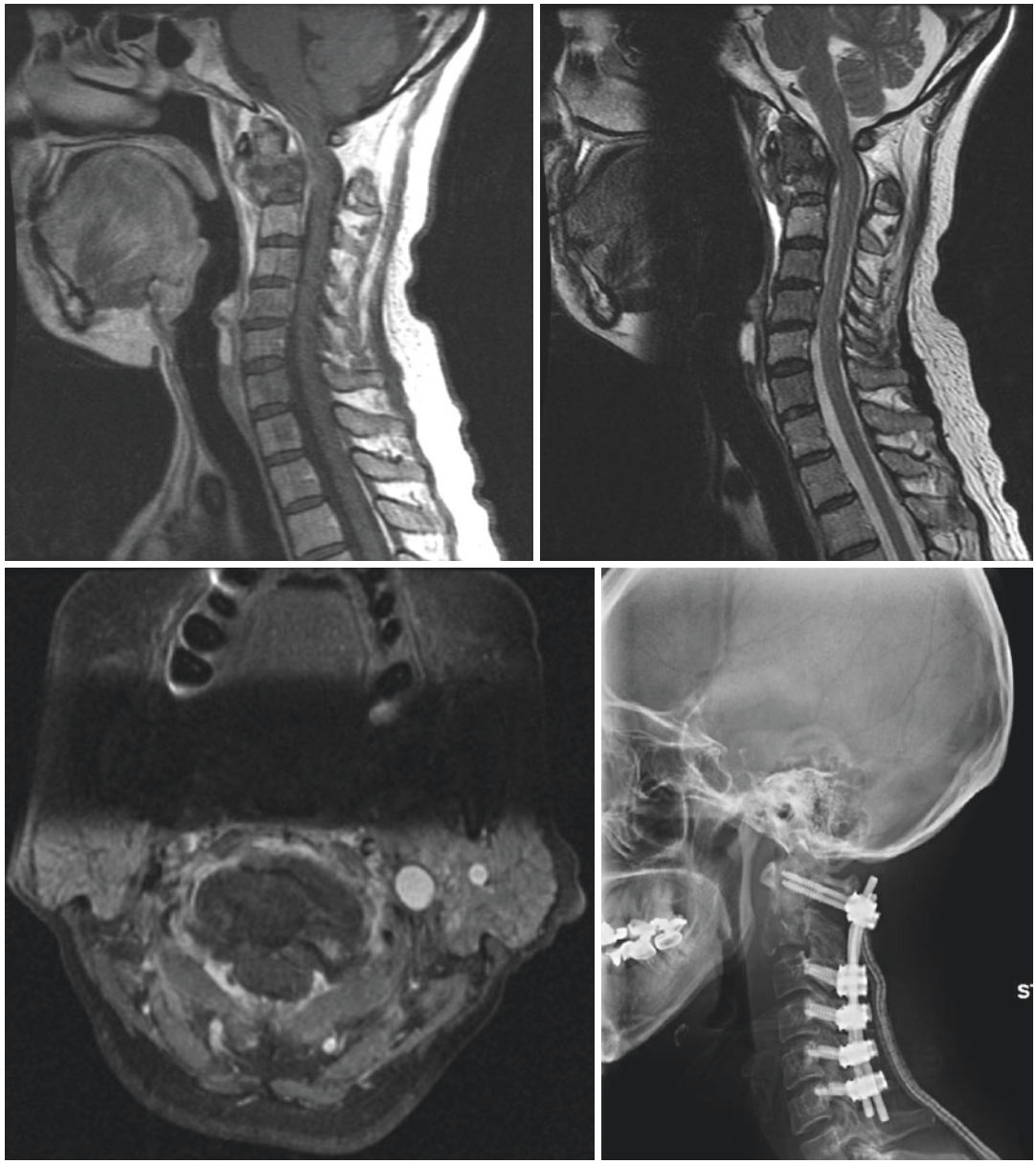

Fig. 40.1 Fixation following resection of C2 metastasis. MRI imaging of a patient with destructive colon cancer metastasis with a C2 metastasis causing a pathologic fracture at C2 with atlantoaxial instability and epidural spinal cord compression, and a separate lesion causing cervical stenosis at C5/6 (T1-weighted contrast-enhanced sagittal [top left] and axial [bottom left] images, T2-weighted sagittal image [top right]). Patient underwent multilevel cervical decompression, reduction of C1/2 fracture, and C1–C6 posterior cervical fusion followed by Cyberknife radiosurgery to both lesions (postoperative lateral XR [bottom right]). Cervical fixation extended to cover all levels of involvement given extent of disease and need for potentially destabilizing adjuvant radiosurgery

across the facets. These spacers can also help increase foraminal area and provide additional stiffness to cervical constructs to enhance fusion [62, 63]. Titanium rod diameters generally range from 3 to 3.5 mm and are easily contoured to fit. Excessive force in rod persuasion or in set-screw final tightening with antitorque should be avoided since the lateral mass is more

fragile than the pedicle and more prone to fracture or screw pullout. Screwheads are generally polyaxial to allow for maximal degrees of freedom for accommodation of rod fixation. Anatomically, the C7 and T1 lateral masses are smaller than other cervical levels and, generally, pedicle screws are preferred at these levels. Cervical pedicle screw placement at levels C6 and above carries a higher risk of vertebral artery injury and is, thus, utilized only in extenuating circumstances [64].

Cervical–Thoracic Junction

Metastasis located at the cervicothoracic junction provides a unique challenge due to the critical surrounding anatomic structures and the unique biomechanical considerations of transitioning from a mobile and lordotic cervical spine to a rigid and kyphotic thoracic spine. Generally, decompression without fusion at the cervicothoracic junction predisposes toward postlaminectomy kyphotic deformity [65]. Laminectomy disrupts the posterior tension band and shifts the weight-bearing axis ventrally, putting the dorsal muscle groups at a significant mechanical disadvantage [66]. Thus, posterior instrumentation and fixation across the junction should be strongly considered. Several studies comparing the methods of fixation at the cervicothoracic junction find that lateral mass screws, pedicle screws, and ventral interbody grafting with or without plating can all provide adequate stabilization across the junction [67–71]. The degree of three-column involvement is crucial to selecting the correct stabilization strategy. In biomechanical studies, dorsal fixation alone is sufficient to stabilize a dorsal two-column injury but not with involvement of the anterior column [69]. Thus, ventral and dorsal instrumentation, mostly common in the form of a ventral interbody graft plus posterior screw and rod fixation, should be utilized for three-column injuries [70]. In terms of rod choice, there were no significant differences in flexion bending and axial rotation between a transitional dual-diameter rod (3.5 and 5.5 mm) versus a solid side-to-side domino connector extending between two separate rods of the same diameters (3.5 and 5.5 mm). Utilization of a side-to-side connector was found to have similar stiffness but lower ultimate and yield force [71]. Finally, the length of the construct must be chosen carefully by tailoring to the curves surrounding the junction. Focal and gradual curves, as well as apical and neutral vertebrae in both sagittal and coronal planes, must be identified. Apical vertebrae are those located at the apex of curvatures in the spine, while neutral vertebrae are the least angulated and typically located between the curves [72]. Constructs should not end at or near apical vertebrae because angulation of the endogenous curve at that level will increase the loads experienced in relation to the construct and accelerate adjacent level breakdown. Similarly, constructs should not end at the level of the junction since it is prone to angular and translational deformation between the relatively flexible cervical spine and the rigid thoracic spine stabilized by a ventral rib cage. Other considerations include avoiding ending at levels with advanced degenerative disease and/or spinal stenosis, as well as extending constructs in patients with poor bone quality and density for extra points of fixation [73].

Biomechanics of Thoracolumbar Fixation

Anterior Fixation

Approaches to metastasis in the thoracolumbar spine encompass anterior, anterolateral, lateral, posterolateral, and posterior techniques. Approximately two-thirds of spinal metastasis are found in the vertebral body and pedicles necessitating access to the ventral spinal column. Anterior, anterolateral, or lateral approaches involve a thoracotomy or retroperitoneal exposure to complete a corpectomy. If the posterior elements are intact, then posterior instrumentation following these approaches may not be necessary from T1 to T9 levels as they are buttressed by the rib cage. Supplemental instrumentation

may help provide additional support in cases where the tumor or tumor resection has disrupted the anterior and middle columns [74, 75]. These include single-rod [76], double-rod [77], or anterior plate and screw constructs. An anterior dual-rod construct allows for rigid stabilization against axial compression, flexion, extension, and rotation. Single-rod construct provides a lesser degree of stabilization against flexion, extension, and rotational forces [78]. Anterior plate and screw fixation are similar to dual-rod constructs in that it provides added resistance against flexion, extension, and rotation by recreating a portion of the ventral tension band and employing fixed moment arm cantilever beam fixation. However, they lack the ability to distract or compress the vertebral bodies in order to accommodate graft reconstruction or compress a graft. Single-rod constructs may be necessary when the vertebral bodies are small or partially destroyed by tumor [79]. Above T10, vertebral body size makes anterolateral screw placement more difficult, though in select cases screws may be placed as high as T6. Below L4, the iliac veins and origin of the Inferior vena cava (IVC) also impede safe placement of anterolateral screws.

Posterior Fixation

Posterior fixation via pedicle screw and rod instrumentation has become the standard for thoracolumbar tumor resection. If there is posterior element or dorsal/circumferential epidural involvement, then posterior instrumentation will be necessary since the posterior column will be disrupted to achieve tumor resection and complete neural element decompression. For lesions involving levels T10 and below, there is little or no additional support from the rib cage and a greater degree of extension with spinal motion. Supplemental posterior instrumentation is generally required to prevent excessive motion than can lead to graft extrusion [80, 81]. Finally, advances in posterolateral approaches can also afford increasing access to the ventral spinal column via transpedicular, costotransversectomy, or lateral extracavitary exposures, allowing surgeons to avoid the morbidity associated with a thoracotomy or retroperitoneal anterior exposures (Fig. 40.2).

These approaches generally necessitate pedicle screw fixation of at least two levels above and below the involved segments to provide for multiple points of fixation above and below what is essentially a three-column injury created by the lesion and resultant surgical exposure. Though short-segment (one level above and below) fusions have shown efficacy in thoracolumbar trauma [82, 83], loss of anterior column integrity with metastatic lesions leads to higher rates of short-segment fixation failure when not supplemented with anterior column reconstruction or extension of posterior fusion constructs [84, 85]. Longer constructs also distribute the load over more segments, which is particularly helpful in patients with osteoporotic bone. Constructs should be designed to avoid ending at intermediate junctions (cervicothoracic and thoracolumbar junctions) given the transitional anatomy present at these points. Ending long constructs at these junctions leads to higher implant loads, higher failure rates, and a greater likelihood of adjacent segment disease. More rigid fixation is required at the terminal ends of the spine, and a higher flexion–extension bending moment exists at the lumbosacral junction. Thus, multiple points of fixation are required for long constructs ending at L5–S1 and addition of iliac screws, or S2-alar-iliac screws can decrease the strain on S1 screws and improve fusion rates [86, 87] (Fig. 40.3). Longer rod constructs also lead to greater torsional forces on rods that can lead to rod fracture and pseudoarthrosis. Cross-fixation between long-segment rods can improve the torsional stability and lateral bending stiffness of a construct [88]. This is more crucial when using hook anchors to improve hook stability and not as advantageous with distal pedicle screw fixation [89]. A box construct of two cross-links is the optimal configuration, ideally with links placed at the junction of the middle and terminal thirds of the construct [90].

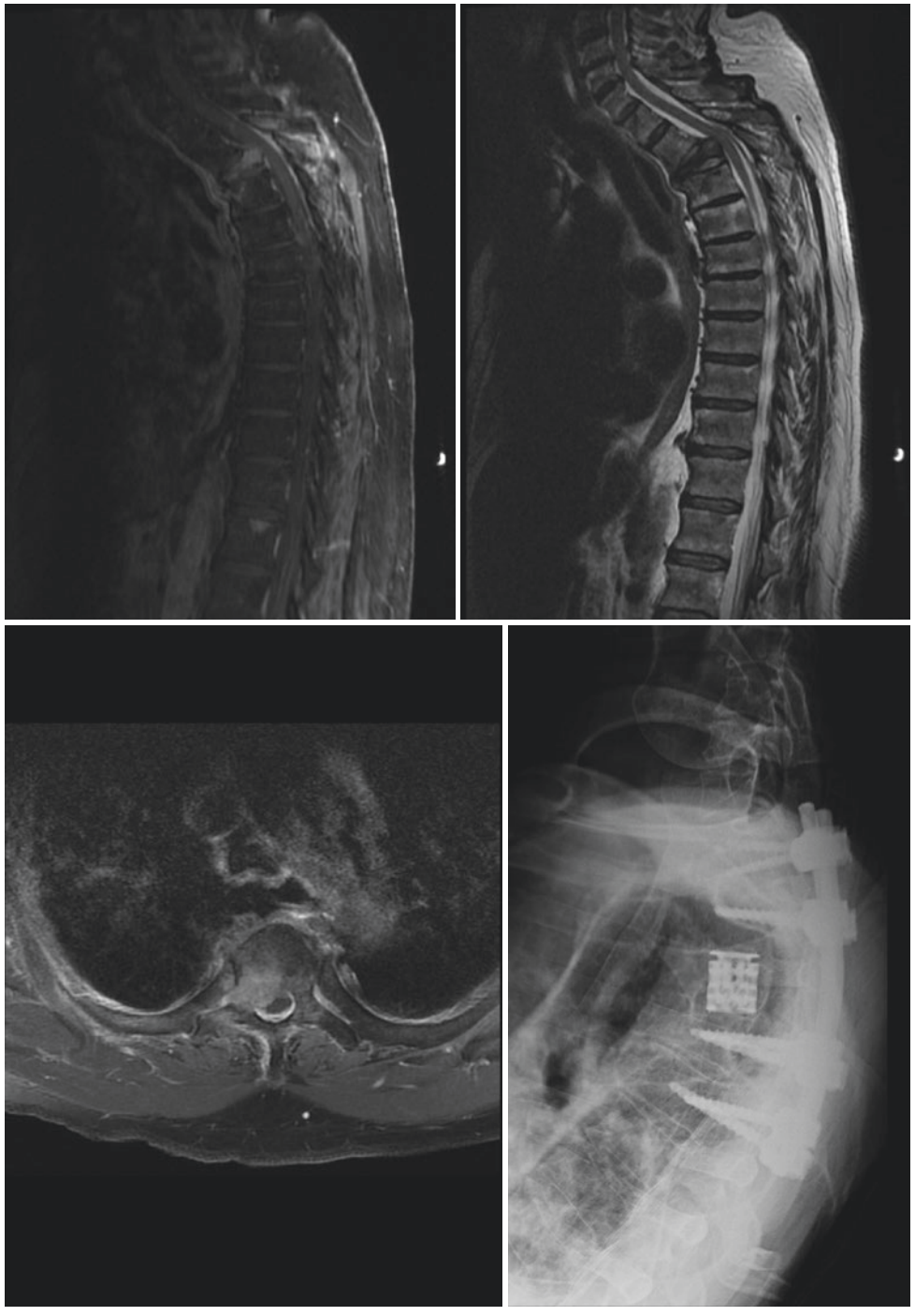

Fig. 40.2 Fixation following resection of thoracic metastasis. Total invasion of T3 vertebral body with metastasis leading to complete collapse and vertebra plana causing a severe kyphotic deformity and ventral cord impingement (T1-weighted contrast-enhanced sagittal [top left] and axial [bottom left] images, T2-weighted sagittal image [top right]). A right-sided costotransversectomy approach was taken to resect the lesion and complete a corpectomy at this level with removal of disc above and below. An expandable titanium cage was utilized to correct the kyphotic deformity and deployed and expanded gradually endplate to endplate. Thoracic pedicle screws were placed two levels above and below for stabilization and fusion (postoperative lateral XR [bottom right])

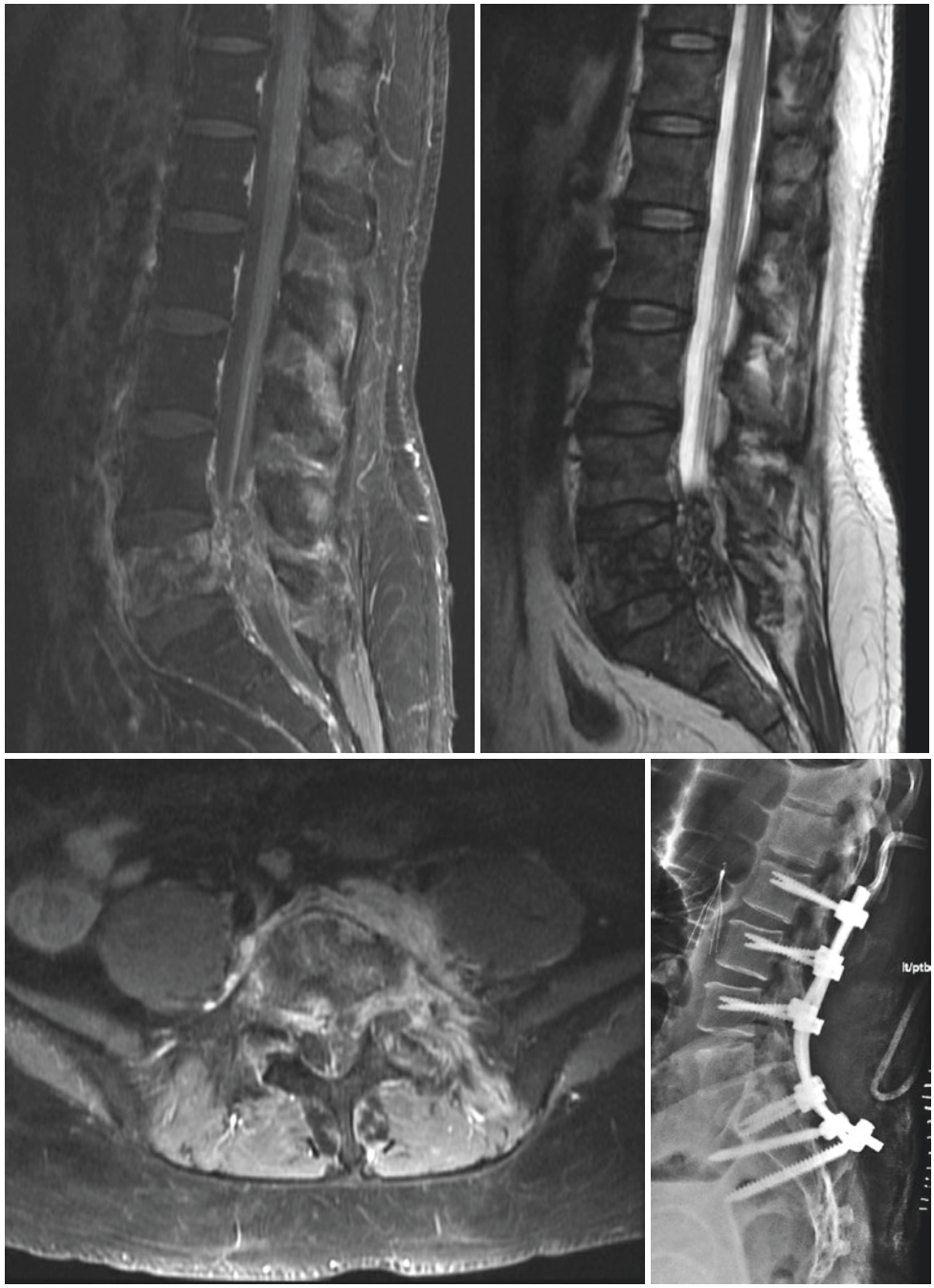

Fig. 40.3 Fixation following resection of lumbar metastasis. Patient with low back pain and bilateral lower extremity radiculopathy was found to have a liposarcoma at the L5 level with invasion of the epidural space causing central and foraminal stenosis that was unresponsive to chemotherapy (T1-weighted contrast-enhanced sagittal [top left] and axial [bottom left] images, T2-weighted sagittal image [top right]). Patient was taken to the operating room for potential full L5 corpectomy and multilevel fusion with pelvic fixation. Pedicle screws were placed at L2, L3, L4, S1, and the pelvis prior to decompression of the level for stabilization and support prior to complete destabilization of the spine via decompression of the L5 level. A left-sided transpedicular decompression with complete removal of the facet joint allowed complete access to the vertebral body and ventral to the thecal sac. Total resection of the epidural lesion was achieved and partial corpectomy of the L5 level revealed only partial tumor invasion and normal bone margins anteriorly. The decision was made to then leave the majority of the vertebral body in place for adjuvant radiosurgery, and the lumbar spine was stabilized with screw and rod instrumentation (postoperative lateral XR [bottom right])

Conclusion

An understanding of biomechanical principles is essential toward individualizing fixation strategies in patients with metastatic spine lesions. Patients with spinal metastases have unique management issues related to osteoporosis and performance status that necessitate considered planning of stabilization strategies. Finally, given the long-term survival of many patients with spinal metastases, fixation strategies that are biomechanically sound will mitigate against future hardware failure or adjacent segment disease.

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41 Separation Surgery for Spinal Metastases

Robert J. Rothrock, Ori Barzilai, Ilya Laufer, and Mark H. Bilsky

Introduction

Advances in systemic treatment for metastatic cancer have led to longer patient survival, paradoxically increasing lifetime risk for development of distant metastases [1]. As the incidence of spinal disease increases, so does the importance of effective management of spinal metastases and surgical strategies that minimize the need for interruption of systemic therapy [2]. Surgical care for spinal metastases has evolved over time in concert with other oncologic improvements. Historically, in the setting of lacking alternative strategies for local control, surgery for metastatic epidural spinal cord compression (MESCC) centered on gross total tumor resection, coupled with mechanical reconstruction. This often involved extended circumferential approaches with multilevel vertebrectomy, prolonged surgical duration, risk of significant perioperative complications, and, importantly, prolonged recovery times for patients [3].

Stereotactic body radiotherapy (SBRT) provides reliable and durable local tumor control, which has significantly changed the paradigm for management of metastatic spinal disease. Hybrid therapy combines and optimizes surgical and postoperative SBRT in order to minimize treatment morbidity and to maximize local control and safety [4]. Hybrid therapy describes the combination of separation surgery promptly followed by SBRT to treat remaining noncompressive osseous and paraspinal disease. The surgical strategy of separation surgery provides circumferential decompression of the spinal cord and stabilization of the spinal column, without the goal of gross total resection of osseous and paraspinal tumor. Local tumor control is dependent on the response to SBRT rather than cytoreduction. The surgery, in turn, provides optimal conditions for SBRT, allowing the safe delivery of tumoricidal radiation dosing. Although the surgical management of spinal metastatic disease is palliative by nature, separation surgery allows for effective treatment of spinal metastatic tumor with demonstrated improvement in local recurrence, increased patient-reported quality-of-life indicators, and preservation or restoration of patient mobility [5–8].

Indications for Surgery

The NOMS decision framework provides a comprehensive assessment of four sentinel decision points: neurologic, oncologic, mechanical stability, and systemic disease [9]. This framework standardizes the assessment of patients with metastatic spine tumors and allows for the

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incorporation of evidence-based medicine, which promotes the rational use of new radiation, surgical, interventional radiology, and systemic therapies.

The neurologic assessment evaluates both clinical and radiologic parameters, including the presence of myelopathy, functional radiculopathy, and the radiographic degree of epidural tumor extension, and spinal cord compression. A validated magnetic resonance–based epdirual spinal cord compression (ESCC) scoring system, known as the Bilsky score, is used to define the extent of epidural spinal cord compression [10]. Patients with Bilsky grades 0 and 1 have tumors that either are confined to bone or exhibit epidural extension without displacement or compression of the spinal cord. Patients with Bilsky grades 2 and 3 have tumors that displace, deform, or frankly compress the spinal cord. Patients with Bilsky grades 0 and 1 have low-grade MESCC, and patients with Bilsky grades 2 and 3 have high-grade MESCC.

The oncologic consideration is based on the expected local tumoral response, principally to conventional external beam radiation therapy (cEBRT) and systemic therapy. cEBRT provides local control for radiosensitive tumors such as lymphoma, prostate, and breast adenocarcinoma. Remaining solid tumor metastases generally exhibit radioresistance when treated with cEBRT. Thus, tumors exhibit a range of radioresistance with primary tumor histology as the most commonly used predictor of sensitivity. However, SBRT, through the delivery of high-dose conformal radiotherapy, can overcome radioresistance, providing durable local control regardless of tumor histology and volume. The neurologic and oncologic assessments are combined to determine the optimal radiation strategy to achieve tumor control and/or the need for a surgical decompression of the spinal cord.

Mechanical instability is a separate consideration and is generally defined according to the Spinal Instability Neoplastic Score (SINS) criteria [11]. Patients with mechanical instability typically require stabilization with bone cement or spinal instrumentation. The fourth consideration is the extent of systemic disease and medical comorbidities that affect the risk–benefit ratio of a proposed intervention, taking into account the overall expected survival and the ability of a patient to tolerate spine-specific treatment.

The NOMS decision framework allows for flexible, multifactorial decision-making to help define the appropriate balanced treatment plan for a given metastatic cancer patient. Using this framework, indications for separation surgery include patients with radioresistant tumor histology with high-grade ESCC, who can tolerate surgery from a medical and systemic perspective [12]. There is also a role for stabilization surgery in patients with mechanical instability without overt spinal cord compression, which is discussed elsewhere in this textbook [13].

Rationale for Approach

The rationale for hybrid therapy is based on numerous studies demonstrating both a benefit to surgical decompression of high-grade ESCC and durable local tumor control with prompt postoperative SBRT. Patchell et al.'s randomized controlled trial comparing patients receiving fractionated conventional external beam radiation therapy (cEBRT) alone versus surgical decompression followed by cEBRT for spinal cord compression due to metastatic cancer was stopped early when significantly more patients from the surgical arm of the study were able to walk after treatment (84% vs 57%, odds ratio 6.2 [95% CI 2.0–19.8] $p = 0.001$) [14]. The prescribed dose of radiation was standardized in the trial to 30 Gy in 10 fractions in each arm. Although it was not the primary outcome, there was an overall survival advantage in the surgical arm of the study. Patchell's trial is credited with establishing surgery as the standard of care for single-level MESCC in a symptomatic patient with solid tumor malignancy who has an acceptable life expectancy based on extent of disease, systemic treatment options, and medical comorbidities [15].

With SBRT providing effective local control regardless of tumor volume, gross total tumor excision is no longer necessary to optimize tumor control. In the absence of spinal cord compression,

SBRT can be used as definitive therapy to deliver an ablative dose to the entire tumor volume. SBRT doses commonly used are 18–24 Gy in single fraction or 24–30 Gy in three fractions. In a recent series reporting single fraction outcomes, a median dose of 22.4 Gy resulted in 98% 4-year local control rates even for radioresistant tumors such as renal cell carcinoma and sarcoma metastases [15, 16].

The ability to deliver an ablative radiation dose to the entire tumor volume, particularly at the epidural margin, is limited in the setting of high-grade spinal cord compression. The spinal cord is the most critical organ at risk (OAR), which limits radiation dose to the dural margin without the risk of iatrogenic spinal cord injury. However, when the tumor is separated from the spinal cord by 2–3 mm, the entire tumor volume can be treated with an effective SBRT dose without exceeding the accepted spinal cord constraints. Due to the improved local tumor control observed with SBRT, the oncologic goals of achieving local tumor control have transitioned from gross total excision to simple separation surgery. The goal of separation surgery is circumferential excision of epidural tumor to reconstitute the thecal sac creating a 2-mm margin for the safe delivery of an ablative radiation dose.

Most centers use a 1.5- to 2-mm margin to the thecal sac as a planning OAR volume. The cumulative acceptable point exposure dose to the spinal cord is considered 10 Gy to 10% of the epidural volume or a cord Dmax of 14 Gy [17]. Al-Omair et al. demonstrated that the degree of resection of epidural disease (surgical downgrading of Bilsky grade for MESCC) has a significant impact on long-term local tumor control in the context of hybrid therapy [18]. Thus, thorough separation surgery not only directly addresses spinal cord compression but also allows a safe corridor to effectively treat remaining osseous and paraspinal tumor. In our previous analysis of 186 patients undergoing hybrid therapy, the cumulative incidence of local failure was 16.4% for 1 year after SBRT [5]. In patients receiving a 24-Gy single fraction or 24–30 Gy in three fractions, the 1-year local failure rate was less than 10%. This is far superior to historical controls undergoing aggressive resection followed by conventional external beam radiation with 1-year local failures up to 70% [19].

Separation surgery requires spinal instrumentation to treat existing spinal instability and prevent iatrogenic instability. Patients undergoing separation surgery require spinal instrumentation and fixation, since anterior and middle column integrity is usually compromised by tumoral invasion, and decompression requires removal of the lamina and pedicle/joint complex (posterior column) [11]. In addition, the need for multiple levels of decompression and adjacent level involvement are not uncommon, requiring larger constructs. Complicating matters further, potential bony fusion, is severely compromised in oncologic patients due to poor bone quality, radiation and chemotherapy effects, and overall expected survival [20]. Based on these features and the risk of tumor extension to adjacent levels, posterior spinal instrumentation has usually extended at least two levels above and below the surgical index level(s), and sometimes greater if crossing a junctional area or in the setting of markedly poor bone quality [11].

Surgical Considerations

There are many involved preoperative considerations for patients undergoing separation surgery. By definition, most cancer patients have an American Society of Anesthesiologists (ASA) Score of IV or greater, placing them at higher perioperative risk for mortality as validated by numerous clinical studies [21–23]. Given this increased risk, optimization for surgery demands an interdisciplinary discussion, generally involving the patient's oncologist in order to determine the availability of further systemic therapy, provide perioperative risk stratification, and confer with the anesthesia team. Patients with poor pulmonary function and significant liver tumor burden generally represent the highest-risk patient populations. Furthermore, extensive tumor infiltration of the bone marrow or the effects of chemotherapy may lead to chronic thrombocytopenia. Finally, cancer

predisposes patients to the development of deep venous thrombosis, with 9.5% of patients undergoing spinal surgery in this setting having preoperative DVT and 24% of nonambulatory patients having a DVT [24].

Several metastatic tumor types, such as renal cell carcinoma and solitary fibrous tumor, have a robust vascular supply, which may lead to significant intraoperative blood loss. Therefore, preoperative embolization is used to minimize the risk of severe blood loss in the setting of patients with vascular tumors. Furthermore, patients with prior radiation to the surgical field or on active cytotoxic chemotherapy at the time of surgery generally benefit from involvement of plastic surgeons in the surgical closure or reconstruction.

Surgical Approach

Patients are sedated under general anesthesia, and an arterial line and Foley catheter are placed. Intraoperative neurophysiological monitoring (IONM) is routinely used, including EMGs, SSEPs, and MEPs. Following prone positioning on a four-post radiolucent table, fluoroscopic localization is used to plan a midline linear skin incision. Midline subperiosteal exposure of the posterior spinal elements is performed using monopolar cautery and Cobb periosteal elevators [4]. Our practice is to place instrumentation prior to beginning decompression and resection of the epidural tumor. Pedicle or lateral mass screws are placed via anatomical freehand technique or by various navigational guidance systems [25]. As described above, due to both the need for bilateral facetectomies at the index level and the inherently compromised bone quality in these patients, it is our practice to incorporate at least two levels above and below the tumoral level into the final surgical construct when open surgical approaches are used. Rods are contoured to approximate the anatomical kyphosis or lordosis depending on the spinal segment, and screw caps are tightened to lock the construct.

Next, attention is turned to posterolateral decompression of the spinal canal. In the setting of high-grade epidural spinal cord compression, it is crucial to avoid transmitting pressure to the spinal cord during decompression. Our practice is to drill the posterior elements using a high-speed 3-mm matchstick burr. The laminae are egg-shelled, and the remaining bone and ligamentum flavum are resected away from the spinal cord. Depending on tumoral location, a surgical corridor to the ventral epidural space is created via unilateral or bilateral removal of the facet joint(s) and pedicle(s) using the drill. Normal anatomical planes above and below the tumor level are defined prior to tumor excision in order to facilitate safe separation of the tumor from the dura. We use a combination of tenotomy scissors, Penfield dissectors, forceps, and pituitary rongeurs to resect the epidural tumor and to maintain a safe epidural plane.

To ensure circumferential decompression is achieved, the ventral epidural component of the tumor must be visualized and dissected away from the dura. Delineation of the posterior longitudinal ligament (PLL) is crucial in adequately visualizing the ventral epidural tumor that is generally deep to the PLL. The PLL is sectioned using tenotomy scissors, providing exposure of the ventral epidural tumor and the vertebral body, and a Woodson dissector is used to clear the ventral dural margin and to decompress the spinal cord. A partial vertebrectomy is performed to maintain a safe corridor, and usually approximately 20% removal of the involved vertebral body is sufficient. Once a ventral cavity has been created, a Woodson dissector can be used to further separate the tumor from the dura and to ensure adequate ventral epidural decompression.

If a large portion of the vertebral body is removed or compromised, anterior column support can be achieved by inserting poly-methylmethacrylate (PMMA) into the anterior vertebral cavity as previously described [13]. In cases of extended vertebral body removal, an expandable or stackable cage may be used for anterior column reconstruction. If a cage is used, then either a polyetheretherketone (PEEK) or a Harms titanium mesh cage is preferred to minimize radiographic magnetic resonance imaging (MRI) artifact. Importantly, aggressive or gross-total resection of the vertebral body or paraspinal

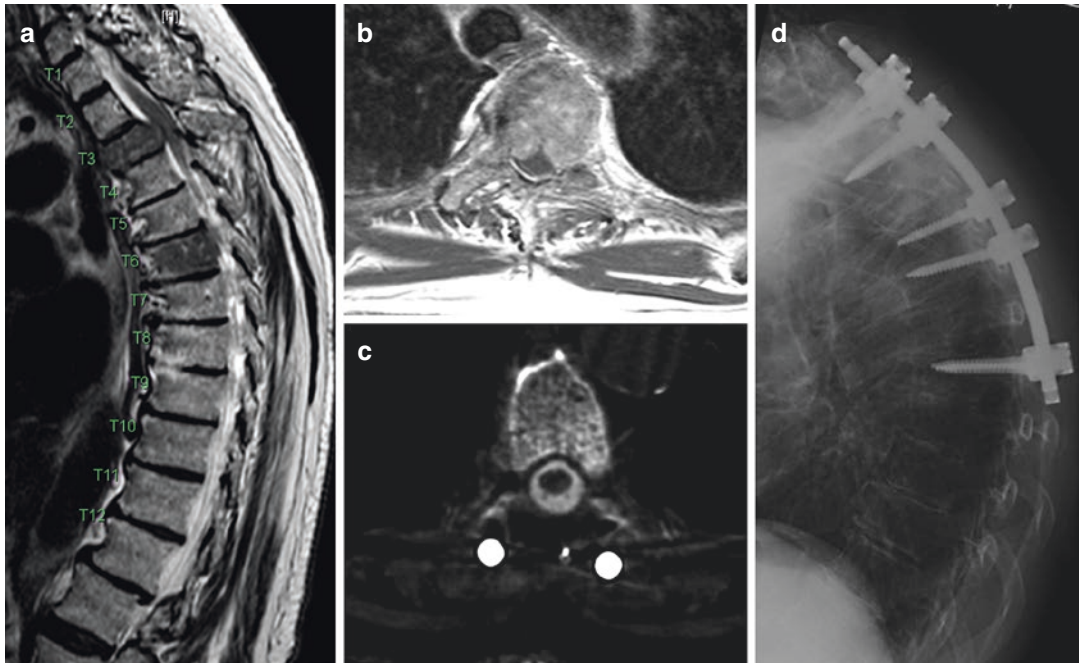

Fig. 41.1 (**a**, **b**) Seventy-four-year-old woman who presented with high-grade malignant epidural spinal cord compression (Bilsky grade 3) at T3–T4 from non-small-cell lung adenocarcinoma with associated back pain and ataxic gait. She underwent separation surgery with decompression from T3 to T4 and instrumentation from T1 to T7. (**c**) Postoperative CT myelography was obtained on postoperative day 2 with demonstration of circumferential decompression. (**d**) Postoperative X-ray demonstrates the surgical construct. She was treated with 27 Gy in three-fraction SBRT beginning approximately 2 weeks after separation surgery

tumor is not required since postoperative SBRT will effectively treat these tumor components.

Meticulous hemostasis is achieved, and the wound is irrigated copiously with antibiotic irrigation. The facet joints and transverse processes are decorticated, and autologous bone graft is used to augment bony fusion. Vancomycin powder is left in the operative bed for prophylaxis. At least one subfascial drain is left in place to full suction, and the incision is closed in multiple anatomical layers (Figs. 41.1 and 41.2).

Intraoperative Adjuvants

Ultrasound Guidance

The primary goal of separation surgery is obtaining adequate ventral decompression. The anterior dura is connected to the posterior longitudinal ligament (PLL) via the epidural ligaments of Hoffman, usually requiring resection of the PLL to ensure complete decompression [26]. Because ventral decompression can be difficult to directly visualize, intraoperative ultrasound can be a useful confirmatory adjunct, allowing visualization of ventral cerebrospinal fluid (CSF) pulsatility and dural planes [27].

Vertebroplasty

In cases where there is a related pathologic fracture or compression deformity, intraoperative vertebroplasty can be a useful adjunct in the treatment of mechanical pain [28]. Although violation of the posterior wall of the vertebral body by tumor has been cited as a relative contraindication to vertebroplasty, there is evidence that it can still be safely performed in this setting [29].

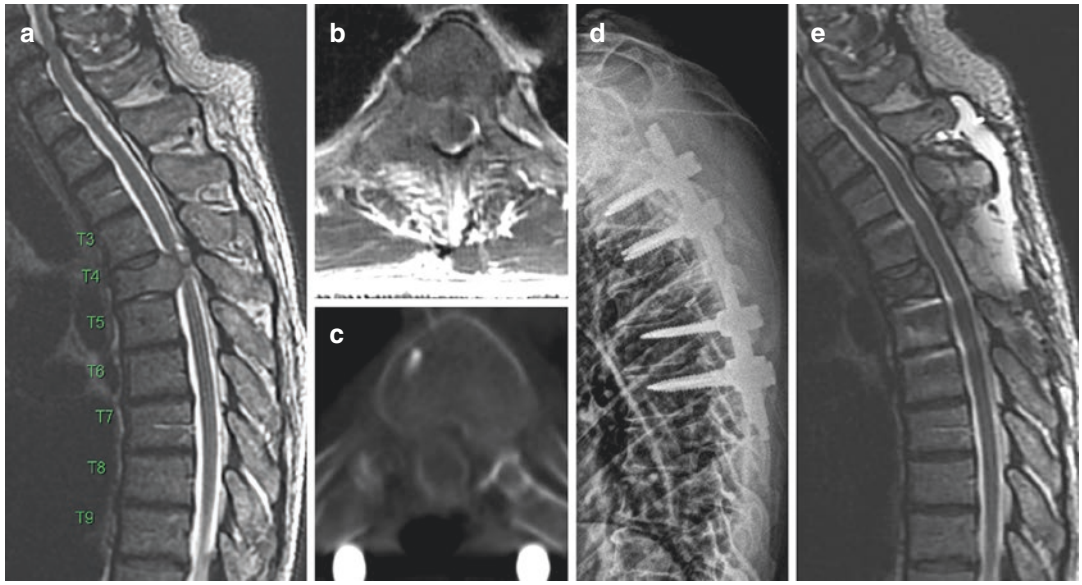

Fig. 41.2 (**a**, **b**) Fifty-year-old man who presented with severe upper back pain from a pathologic fracture and high-grade malignant epidural spinal cord compression (Bilsky grade 3) at T3–T5 from non-small-cell lung adenocarcinoma. He underwent separation surgery with decompression from T3 to T5 and instrumentation from T2 to T6. (**c**) Postoperative CT myelography was obtained on postoperative day 2 with demonstration of circumferential decompression. (**d**) Postoperative X-ray demonstrates the surgical construct. He was treated with 27 Gy in three-fraction SBRT beginning approximately 2 weeks after separation surgery. (**e**) Three-month follow-up thoracic MRI demonstrates durable local tumor control

Fenestrated Screws/Cement Augmentation

In patients with widespread bony metastases, bone quality and screw purchase can be severely affected. In these cases, cement augmentation of the screws or the anterior column can aid in bony purchase and decrease the risk of hardware failure [13, 30]. Cement injection through fenestrated screws provides a facile way to cement-augment the osseous screw purchase in cancer patients [31]. Intraoperative kyphoplasty can augment the anterior column structure even in patients with compromised posterior vertebral cortex.

P32 Brachytherapy

One of the greatest challenges for hybrid therapy is in the case of recurrent tumor that was previously irradiated and presents with circumferential compression of the thecal sac. Often in the case of previous radiation, the spinal cord has already been exposed to substantial radiation dose, and further exposure might place it at risk of toxicity [17]. The predominant pattern of disease recurrence after postoperative SBRT is within the epidural space. In their series, Al-Omair et al. demonstrated that when treatment failure occurred, it was exclusively in the epidural space in two-thirds of patients [18].

In the setting of circumferential tumor infiltration and previously irradiated targets, one solution is to deliver a therapeutic radiation dose to the dural margin with single-dose intraoperative brachytherapy [32]. The P32 brachytherapy plaque delivers a high radiation dose (median 27 Gy to 1 mm) with a steep dose-fall off (3 mm) making it an ideal dural radiation plaque. The plaque is brought into the operating room, laid directly into the targeted epidural space, and removed after therapeutic dose has been delivered. In several series, P32

brachytherapy has been shown to be a useful adjunct to surgical intervention following epidural decompression [33].

Postoperative Management

The second phase of hybrid therapy is the postoperative SBRT delivery. SBRT is defined as "the precise delivery of highly conformal and image-guided hypo-fractionated external beam radiotherapy, delivered in a single or few fraction(s), to an extra-cranial body target with doses at least biologically equivalent to a radical course when given over a conventionally fractionated (1.8–3.0 Gy/ fraction) schedule" [16]. Circumferential decompression achieved via separation surgery allows for tumoricidal SBRT doses to be delivered to the entire tumor volume within the constraints of spinal cord tolerance. Planning for SBRT typically begins while the patient is still in the hospital and recovering from surgery.

Simulation

In our practice, simulation is performed on postoperative days 2 and 3, with the goal of SBRT treatment approximately 2 weeks following separation surgery. Because MRI-related artifact from hardware can limit radiosurgical treatment planning, we utilize CT myelography to better visualize the neural elements, surgical construct, and organs at risk (OARs) [34, 35]. Patients are immobilized during simulation in a reproducible manner using a patient-specific positioning frame. Preoperative images (usually MRI with and without contrast) are used to delineate to the preoperative tumor volume, and this volume is outlined on the postoperative simulation imaging (CT myelogram) for accurate delineation of tumor target, OARs, and treatment planning.

SBRT

The Spine Radiosurgery Consensus Consortium contouring guidelines for spinal stereotactic radiosurgery and subsequent postoperative guidelines provide the basis for treatment planning [15, 35, 36]. Target volumes are defined according to the definitions set by the International Commission on Radiation Units and Measurements Report 50 [35, 37]. Gross tumor volume (GTV) describes observed disease at surgery or gross tumor seen on imaging. Clinical target volume (CTV) is the region of potential microscopic spread of tumor cells that includes the GTV and represents the total desired treatment volume. The planning target volume (PTV) is a geometric construct that encompasses the CTV and adds an additional margin of tissue to ensure that the CTV receives the intended dose. This margin takes into account factors that are difficult to control, like patient positioning, motion during treatment, physical errors of the treatment machinery, and other random errors that can occur. In modern stereotactic spine radiosurgery, a typical PTV expansion on the CTV is 2 mm.

Treatment planning is ultimately a compromise between the prescribed dose and the allowable dose to surrounding normal structures (OARs). In general for spine radiosurgery, dose uniformity within the target volume is sacrificed for steep dose gradients immediately outside the target volume to allow maximal sparing of OARs such as the spinal cord or esophagus. Radiation "hot spots" over 130% of the prescribed dose are allowed. An ideal treatment plan would be able to cover at least 90% of the PTV with the prescribed dose, but better than 80% coverage of the PTV with the prescribed dose would be still considered acceptable. Due to the complexity of decision-making in the setting of postoperative SBRT, we utilize a multidisciplinary conference between radiation oncology and neurosurgery for treatment planning.

Complications

Immediate

Immediate complications following separation surgery are similar to those for all instrumented

spinal surgery. In patients with highly vascular metastatic disease, such as renal cell carcinoma or hepatocellular carcinoma, there can be high rates of intraoperative blood loss with resultant postoperative anemia [38]. Intraoperative durotomy may be repaired using muscle patching and fibrin glue. In cases of postoperative cerebrospinal fluid (CSF) leaks through the incision and pseudomeningocele formation, placement of a lumbar drain usually results in resolution of the leak. In cases of persistent leaks, plastic surgeons can help to provide extended muscle coverage of the dural defect and soft-tissue reconstruction. Cancer patients are at increased risk of poor wound healing due to poor nutritional status, utilization of systemic therapy that impairs wound healing, and extensive use of radiation [39]. As discussed above, this risk can be mitigated by preoperative identification of patients who might benefit from plastic surgery-assisted closure. Lau et al. examined 106 adult patients undergoing surgery for spinal metastatic disease and found that age greater than 65 years and the presence of contiguous disease in three or more spinal levels were independent predictors of complications from surgery [40].

Delayed

As patient survival improves with advances in systemic cancer therapies, a new set of delayed postoperative complications have emerged in the setting of separation surgery. The highly effective tumoricidal doses of SBRT can result in profound osteonecrosis of the vertebral body, resulting in delayed fracture progression and hardware failure [41]. Delayed vertebral body fracture can be treated with salvage vertebroplasty/kyphoplasty to avoid larger revision surgery in this high surgical risk population [42]. In addition, de novo disease in adjacent segments can be challenging to treat, especially if there is overlap with previous radiation treatment (i.e., dose constraints). Given the low rates of solid arthrodesis, pseudoarthrosis and delayed instability can result in debilitating pain [43]. Esophageal perforation is a rare but known complication of SBRT to the cervical and upper-thoracic spine that can be severely morbid [44].

Conclusion

Hybrid therapy for spinal metastatic disease – concomitant separation surgery and SBRT – is an effective, tolerable, and reproducible treatment. Separation surgery provides rapid decompression, stabilization, and continuation of treatment, generally without a prolonged recovery period. Assuring adequate circumferential epidural decompression is crucial and allows for optimal SBRT dosing and durable local tumor control.

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Vertebrectomy for Spinal Metastases

42

Samuel Kalb and Juan S. Uribe

Introduction

Approximately two-thirds of patients with malignant tumors will develop bone metastasis. Primary tumors that most often lead to bone metastasis in the order of highest incidence are as follows: prostate, breast, kidney, lung, and thyroid cancer. Up to 70% of patients with breast or prostate cancers and 15–30% of patients with lung, colon, bladder, or kidney cancers develop bone metastasis [1].

The spine is the most common site of bone metastasis with an estimated incidence of over 10%. The most common initial anatomic location of metastases within vertebrae is the posterior portion of the body [2]. CT scans of affected individuals usually show the body of the vertebra being involved before the pedicles, although destruction of the pedicles is the most common finding on plain X-ray films. Destruction of the pedicles occurs only in combination with the involvement of the vertebral body.

Symptomatic lesions occur more frequently in the thoracic region (70%), while the cervical spine is the least involved with only about 10% of cases. More than 50% of patients with spinal metastasis have multiple levels involved. Lung and breast cancers metastasize preferably into the thoracic spine since the venous drainage of the breast through the azygos vein communicates with the plexus of Batson in the thoracic region [3].

Spinal metastases are classified according to their anatomical location. Almost 95% of spinal metastases are extradural lesions. The remaining lesions are either intradural extramedullary or intramedullary metastases. Lesions located purely within the epidural compartment and without bone involvement account for only a small fraction of extradural metastases [4].

The management of patients with symptomatic metastatic spinal lesions is carried out to relieve pain and to preserve or restore neurological function. Life expectancy is often fairly short, with median survival ranging from 4 to 15 months. Since a cure is not a realistic expectation, palliation is usually the aim of therapy.

Treatment options vary based on the presentation of complete or incomplete neurologic deficits. Traditionally, decompressive laminectomy was performed in an attempt to alleviate cord compression. However, simple laminectomy provides insufficient decompression in cases where tumors are either anteriorly or laterally located. Laminectomy alone is also likely to aggravate mechanical spinal instability, especially in the case of vertebral collapse.

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Improvement of minimally invasive surgery (MIS) techniques, such as the anterior or lateral exposures, along with the ongoing development and evolution of spinal stabilization instrumentation, has greatly improved the efficacy and morbidity/mortality of surgical intervention. Numerous studies have validated the efficacy of MIS approaches to alleviate pain and improve functional outcomes in the setting of metastatic vertebral lesions [5].

Vertebrectomy constitutes the foundation for restoration of the ventral spinal column during surgery for metastatic tumors. This operative strategy facilitates correction of deformity and immediate stabilization. With the advances in chemotherapy and radiation therapy, the indications for vertebrectomy in the setting of metastatic spine tumor have decreased over time. Nonetheless, current indications to perform a vertebrectomy as part of the surgical treatment include the following:

1. Oligo metastatic disease (one lesion and no systemic disease), therefore, taking out the single and only tumor can eliminate tumor burden.
2. Expected long survival and risk of potential hardware failure. Anterior column reconstruction offers better long-term support.
3. Significant kyphotic deformity associated to the lesion (pathological fracture leading to deformity).
4. Highly vascular lesion, thus, the whole tumor needs to be resected in order to control bleeding as with renal cell or melanoma.

Vertebrectomy can be achieved through different surgical approaches including anterior, posterior, lateral, or a combination of each. In an effort to reduce morbidity related to a thoracotomy or the extensive tissue damage from a posterior approach, lateral-based approaches have gained popularity in recent years. This technique allows direct view of the neural elements without the need to dissect or sacrifice the intercostal nerve or intraforaminal radiculomedullary artery. In addition, the extrapleural nature of the approach decreases the risk of injury to the aorta, vena cava, and sympathetic plexus, as well as reducing the risk of developing a pleural CSF fistula. The MIS version of the lateral approach allows for a significantly smaller incision with smaller amount of rib retraction, ultimately resulting in decreased blood loss, postoperative pain, time to mobilization, and reduction in the length of hospital stay [6].

This chapter focuses on the lateral minimal invasive approach to access the spine when vertebrectomy for tumor is warranted.

Preoperative Planning

The preoperative planning starts with a complete history and physical examination. Most patients will complain of back pain, which is either localized or in a radicular distribution. Neurological deficits, which include motor weakness and/or sensory derangement as well as bowel/bladder insufficiency or retention, may or may not be present depending on the patient pathology. When present, one should suspect compression of the spinal cord or nerve roots, especially for intradural tumors. In addition, the presence of spinal deformity should be taken into account.

Radiographic evaluation should always accompany any patient with suspected vertebral or spinal cord involvement in the setting of metastatic disease. Magnetic resonance imaging (MRI) with and without contrast is the ideal imaging technique. If MRI is not possible, a computer tomography (CT) myelogram is recommended. In both cases, imaging is necessary to delineate the extent of the lesion, determine the anatomical involvement, and evaluate the degree of neural compression. In addition, a plane CT is recommended to determine the extent of vertebral involvement, and

standing scoliosis films to evaluate for any form of deformity are essential for surgical planning [6].

In the setting of known metastasis, radioisotope bone scans can be used to detect small bone lesions, as it is sensitive in detecting osteolytic or osteoblastic activity. Angiography is beneficial when a hypervascular lesion is suspected. It is both a diagnostic tool to determine the blood supply as well as a therapeutic option in order to initiate preoperative embolization with the aim of reducing intraoperative blood loss. Examples of metastatic lesion that benefit from angiography include renal cell carcinoma, melanoma, and chordoma.

Surgical Techniques

Minimal Invasive Lateral Retropleural/Transthoracic Approach

The minimal invasive retropleural approach to the thoracolumbar junction is considered a variant of the lateral retropleural thoracotomy. In its essence, it combines many of the features of both the anterolateral transthoracic and the lateral extracavitary approaches. It grants the surgeon the ability to remain outside the pleura while achieving a ventral decompression of the dural sac.

The advantage of having lateral exposure of the thoracolumbar spine is that it allows the surgeon to visualize the thecal sac during the approach to the tumor. The surgeon will then have control of both the thecal sac and pathology, as compared to more ventral approaches in which the thecal sac is not visualized until the disease process is resected [7].

More recently, a mini-open anterolateral approach to the thoracolumbar has been described as a method to access the spine. The potential advantages of this MIS approach include independence from an access surgeon, small incision, little blood loss, and short convalescence. However, this is technically a demanding methodology. An understanding of regional neurovascular and visceral anatomy is vital, and experience with small working corridors, tubular retractors, and minimally invasive instrumentation are required. However, the overall outcomes have been remarkably well with overall complications of 12.5% [8].

The surgical techniques for the MIS lateral approach for access to the thoracic spine begins with the patient positioned under fluoroscopic guidance in a true and direct lateral decubitus position on a flexible radiolucent surgical table. For procedures involving only thoracic levels, the patient is positioned with the table break under the mid-surgical level. The side of the approach is chosen depending on the location of the tumor, surrounding viscera, and the vertebral level. Under fluoroscopic guidance, the index vertebral body level and tumor are located and marked on the skin. A 3- to 6-cm oblique incision is marked parallel to the rib traversing the pathologic vertebral body at the midaxillary line.

The incision is made obliquely over the rib across the region delineated by the skin markings. Dissection is carried down through the subcutaneous tissue to the ribs or intercostal space. Five to seven centimeters of the immediately underlying rib, directly over the lesion, are dissected in a subperiosteal fashion. Using a rib dissector or Cobb elevator, the rib is removed from the underlying pleura and neurovascular bundle, removed, and saved for autograft at the end of the case. The intercostal muscles and parietal pleura are incised to enter the thoracic cavity for a transthoracic approach, while the parietal pleura is swept anteriorly with blunt finger dissection for a retropleural approach. Further rib resection may be required if a larger exposure is needed. The rib resected for access to the thoracolumbar junction usually corresponds to 2 levels above the desired

vertebral level (i.e., 10th rib for access to T12, 11th rib for L1, and 12th rib for L2).

Once the rib is removed, an index finger is used to enter the pleural space (for a transpleural approach) or the plane between the endothoracic fascia and pleura (for a retropleural approach). The appropriate plane is developed, and diaphragm and/or lung are mobilized anteriorly using a finger and/or sponge stick until the lateral face of the vertebral body, pedicle, and adjacent intervertebral discs are exposed. For access to the thoracolumbar junction, it should be noted that removal of the diaphragmatic-costal attachment may be required. Because of the lateral (costal) diaphragmatic insertion, and for access to L1, the lumbar or posterior attachments of the diaphragm must be sharply transected off the transverse process of L1. The intervening attachment between the medial and lateral arcuate ligaments must also be cut to fully expose the lateral vertebral body. If more anterior exposure of the vertebral body is needed, the ipsilateral crus, which extend along the anterolateral spine to L2 on the left and L3 on the right, may also be transected.

For a left-sided approach, the aorta and hemiazygos vein are also retracted anteriorly. Segmental vessels are ligated as proximally as possible. Sequential tubular dilators are then inserted, and an expandable retractor system is inserted over the largest dilator and secured with a flexible table-mounted arm assembly.

With the retractor placed and adequate exposure obtained, the next step before proceeding with the corpectomy is to expose the dura by removing the pedicle with rongeurs and a high-speed drill. The intervertebral discs above and below the vertebral body of interest are then removed, and osteotomes are used to delineate the area of the corpectomy. At this point, bony removal can be achieved using a combination of rongeurs, curettes, high-speed drills, and osteotomes. A thin layer of bone on the ventral and contralateral sides of the body and the anterior longitudinal ligament are preserved to protect mediastinal and thoracic structures.

Once the corpectomy is done and decompression of the thecal sac when necessary is completed, ventral reconstruction is performed using expandable titanium cages, biological allograft, and the rib autograft harvested during the approach. Spinal instrumentation is completed using ventrolateral plate/screw fixation through the expandable retractor and/or percutaneous posterior pedicle screw/rod fixation. Dural repair, when necessary after resection of intradural tumor or iatrogenic CSF leak, is performed with a running 5-0 suture. The dural repair is reinforced with fibrin glue, and CSF is drained through a lumbar catheter.

Following a transthoracic approach or in the event of a pleural violation air must be removed from the pleural cavity, which is traditionally accomplished by placement of a chest tube. Alternatively, a red rubber catheter can be situated in the pleural space through the wound, and placed under a water trap (i.e., with the distal end submerged under water). The surgical wound is closed in standard fashion, including the muscular and fascial layers. The red rubber catheter is secured with a purse-string stitch, and a Valsalva maneuver with end-inspiratory hold is performed until no more air bubbles are observed to emanate from the submerged distal end of the catheter, representing evacuation of all air from the thoracic cavity. The red rubber catheter is removed as the purse string is tied. This technique obviates the use of a chest tube.

A chest radiograph is obtained immediately after surgery and on the morning of postoperative day 1, to verify the absence of pneumothorax if the aforementioned red rubber technique was used, or to verify placement and position of a chest tube if one was placed intraoperatively. In this case, it is initially placed on suction and weaned to water seal. Serial chest radiographs are obtained to confirm re-expansion of the lung

before removal of the chest tube. Declining oxygen saturation or recurrence of a pneumothorax warrants further evaluation and, if necessary, surgical re-exploration. The patients are encouraged to ambulate postoperatively with thoracolumbosacral orthoses. Obtaining upright radiographs are recommended to verify hardware placement and stability.

Case Example

Preoperative and postoperative images of a young (mid-30s) female patient with known metastatic breast cancer who underwent minimally invasive lateral retropleural T10 corpectomy with cage fixation and fusion (Figs. 42.1, 42.2, and 42.3).

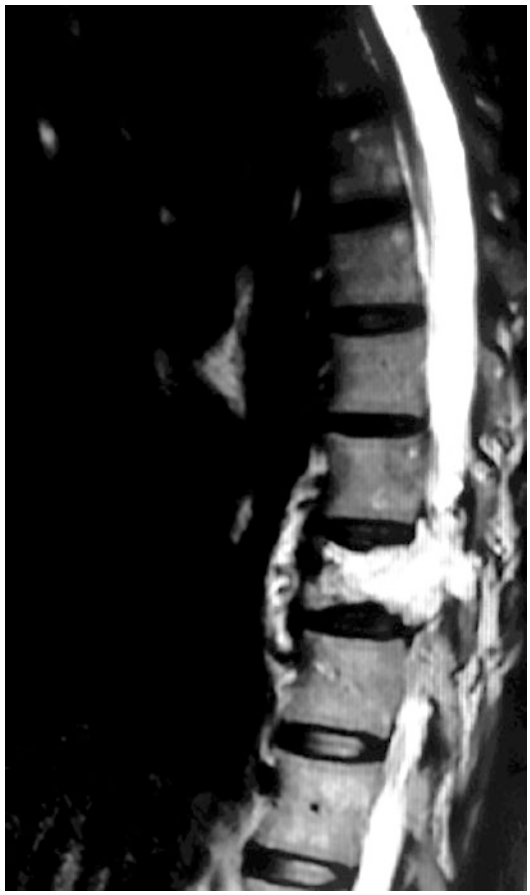

Fig. 42.1 Preoperative T2 sagittal MRI images reveal tumor involving T10 vertebra in all three columns. Spinal and paraspinal enhancement represent recurrent tumor and postsurgical effects

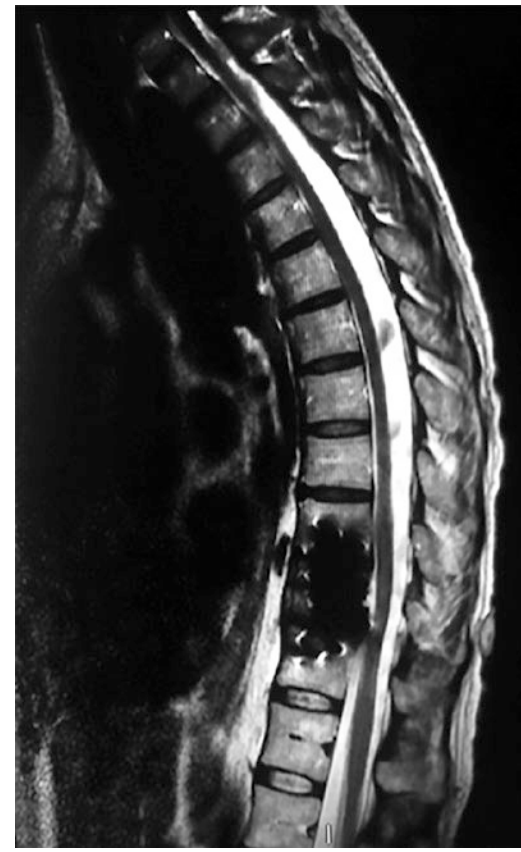

Fig. 42.2 Postoperative T2 sagittal MRI images show adequate decompression of the spinal cord

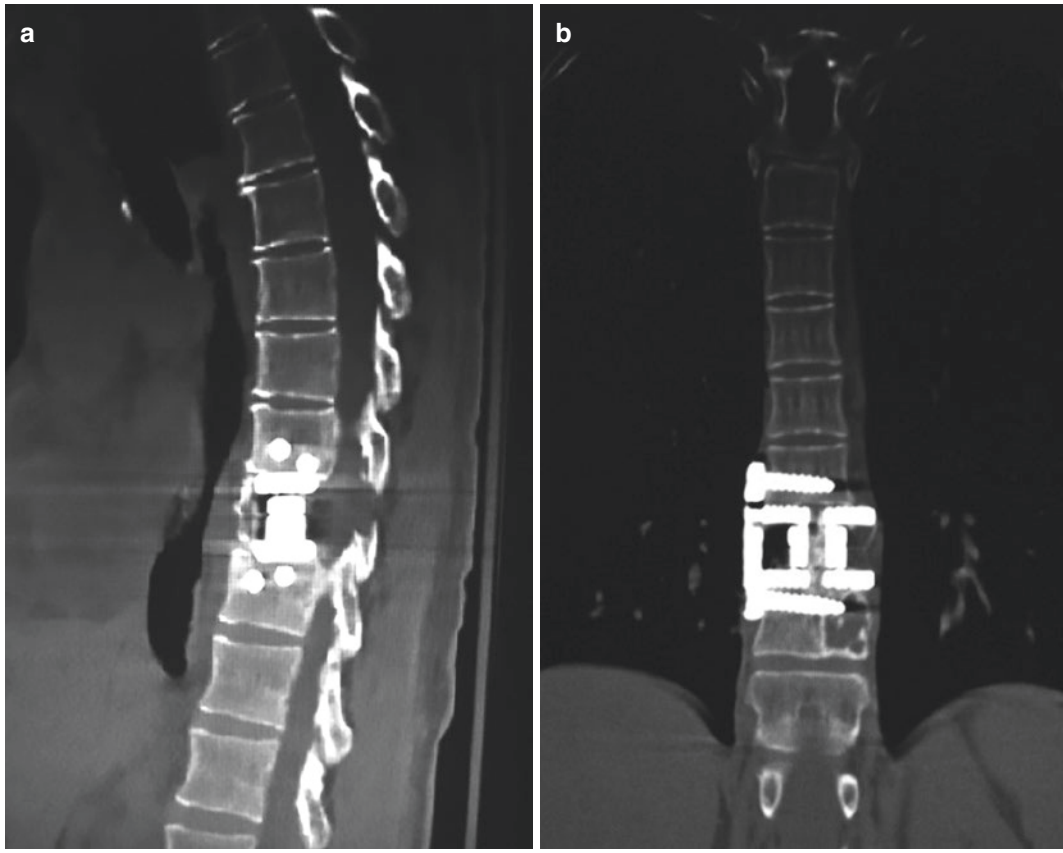

Fig. 42.3 Sagittal (**a**) and (**b**) Coronal CT scan show T10 corpectomy with cage and plate instrumentation

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Minimally Invasive Surgery for Spinal Metastases

43

Robert J. Rothrock, Ori Barzilai, Mark H. Bilsky, and Ilya Laufer

Introduction

Surgical care for spinal metastases has evolved over time in concert with other cancer-treatment improvements. Historically, surgery for spinal metastases centered on gross total or en-bloc resection, coupled with mechanical reconstruction. This often involved combined approaches (i.e., front-back) with multilevel vertebrectomy, prolonged operative times, relatively high perioperative complication rates, and, importantly, prolonged recovery times for patients with systemic cancer and thus increased peri-operative morbidity [1–4]. With the advent of stereotactic body radiation therapy (SBRT) and improved tumor control, through better radiation and systemic therapies, the paradigm for management of metastatic epidural spinal disease has shifted to hybrid therapy [5]. Hybrid therapy describes the combination of separation surgery promptly followed by stereotactic body radiation therapy (SBRT) to treat remaining noncompressive osseous and paraspinal disease. Separation surgery describes circumferential decompression of the spinal neural elements and stabilization of the spinal column, without the goal of gross total resection of osseous and paraspinal disease.

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While decompression surgery remains a standard approach for the treatment of symptomatic, spinal cord compression from epidural metastatic disease, other surgical indications have emerged for treatment of spinal metastatic disease. Pathologic fractures from tumor erosion and infiltration are a debilitating source of pain in patients with metastatic spinal disease [6]. Although they do not necessarily have associated neurologic deficits, especially in the absence of compressive epidural disease, the pain associated with spinal metastatic disease can decrease patient mobility, with deleterious effect on survival and negative effects on quality of life [7, 8]. For patients without high-grade spinal cord compression or in whom epidural disease can be effectively treated with SBRT, but still have tumor-related instability, minimally invasive surgical stabilization can be a useful and efficacious treatment [9, 10].

Minimally Invasive Surgery for Spinal Metastases

Minimally invasive surgical (MIS) approaches have gained popularity in treating spine trauma, deformity, and degenerative disease. In cancer patients, spinal MIS techniques might offer some advantages over open techniques [11]. Smaller incisions help to minimize risk of intraoperative and postoperative blood loss, and there is some

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evidence that they have less associated postoperative pain [10]. Importantly within the context of cancer care, MIS techniques facilitate the return to early systemic and radiation therapy with smaller incisions and less healing time [12]. MIS approaches may offer benefit to patients with advanced systemic disease and higher perioperative risk who might not tolerate more extensive intervention.

Although the goal with instrumented spine surgery is usually solid arthrodesis, the combination of poor bone quality, radiation, and chemotherapy severely undermines the potential for osseous healing in cancer patients [13]. Given that instrumentation for cancer-associated spinal instability does not necessarily have the goal of eventual solid bony fusion, it is well suited to minimally invasive techniques [10]. As in all relevant areas of spine surgery, however, MIS techniques must be implemented with a clear understanding of the surgical goals and without compromising the ability to safely accomplish them.

Contraindications to MIS Approach

Multi-level tumors and high-grade spinal cord compression present significant challenges in the application of MIS techniques [14]. Sometimes, however, a minimal access type approach can be employed to achieve circumferential separation coupled with percutaneous instrumentation. Highly vascularized tumors such as renal cell carcinoma and solitary fibrous tumors also favor open surgical approaches to allow open access for hemostasis and rapid tumor removal [14]. MIS approaches for metastatic spinal disease have been largely limited to the thoracic and lumbar spine, and have not been widely utilized in the cervical spine [15]. There are reported cases, however, of percutaneous, navigated instrumentation in the cervical spine [16].

NOMS Framework and SINS

The NOMS decision framework allows for flexible, multifactorial decision-making to help define the appropriate balanced treatment plan for a given metastatic cancer patient. It utilizes four sentinel decision points to assess disease: neurologic, oncologic, mechanical stability, and systemic disease [17, 18]. This framework standardizes assessment and allows for the incorporation of evidence-based medicine and the rational use of new radiation, surgical, interventional radiology, and systemic therapies. The neurologic assessment evaluates both clinical and radiologic parameters, including the presence of myelopathy, functional radiculopathy, and the degree of epidural spinal cord compression (ESCC). A validated magnetic resonance–based scoring system (known as the Bilsky Grade) is used to define the extent of epidural spinal cord compression, and patients are dichotomized into high-grade and low-grade ESCC groups [19]. The oncologic consideration is based on the expected tumoral response, principally to radiation, but also to systemic therapy. Tumor histology is categorized according to the response to conventional external beam radiation therapy (cEBRT) as radiosensitive or radioresistant. The neurologic and oncologic assessments are combined to determine the optimal radiation strategy to achieve tumor control and/or the need for a surgical intervention.

Mechanical instability is a separate consideration, and is generally defined according to the Spinal Instability Neoplastic Score (SINS) criteria [20]. In this classification system, tumor-related instability is assessed by adding together six individual component scores: spine location, pain, lesion bone quality, radiographic alignment, vertebral body collapse, and posterolateral involvement of the spinal elements [21]. The minimum score is 0 and the maximum is 18. A score of 0–6 denotes stability, 7–12 denotes indeterminate (possibly impending) instability, and 13–18 denotes instability. Patients with mechanical instability typically require stabilization with spinal instrumentation or cement. Spinal instability serves as a separate surgical indication as there is a role for stabilization surgery in patients with mechanical instability but without overt spinal cord compression [12]. We have previously published our algorithm for minimally invasive treatments for pathologic vertebral compression fractures (Fig. 43.1) [9].

The fourth consideration is the extent of systemic disease and medical comorbidities that

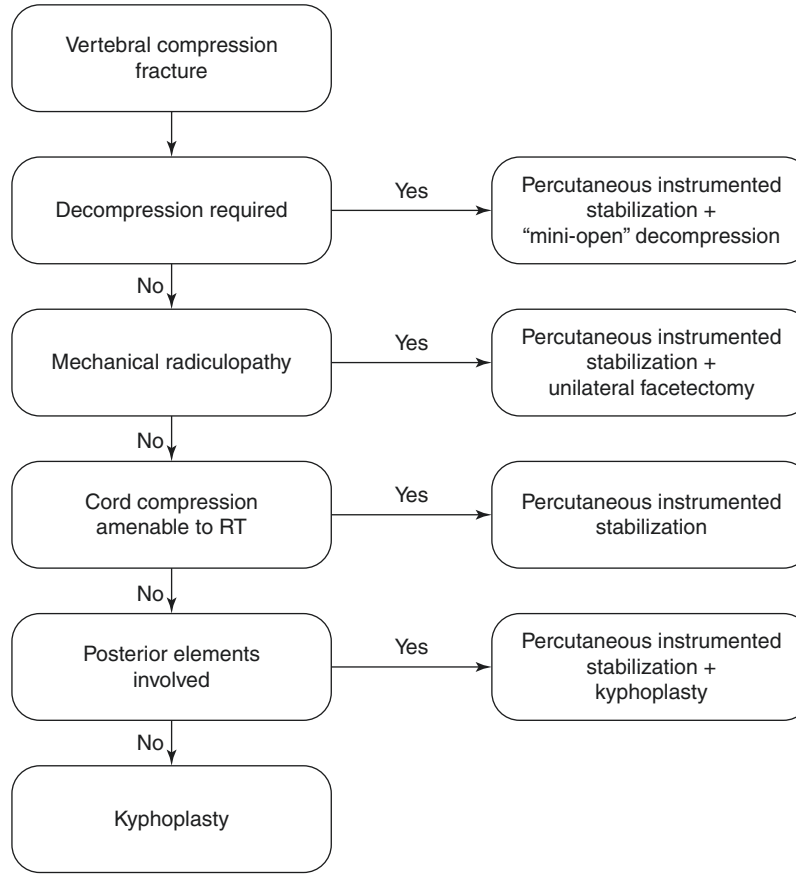

Fig. 43.1 Memorial Sloan Kettering Cancer Center (MSKCC) treatment algorithm for metastatic thoracolumbar compression fracture

affect the risk–benefit ratio of a proposed intervention, taking into account the overall expected survival and the ability of a patient to tolerate spine-specific treatment.

Minimal Access Surgery (MAS) for Decompression and Stabilization

Using the NOMS framework, indications for separation surgery include patients with radioresistant tumor histology with high-grade ESCC with or without mechanical instability, who can tolerate surgery from a medical and systemic perspective [22]. For patients who require separation surgery for preserved ambulation, minimal access techniques coupled with percutaneous instrumentation offers an efficacious alternative with demonstrated improvement in patient reported outcomes [9, 10]. In this case, bilateral laminectomy and transpedicular ventral epidural decompression can be performed via a mini-open midline incision or via a tubular retraction system. This can then be coupled with transfascial or percutaneous instrumentation. This mini-open approach can allow for circumferential decompression, and spare the more extensive muscle dissection required for open pedicle screw placement traditionally performed with long segment fixation. For patients with compromised bone quality, fenestrated screws with cement can be utilized to augment fixation in both minimally invasive and open surgical approaches [12].

MAS Facetectomy for Mechanical Radiculopathy

Patients with lumbar burst fractures with extension into the pedicle and facet frequently experience mechanical radiculopathy [23]. Mechanical

radiculopathy is a clinical syndrome in which radicular pain results from lumbar instability associated with metastatic disease. In this syndrome, radicular pain occurs with axial loading and/or ambulation, but is absent with recumbence or rest. The presence of mechanical radiculopathy will also correspond with a high intermediate or unstable SINS [10]. In our experience, effective treatment of the radiculopathic component requires instrumented stabilization and thorough decompression of the thecal sac and exiting nerve root, usually requiring ipsilateral facetectomy and pediculectomy (Fig. 43.2). In a series of 55 patients undergoing surgical decompression and stabilization for mechanical radiculopathy, 98% of patients had a significant improvement in visual analog scale (VAS) scores and 41.5% had a significant improvement in Eastern Cooperative Oncology Group (ECOG) status at 3-month follow up [23].

Our paradigm for minimally invasive treatment of mechanical radiculopathy includes percutaneous short-segment instrumented stabilization with fenestrated screw cement augmentation, kyphoplasty at the level of the burst fracture, and minimal access surgery (MAS) facetectomy with pediculectomy or decompression of the affected nerve root. The MAS facetectomy is performed using an expandable retractor inserted on the side ipsilateral to the radiculopathy, usually through one of the incisions created for screw placement, and the facet and pedicle are resected until full decompression of the exiting and traversing nerve roots is achieved [9].

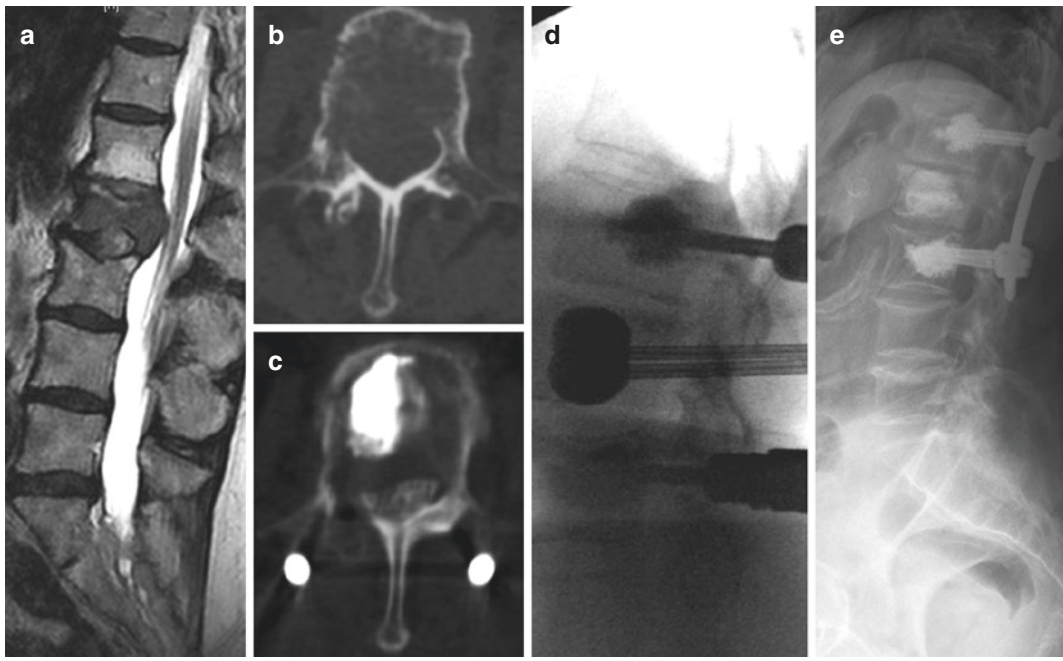

Fig. 43.2 (**a**) A 71-year-old female with metastatic lung adenocarcinoma who presented with severe low back pain and right lower extremity radiculopathy from a metastatic lesion to L2. Both her back pain and leg pain completely resolved with recumbency, and her clinical exam and syndrome were consistent with mechanical radiculopathy. Her SINS was 8 and there was Bilsky Grade 1c epidural disease at L2. (**b**) Axial CT demonstrates the lytic lesion at L2. (**c**) Patient underwent right L2-L3 MAS facetectomy with excision of the L2 pedicle and cement-augmented percutaneous bilateral instrumented stabilization from L1 to L3. Axial CT demonstrates the amount of right L2 pedicle removal necessary to thoroughly decompress the dorsal root ganglion. (**d**) Intraoperative kyphoplasty was performed at L2 to augment the lytic pathologic fracture. (**e**) Standing lateral X-ray demonstrates the final surgical construct. The patient underwent CT myelography for simulation on postoperative day 2 and was treated with 27 Gy in three fractions SBRT to L2 beginning approximately 2 weeks after surgery

Percutaneous Pedicle Screw Fixation for Tumor-Induced Spinal Instability

In patients with mechanical instability without high-grade ESCC or with highly radiosensitive tumor with ESCC, percutaneous pedicle fixation can offer durable stability without open surgical arthrodesis [12]. In the case of highly radiosensitive epidural tumor such as lymphoma and multiple myeloma, conventional radiation therapy offers effective tumoricidal control without the need for decompressive surgery [24]. In the absence of high-grade ESCC, patients with mechanical instability due to extensive cortical destruction or a fracture extending into the posterior elements can be treated with percutaneous instrumented stabilization, since kyphoplasty would not provide adequate stabilization. Short constructs (one level above, one level below the index treatment level) can be combined with screw cement augmentation by using fenestrated screws [12]. In addition, in patients with mechanically unstable fractures without significant epidural extension, balloon kyphoplasty can be a useful adjuvant to the percutaneous instrumented constructs, providing additional anterior column support [9, 25]. Intraoperative imaging- either a navigation system or standard fluoroscopy- is used for localization and incision planning, cannulation of pedicles, and screw placement. Fluoroscopy is required for monitoring the cement injection (Fig. 43.3).

Vertebroplasty/Kyphoplasty

Vertebroplasty and Kyphoplasty are both effective procedures utilized in the treatment of pain from pathologic vertebral body fractures.

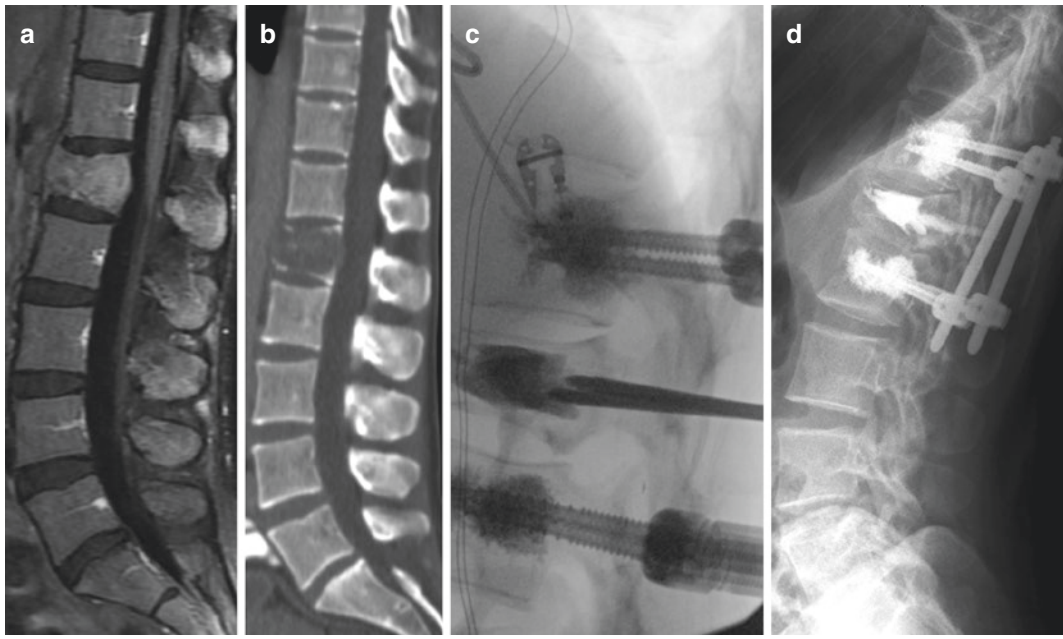

Fig. 43.3 (**a**) 35-year-old BRCA1-positive female with metastatic breast adenocarcinoma who presented with severe axial low back pain, prompting MRI and revealing a pathologic fracture at L1. (**b**) CT L-spine demonstrates a lytic lesion at L1 with SINS 10 and Bilsky grade 1a epidural disease. (**c**) Patient underwent cement augmented percutaneous bilateral instrumentation from T12 to L2 with intraoperative kyphoplasty at L1 to augment the lytic pathologic fracture. (**d**) Standing lateral X-ray demonstrates the final surgical construct. The patient underwent CT simulation on postoperative day 2 and was treated with 27 Gy in three fractions SBRT to L1 beginning approximately 2 weeks after surgery

In kyphoplasty, a balloon is inflated in the vertebral body to create a cavity into which bone cement can be injected, while in vertebroplasty, bone cement is injected into the vertebral body without the balloon [26]. In a randomized, controlled trial of balloon kyphoplasty versus nonsurgical treatment of symptomatic pathologic fractures in patients with one to three lesions, patients undergoing intervention had a significant improvement in Roland-Morris disability questionnaire (RDQ) score at 1 month compared to controls [27]. Vertebral bone-cement augmentation can be used in conjunction with SBRT and can be performed without interruption of chemotherapy or other systemic therapy [28]. We utilize isolated vertebroplasty/ kyphoplasty in the setting of painful compression fractures without involvement of the posterior elements (Fig. 43.1).

Ablation

Image-guided ablation therapies for spinal metastases have been introduced as a minimally invasive alternative to conventional surgical interventions for patients who are not good surgical candidates [29]. CT/fluoroscopic-guided techniques include radiofrequency ablation (RFA), cryoablation (or cryotherapy), and microwave ablation [29]. MRI-guided techniques include laser interstitial thermal therapy (LITT) and focused ultrasound [29]. In these procedures, a probe is directly inserted into the targeted tissue and activated to directly injure tumor.

CT/fluoroscopic-guided thermal ablation can be performed in conjunction with vertebroplasty/ kyphoplasty to treat pathologic fractures with the advantage of combining both treatments into one outpatient procedure. Combination RFA and vertebral augmentation has been shown to be a safe and effective therapy for palliation of painful spinal metastases in carefully selected patients [30]. RFA and cryoablation (X-ray guided techniques) are usually reserved for lesions within the vertebral body as there have been reports of thermal injuries to the spinal cord and nerve roots during treatment of extravertebral lesions [31, 32].

MRI-guided laser interstitial thermal therapy (LITT) has the advantage of real-time thermal monitoring to help prevent direct injury to adjacent tissues during treatment. MRI thermography enables noninvasive, real-time monitoring of the ablation zone [33]. Using this technology, the surgeon can monitor heat intensity and spread in real time to customize treatment. In select cases, spinal LITT has been used as a minimally invasive approach to treat asymptomatic high-grade compressive epidural tumor without interruption of systemic therapy [33].

Conclusion

Surgical intervention in the metastatic cancer population is palliative, and thus these patients should be considered for less-invasive procedures that limit the interruption of systemic therapy and allow for the delivery of early adjuvant radiation. As in all relevant areas of spine surgery, however, MIS techniques must be implemented with a clear understanding of the surgical goals and without compromising the ability to safely accomplish them. MIS approaches may offer benefits over open approaches to patients with advanced systemic disease and higher perioperative risk who might not tolerate more extensive intervention.

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Deformity Secondary to Vertebral Body Metastases

44

Zach Pennington, A. Karim Ahmed, and Daniel M. Sciubba

Introduction

Neoplastic disease is the second most common cause of death in the United States, claiming nearly 600,000 lives in 2017 [1]. Yet advances in radiation and chemotherapeutic regimens continue to drastically increase life expectancies across all stages of malignancy [2]. Consequently, more and more patients are living with the long-term stigmata of cancer, namely, metastatic disease, which is now reported in up to 64% of patients at the time of diagnosis [3–6]. Within bony metastases, the most common site for metastatic disease is the mobile spine [7, 8] with some evidence suggesting that up to 70% of patients have spinal involvement at the time of death [9], most commonly in the thoracic (70%) and lumbar regions (20%) [10–18]. Though these metastases are often asymptomatic or so clinically indolent as to be masked by a patient's other symptoms, more than 1 in 10 patients will have associated symptoms severe enough to require surgery [12–15, 19–28]. Operative indications for these lesions can be broken into neurologic and structural indications. The former topic is covered extensively elsewhere; in this chapter, we will focus on structural indications, namely, the instability and deformity that may occur secondary to bony destruction. We begin with a brief overview of the biomechanics of the mobile spine, followed by a description of the etiology of bony destruction, and finishing with diagnosis and treatment of mechanical instability and deformity secondary to metastatic disease.

Biomechanical Model of the Spine

Overview and the Basis of Focal Kyphosis

Analysis of the biomechanics of the bony spine requires considering both the bony and non-bony elements, including the ligamentous complex and paraspinal musculature. Additionally, though uninvolved in the support of the spine itself, the truncal soft tissues – namely, the thoracic contents and abdominal viscera – must be considered for their ability to alter the forces applied to each bony level. Much of the data describing the contributions of each of these elements to the structural integrity of the spine has derived from the trauma literature, and so our knowledge of how each contributes to the spine integrity results from examining the instability created by its disruption.

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In all models, biomechanics of the spine can be best described by treating each vertebra as an individual segment subject to a finite set of forces and torques. The vertebra is broken into the large vertebral body, which supports most of the loading from the superior and inferior vertebral levels under physiological conditions, and the posterolateral elements comprised of the pedicles, facets, laminae, and spinous process. Compared to the forces supported by the vertebral body, those supported by the facet joints are trivial in young patients. As patients age though, the intervertebral disks that allow force transfer between the vertebral bodies degenerate, compressing the vertebral bodies together. The posterior elements and the facet joints that divide them experience smaller decreases in joint thickness though, producing an asymmetrical settling of the vertebrae and induction of a small kyphosis at each level. This results in two effects. First, the realized axis of rotation of the vertebra shifts backward toward the facet joint, and second, a greater proportion of the static forces that each vertebra applies to the other is applied through the facet joints (Fig. 44.1). When said changes occur at multiple levels, there is a global kyphosing of the spine, giving rise to the so-called Dowager's hump. If this process occurs in only one segment, as might occur with a neoplastic or fragility-related compression fracture, then a focal kyphosis will develop, producing a de novo deformity.

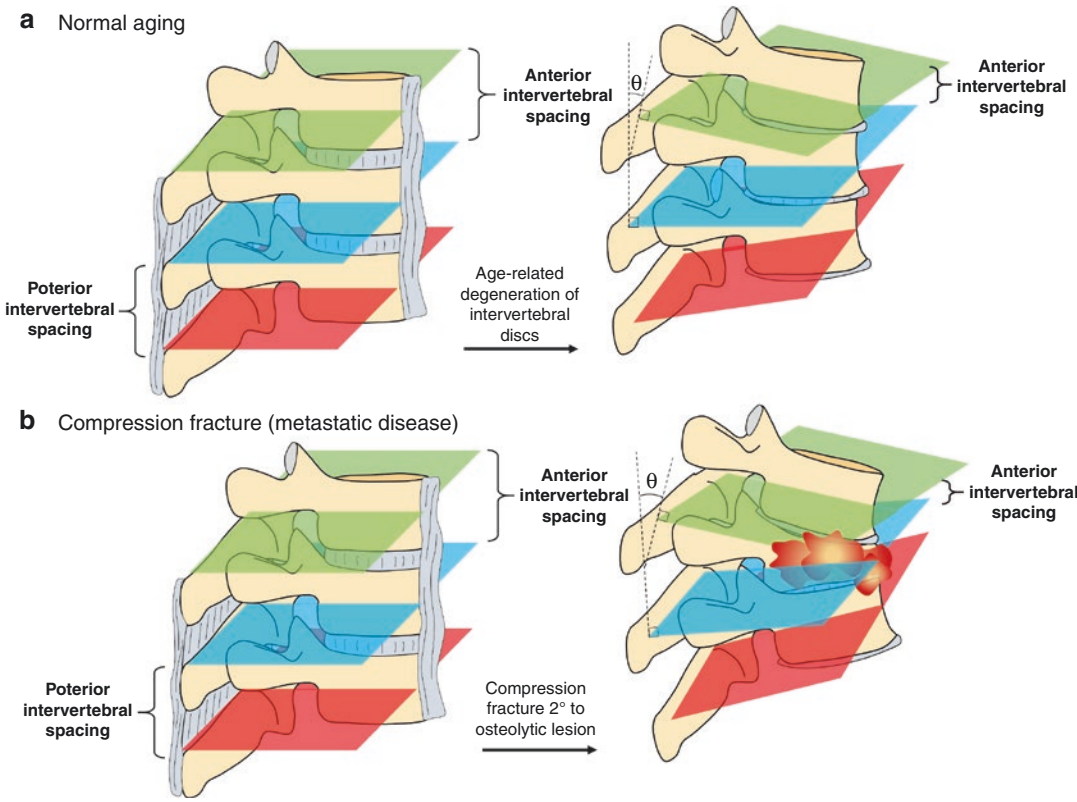

Fig. 44.1 Diagram illustrating age-related kyphosing of the thoracic spine. As the intervertebral discs degrade (**a**) there is a reduction of the anterior intervertebral spacing without concomitant decreases in posterior intervertebral spacing. This leads to an increased shift of force onto the facet joints and posterior movement of the instantaneous axis of rotation within each vertebra. This kyphosing (represented by θ, right diagrams) is exacerbated by collapse of the vertebral body (**b**) such as occurs in osteoporosis or metastatic disease of the spine, resulting in de novo deformity

Denis Three-Column Model and Its Application to Metastatically Involved Vertebrae

The most well-known model of spine biomechanics is that proposed by Francis Denis who used a series of several hundred thoracolumbar injuries to develop what is now known as the three-column model (Fig. 44.2a) [29]. Denis' model built on the older model of Holdsworth [30, 31] and evaluated spinal biomechanics by considering each vertebra as a separate segment in a larger construct. Using this system, each vertebra is divided into anterior, middle, and posterior columns, respectively, comprised of the ALL and anterior half of the vertebral body, the posterior half of the vertebral body and PLL, and the posterolateral elements (pedicle, laminae, spinous process, and associated soft tissues of the posterior tension band). Using this model, compression fractures – those most commonly seen in the context of metastasis-related deformity – were defined as failures of the anterior column. Burst fractures – the other common fracture type in the metastatic spine – were classified as failures of the anterior and middle column, suggesting that the two fracture types may simply represent different levels of severity on the same spectrum.

Upon examination of the force diagrams in Fig. 44.2b, it is apparent that weakening or destabilization of the anterior column allows the middle column to act as a hinge. Torques applied by the prevertebral soft tissue mass and loading of the superior endplate of the anterior column enable this rotation and collapse the structurally compromised anterior column, producing anterior wedging, eventually followed by complete collapse of the vertebral body (vertebrae plana). In heavily involved vertebrae, the middle column is also compromised, preventing it from acting as a hinge. Here, the instantaneous axis of rotation – normally found within the middle column – is forced dorsally to the zygapophyseal joints. These joints then serve as the fulcrum about which the axial plane of the vertebra rotates, creating focal kyphosis.

The result of this kyphosis may take the form of one of two clinical manifestations. The most obvious is that there is a shortening of the spinal column, which patients may report as decreased height, a steady downward deflection of gaze ("looking at my feet"), and/or the formation of a "hump" as the anterior and middle columns shorten relative to the posterior column. The second consequence of progressive kyphosing of the vertebral bodies is a significant increase in axial back pain. Milder forms of anterior wedging, as are common among the aging population [32], are often unassociated with pain. But more severe compression fractures are generally symptomatic [33] and may require surgical intervention. Furthermore, in the context of metastatic disease, extensive involvement of the vertebrae may also create a baseline oncological pain that is then punctuated by a new mechanical component.

Biomechanical Changes to the Spine in the Context of Osteolysis

As will be discussed later in this chapter, the bone of metastatically involved vertebrae can be divided into osteoblastic and osteolytic lesions. Osteoblastic lesions, also referred to radiographically as sclerotic lesions, are characterized by stimulation of the local osteoblasts and deposition of new bone [34]. By contrast, osteolytic or radiolucent lesions, are characterized by progressive destruction of local bone and stimulation of osteoclasts. Osteolytic lesions are generally more relevant to the discussion of metastasis-effected deformity as they cause greater destabilization of the vertebrae. In both cases though, metastasis formation relies upon interplay between osteoblasts (the bone-forming cells) and osteoclasts (the bone-resorbing cells) which is by and large controlled by the receptor activator of NFκB ligand (RANKL) and its noncompetitive antagonist osteoprotegerin.

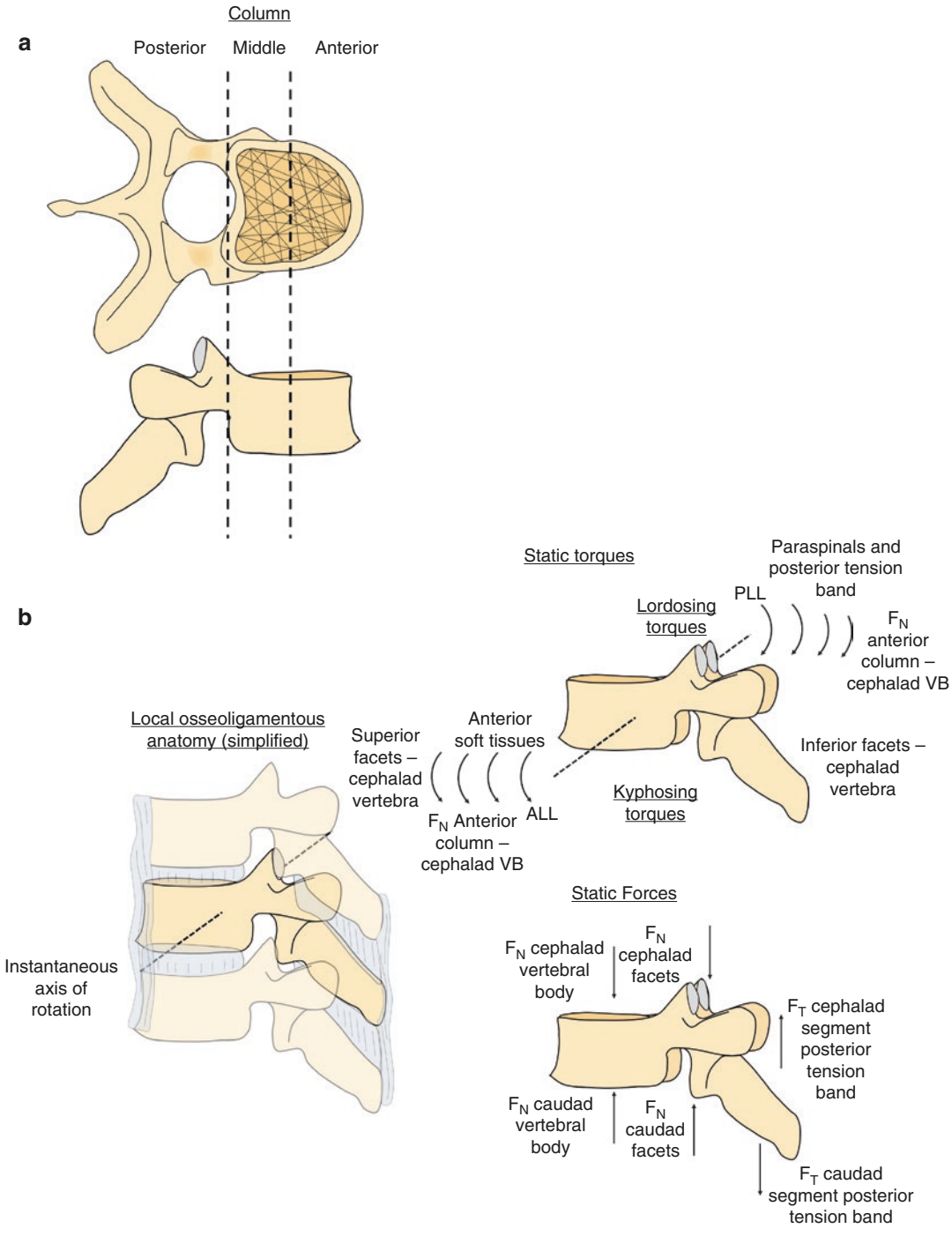

Fig. 44.2 (**a**) Three-column model in thoracic vertebrae as described by Denis. (**b**) Simplified model of locoregional osseoligamentous anatomy (left) with static force (top right) and torque diagrams (bottom right). The instantaneous axis of rotation of the vertebrae runs through the middle column of the vertebral body with the most significant kyphosing torques being applied by the anterior soft tissue mass. Compromise of the structural rigidity of the anterior vertebral body without diminution of this torque *increases the risk of anterior vertebral body wedging with subsequent kyphosis and deformity*

Basic Science of Osteoblastic Lesion Formation

Like all bone metastases, osteoblastic lesions form when circulating tumor cells invade the bone marrow sinusoids and extravasate into the marrow [35]. Once in the bone marrow, the cells release VEGF, which (1) stimulates adhesion to the surrounding matrix through upregulation of adhesion molecules and (2) promotes angiogenesis, generating a vascular supply for the cells of the nascent metastasis [36]. As lesions destined to be osteoblastic progress – such as those seen in prostate cancer – tumor cells begin to upregulate dickkopf-1 (DKK-1) [37], an inhibitor of the Wnt-Frizzled pathway, which promotes bone turnover. Then, as the lesions mature, DKK-1 expression decreases, disinhibiting the Wnt pathway and leading to increases in osteoblastic activity [35, 36]. This differential upregulation in osteoblastic activity produces a sclerotic or osteoblastic lesion that has higher density than the surrounding bone. Despite this net increase in bone density, osteoblastic lesions have abnormal bony architecture due to gross increases in both osteoblastic and osteoclastic activity relative to normal bone [38]. This is akin to what is seen in Paget's disease of bone, resulting in dense but brittle bone that may be mechanically unstable relative to normal bone [39] and may have decreased pullout strength. Additionally, in patients with both osteoblastic and osteolytic lesions, the difference in bulk moduli between adjacent osteoblastic and osteolytic lesions may increase the risk of compression fracture within the osteolytic vertebra.

Previous evidence has suggested that circulating parathyroid hormone (PTH) levels may also influence the development of osteoblastic metastases by altering the osteoblast-to-osteoclast activity ratio [38]. Evidence for this is still inconclusive though, as some groups [40] have presented evidence supporting an anti-metastatic role for PTH, whereas others have suggested it to promote the formation of osteoblastic [41] and/or osteolytic lesions [42, 43]. The reason for this heterogeneity of results may be tied to differences in PTHrP-1 receptor signaling in osteocytes [44], with decreased PTHrP-1 signaling leading to decreases in osteoclastic activity and subsequent sclerosis of local bone. In addition to PTHrP-1 signaling downregulation, osteoblastic lesions may secrete bone morphogenic proteins 4, 6, and 7, insulin-like growth factors 1 and 2, endothelin-1, and platelet-derived growth factor [38, 45]. These secreted factors stimulate osteoblasts and thereby promote bone deposition. The osteoblasts in turn release VEGF, monocyte chemotactic protein-1 (MCP-1), IL-6, and macrophage inflammatory protein-2 (MIP-2), factors that promote further metastatic cell invasion and tumor growth [38].

Basic Science of Osteolytic Lesion Formation

As alluded to in the introduction to this section, the formation of osteolytic lesions is more common than the formation of osteoblastic lesions, However, like osteoblastic lesions, osteolytic lesions rely upon the activity of both osteoblasts and osteoclasts. Stimulation of osteoblasts by cancer cells leads to the release of multiple inflammatory cytokines, including MCP-1, IL-6, IL-8, MIP-2, and VEGF, all of which are osteoclastogenic. Activated osteoblasts, such as those stimulated by cancer cell-derived PTHrP, also release RANKL, which activates receptors on osteoclasts, promoting bony resorption.

These secreted factors, among others, mediate bony destruction through both RANKL-dependent and RANKL-independent mechanisms [39]. TGF-β notably upregulates the production of PTHrP by tumor cells [46]. PTHrP in turn activates PTH receptors on osteoblasts, stimulating RANKL release and osteoclast activation [38, 46, 47]. The osteoclasts fuse into multinucleated cells and form a ruffled border that releases H^+ and cathepsin K to degrade the surrounding bone [47, 48]. TGF-β also stimulates metastatic cells to release IL-8 and IL-11, which increases osteoclast formation in a RANKL-independent fashion [39, 47, 49]. The aforemen-

tioned mechanisms beget a vicious cycle, as increased bone resorption stimulates osteoblast differentiation, in turn promoting further RANKL release and osteoclast activation. This leads to formation of overt lesions and also promotes release of TGF-β and other growth factors as bone matrix is progressively resorbed [47]. The elevated local TGF-β inhibits osteoblast differentiation and promotes progression of the osteolytic metastasis [38].

Tumor cells may also directly release RANKL through suppression of the Wnt/β-catenin signaling pathway, as seen in models of multiple myeloma that overexpress DKK-1 and sclerostin – two negative regulators of this pathway [50]. As with osteoblast-derived RANKL, myeloma-derived RANKL increases bone resorption and turnover, giving rise to an osteolytic lesion [36, 51, 52]. The key role of RANKL in progression of these and other osteolytic lesions has been confirmed clinically through the administration of denosumab, an anti-RANKL antibody [53, 54]. Because it addresses a key step in the major pathway of osteolysis, denosumab use may even be superior to bisphosphonates [55] – the current standard of care – in preventing vertebral compression fractures in involved segments [56].

Lessons from the Osteoporotic Spine

The majority of systems for classifying spinal instability to date have been established to describe traumatic injuries [57]. These injuries involve a combination of damage to the bony and soft tissue elements of the spine. By contrast, metastatic disease rarely affects the soft tissues; the ligaments, muscles, and cartilaginous elements of the spine are seldom involved. Because of this, the biomechanics of the metastatic spine are highly similar to those of the osteoporotic spine, which is also characterized by almost exclusively bony degradation. In both osteolytic lesions and osteoporotic vertebrae, there is a gross decrease in spinal bone mineral density with significant involvement of the vertebral body. This decrease in vertebral body integrity predisposes to compression fractures, and in many cases, one or more segments may have undergone such trauma by the time the patient comes to clinical attention. Underlying the propensity to suffer compression fractures is the preference of metastatic cells to lodge in the vascular trabecular bone. Trabecular bone microstructure is essential for bone to resist repetitive axial compression loads [58]. Consequently, its destruction – seen in osteoporosis as gross bony loss and metastatic disease as tumor-initiated resorption of local bone – diverts forces into the cortical shell (now responsible for up to 97% of normal load forces) [59] with a disproportionate decrease in the ability of the vertebral body to resist axial loading [58]. For this reason, compression fractures are also known as trabecular fractures [58].

Studies of human cadaveric vertebrae have also demonstrated that uniform bone loss is associated with significantly higher levels of weakening in compression [58]. Vertebrae of equivalent density but with different levels of intervertebral heterogeneity will display distinct yield strengths, with higher heterogeneity being associated with higher yield strength [58]. As applied to metastatic vertebrae, this suggests that mixed osteoblastic/osteolytic lesions will be disproportionately stronger than purely lytic lesions of equivalent bone mineral density.

Given that all subunits of the bone then determine fracture risk in aggregate, it is also germane to consider the changes that have occurred in the healthy bone of patients with metastatic disease, as this provides the bulk of mechanical strength in the affected vertebra. To be succinct, this healthy bone is often compromised, as most patients with metastatic spinal disease are in the sixth decade or beyond [60], and so this healthy bone has already begun to undergo changes characteristic of the aging process. This includes depletion of trabecular bone and cortical thinning [61], which decrease fracture toughness and compressive strength by 10% and 2% per decade, respectively [58, 62]. The increased fracture risk is also attributable to denaturation of bone collagen [63], increases in cortical bone porosity [64, 65], and micro-damage to the bone [66].

Degradation of collagen fibrils and decreased heterogeneity of collagen fibril orientation may also impair the ability of the collagen network to disperse energy applied to the vertebral body [67]. This decreases the elastic modulus of the healthy bone component, thereby increasing the risk of bony fracture in response to non-axial forces, such as may be experienced during ambulation [68–70].

Also gleaned from the osteoporosis literature is the fact that loads are distributed unevenly over the vertebral body itself. With normal aging, a greater proportion of axial compressive loads are shifted to the posterior half of the vertebral body with greater dependence upon cortical bone and the paracortical trabecular bone [58]. This suggests that metastatic segments with solely anterior column involvement have greater intrinsic stability than do equivalently sized lesions involving the middle column, regardless of posterior element involvement.

Unique Features of the Metastatic Spine

In early stages of metastatic disease, the vertebral lesions remain small and biomechanically they may be considered reasonably akin to osteoporotic bone due to their preferential destruction of trabecular bone. However, as the lesion evolves, it progressively destroys trabeculae in the surrounding bone, carving out a cavity completely devoid of normal bony architecture. These osteolytic lesions act very much like an incompressible semisolid [71], and so vertebrae involved by these lesions may be thought of as a soft-boiled egg. The structural integrity of these lesions is solely dependent upon unaffected cortical bone, and axial pressures applied to the endplate are diverted to the lateral cortical walls by the tumoral mass. Axial loading pressurizes the vertebral body contents, causing the incompressible medullary soft tissue mass to deform, redirecting force into the surrounding vertebral cortex. These laterally displaced forces can blowout the vertebral sidewalls and produce wedging – in cases of anterior wall blowout – or spinal canal compromise – in cases of posterior wall blowout [71]. The propensity for blowout lesions is directly correlated to increasing cellular content within the lesion, as this is negatively correlated with tumor bulk modulus [71]. Weakening of the cortical bone also increases the chances of a blowout injury. Such structural changes may already be occurring in this population secondary to normal aging [64, 65] and are liable to be further compromised by tumoral involvement of cortical bone, though this is uncommon in most non-lung primary pathologies [72].

Determination of Mechanical Instability

Animal and Cadaveric Work

Several biomechanical studies have been performed looking at structural instability in cadaver and animal models. One of the first series was described by Silva et al., who used cadaveric thoracic vertebrae to test axial-flexion loading in simulated transcortical defects [73]. They found bicortical involvement significantly decreased failure loads, but unlike later series and the contemporary series of McGowan et al. [74], Silva and colleagues failed to document an influence of tumor size on failure strength. Dimar et al. used an essentially identical model to demonstrate that compressive strength was determined by the interaction of bone mineral density and the proportion of the vertebral cross-section affected by the bony destruction, suggesting that patient age and vertebral lesion size are the best determinants of instability [75, 76]. Whyne et al. also used cadaveric vertebrae with simulated osteolytic defects to test a computerized model of mechanical stability of lumbar vertebrae secondary to tumoral involvement [77]. Across all variables considered, they found that tumor size was the most important predictor of instability, though overall bone density, and the magnitude of axial loading were also significant predictors of instability. This decrease in axial loading strength had been previously demonstrated by Windhagen et al. [78] to pre-

dict mechanical stability in involved vertebral segments.

Ebihara presented the first animal model of simulated osteolytic metastatic spine involvement by generating trabecular and/or cortical defects in fresh ovine thoracic vertebrae using a high-speed burr [79]. They found that lesion size had a significant negative correlation with failure load upon axial compression. Additionally, in lesions involving greater than 40% of the vertebral body, concomitant involvement of the costovertebral joint was independently associated with a decrease in failure strength, demonstrating the rib cage to significantly contribute to stabilization of the metastatic spine. The same year, Hong et al. used simulated lytic lesions in whale vertebrae to demonstrate that the strength of the pathologic vertebrae is set by the weakest cross-section through the vertebrae [80].

As computing power has progressed, computerized modeling software has been used to perform finite element analysis of mechanical instability in simulated vertebrae. Tschirhart et al. used this model to demonstrate that lesion location and tumoral morphology best predict failure method, with upper thoracic location and bicortical involvement decreasing the risk of burst fracture [81].

Osteoblastic Versus Osteolytic Lesions and CT Imaging

Currently, computed tomography (CT) imaging is considered the gold standard for noninvasive assessment of spinal instability [71]. It classifies lesions as osteolytic or osteoblastic depending upon whether they are characterized by increased or decreased radiolucency, respectively. CT imaging demonstrating radiolucent or osteolytic lesions has been correlated with significant decreases in bone density [82]. Additionally, mathematical modeling using CT images from healthy patients and those with vertebral metastases has demonstrated that thresholds for osteoblastic and osteolytic lesions can be generated allowing them to be classified quantitatively [83].

CT can be used to evaluate both size and location of the tumor within the vertebra. Tumor size on CT has been shown to be the most important predictor of metastatic spine instability [71]. Additionally, finite element analysis has demonstrated that posterior displacement of the tumor within the vertebral body increases the risk of burst fracture with subsequent canal compromise [71]. By contrast, displacement into the anterior column increases the risk for compression fracture and subsequent wedging with *de novo* kyphosis [71].

It has been suggested that MR has higher sensitivity and diagnostic accuracy than multidetector CT for the identification of osseous metastases [84]. Use of this modality relies upon unenhanced T1-weighted and STIR sequences. Bony metastases are generally T1-hypointense and demonstrate increased STIR signal due to low fat content relative to surrounding marrow. Lesions also frequently enhance on gadolinium-enhanced T1-weighted lesions due to high vascularity [84]. Yet MR does not provide evaluation of the quality of osseous invasion by the tumor, that is, whether the tumor results in osteoblast or osteoclast-dominated changes. Consequently, MR may be useful for initial identification of osseous lesions, but CT provides an overall better assessment of potential instability.

SINS Framework

The focus of this chapter is correction of deformity; however, the goal of care in the patient with metastatic disease of the spine is to identify at-risk vertebrae prior to the onset of deformity. Vertebrae at risk for deformation are termed mechanically unstable and are far more common than vertebrae which have undergone pathologic collapse – the inciting event for metastasis-related spinal deformity. Diagnosis of mechanical instability relies on a combination of radiographic findings and clinical presentation; patients typically present with complaints of axial (with or without radicular) pain that is worsened with activity and loading of the spine. Mechanically unstable segments also typically

demonstrate extensive osteolysis of the vertebral body, occasionally with involvement of the pedicles and rarely the posterior tension band. Because of the relative commonness of mechanical instability in the metastatic spine – pathologic fractures occur in 10–30% of all cancer patients [34] – extensive work has been put into developing methods for identifying and classifying the mechanical stability of involved vertebral segments. The most widely used system is the Spinal Instability Neoplastic Score created by the Spinal Oncology Study Group [85]. The system scores lesions based upon the location of the metastasis, quality and presence of pain associated with the lesion, the quality of the bone in the affected vertebra, the gross alignment at that segment, the degree of vertebral body involvement, and the degree of posterolateral element involvement (Table 44.1). Based upon these factors, lesions are identified as stable (0–6), unstable (13–18), or potentially unstable (7–12) and recommended for conservative management (stable lesions) or stabilization procedures – cement or pedicle screw augmentation (unstable lesions). Several studies have been performed demonstrating interobserver reliability [86–89]; however, there still remains uncertainty among providers regarding management plan formulation for potentially unstable lesions without associated neural element compression. Consequently, the SINS score, while valuable in presenting a standardized means of assessing mechanical stability, cannot be employed as a definitive decision-making tool; ultimately, the decision of when and how to intervene must be made based upon the experience and clinical acumen of the treating physician.

Interventions for Mechanical Instability

Stabilization

Instrumented fusion is one of the oldest interventions for spinal metastases and is considered the gold standard for treatment of these pathologies owing to class I evidence demonstrating improved survival in patients receiving this intervention [25]. It is also the only intervention capable of correcting significant deformity secondary to osteolytic disease. Current constructs typically employ pedicle screw instrumentation with anchors placed two levels above and below the

Table 44.1 The Spinal Instability Neoplastic Score [87]

Metric	Score	Metric	Score
Location		*Radiographic spinal alignment*	
Junctional (O-C2, C7-T2, T11-L1, L5-S1)	3	Subluxation/translation present	4
Mobile (C3–6, L2–4)	2	De novo deformity (kyphosis/scoliosis)	2
Semirigid (T3–10)	1	Normal alignment	0
Rigid (S2-S5)	0		
Pain quality		*Vertebral body collapse*	
Mechanical	3	>50% collapse	3
Oncologic/nonmechanical	1	<50% collapse	2
Pain-free lesion	0	No collapse with >50% body involved	1
		None of the above	0
Bone lesion quality		*Posterolateral involvement* (pedicles, laminae, costovertebral joints)	
Lytic	2	Bilateral	3
Mixed (lytic/blastic)	1	Unilateral	1
Blastic	0	None of the above	0
Total			
Stable	0–6		
Potentially unstable	7–12		
Unstable	13–18		

lesion, or in the case of concomitant corpectomy, three levels above and below the lesion. As part of preoperative evaluation, computed tomography scans should be acquired of the locoregional spine as multi-ostotic disease is common. In cases with adjacent segment involvement, screw purchase becomes questionable as the pullout strength of tumor is substantially less than that of normal, healthy bone. In many cases, the bone integrity may be so compromised as to preclude screw placement at this level. If the purchase is only questionable in the posterior elements, anterior constructs may be employed, especially if corpectomy and decompression are indicated. Said constructs usually bracket the involved level, only extending one segment above and below the metastatic vertebra. However, anterior approaches cannot be reasonably adopted in patients with intraperitoneal involvement.

Given the similarities between osteolytic and osteoporotic bone, techniques for improving screw pullout strength in patients operated for metastatic disease can be borrowed from the osteoporosis literature. These include proper triangulation of pedicle screws [90–92], larger diameter screws [93], bicortical purchase [94], cement augmentation [95, 96], use of an expandable screw design [96], and decreasing pilot hole diameter [97]. Placing screws without tapping may also increase pullout strength [98, 99] though it may also decrease screw placement accuracy, especially in the thoracic spine [100]. In the past decade, cannulated screws have become available that allow for cement fixation after screw placement, offering the opportunity to revise screw placement intraoperatively prior to reinforcement. However, there is some evidence that the pullout strength of these implants is reduced relative to solid screws placed in tapped screw tracts pre-filled with cement [95]. In cases where solid screws are placed, cement volumes of 1 mL in thoracic spine and 3 mL in lumbar spine have been shown to be safe [101].

Because of the difficulties associated with surgery on the metastatic spine, along with the overall high morbidity of this patient population, surgery is reserved for only select patients. In general, surgical candidates have a life expectancy greater than 3 months [16, 21, 25, 26, 102–109] and have intractable pain [107, 110, 111], spinal instability [25, 110, 112], or metastatic epidural spinal cord compression (MESCC) that is causing progressive neurological dysfunction [12, 14, 15, 17, 21, 103, 107, 108, 110, 111, 113–115]. Patients with expected survival less than 3 months without acute-onset metastasis-related neurological dysfunction should be considered nonsurgical and recommended for cement augmentation (in the case of mechanical instability) with or without concomitant focused radiotherapy. Patients with acute-onset neurological symptoms with limited survival or poor performance status should be recommended for less invasive surgical techniques. For example, these patients may need only a minor decompression with percutaneous pedicle screw fixation to address associated instability. Rapid procedures like this separation surgery minimize recovery times and allow resumption of other adjuvant therapies [116]. But in cases of gross malalignment where patients have good prognoses, limited deformity correction may be indicated. No guidelines or series exist to describe the optimal alignment for these patients, yet given the greater frailty of these patients and generally poorer-quality bone, we recommend less aggressive corrections (i.e., SVA >5 cm). Persistent, mild malalignment is likely to make only minor contributions to the patient's quality of life relative to their systemic disease as compared to instrumentation failure that could occur secondary to overly aggressive deformity correction. The latter may significantly impair these patients and is realistically an unacceptable risk given the possibility that patients may be too moribund at the time of failure to undergo a revision procedure.

Case Example

A 73-year-old woman with history of multiple myeloma presented to the clinic of the senior author with severe mechanical back pain of greater than 6 months duration localizing the apex of his thoracic spine. The patient had

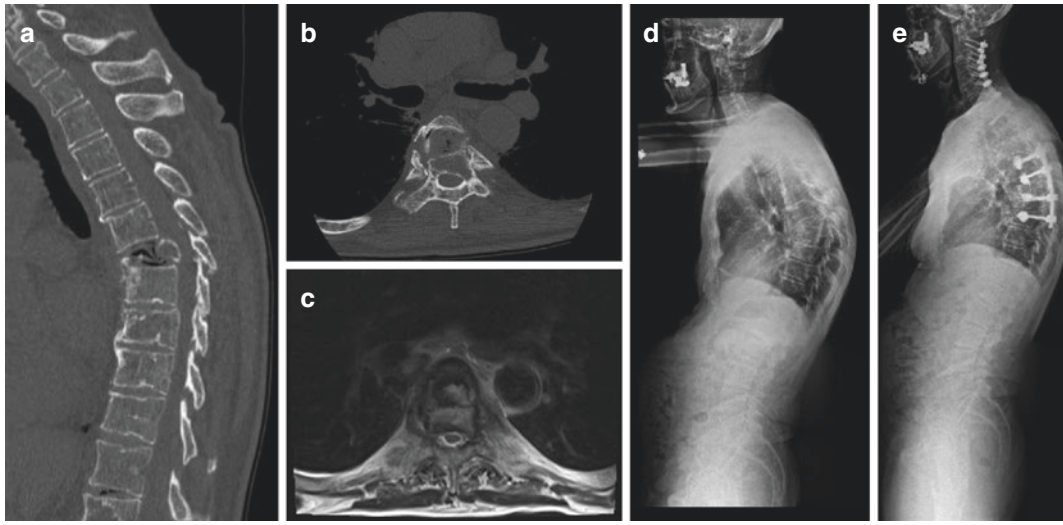

Fig. 44.3 A 73-year-old woman presented with multiostotic multiple myeloma and mechanical pain localizing to the mid-thoracic spine. Preoperative imaging demonstrated extensive destruction of the T7 vertebra on CT with 80% vertebral height loss (**a**), bipedicular involvement (**b**), and epidural disease without abutment or compression of the spinal cord at that level (**c**). Standing films (**d**) demonstrated grossly normal coronal (CVA = 0 cm) and sagittal alignment (SVA = 0.33 cm, LL = 71.42°, PI = 78.32°, PI – LL = 6.90°) though a high degree of pelvic tilt (30.56°) and large thoracic kyphosis (T1–12 = 55.91°) were noted secondary to a focal kyphosis at the fractured level (T6–8 = 41.44°). Postoperative films (**e**) demonstrated similar overall coronal (CVA = 0 cm) and sagittal alignment (SVA = −0.54 cm) with improvement of the pelvic tilt (26.80°) and thoracic kyphosis (T1–12 = 49.25°), following correction of the focal kyphosis (T6–8 = 24.27°)

received both chemotherapy and radiation for his myeloma. Radiographs demonstrated a notable kyphosis at T7 (41.44°) secondary to metastatic involvement (SINS score = 14; unstable) (Fig. 44.3a–d) along with extensive destruction of the C3 vertebral, though the pain associated with this lesion was nonmechanical (SINS score 11; potentially unstable). He was neurologically intact and scheduled for surgical intervention.

The patient underwent a staged surgery with independent C2-T2 and T5–9 instrumented fusions. Facet-based osteotomies (Schwab 1) were performed at C7/T1 and T1/2 to maintain cervical lordosis, as well as at T5/6, T6/7, T7/8, and T8/9 to reduce the thoracic kyphosis. The collapsed T7 vertebral body was corpectomized via a bilateral posterolateral approach, and a titanium cage was placed in the vertebrectomy site both to provide anterior and middle column support and to reduce the focal thoracic kyphosis. Cannulated screws were employed at T5, T6, T8, and T9, and roughly 1 mL of polymethylmethacrylate cement was placed bilaterally to increase screw pullout strength as she had diffuse osteopenia throughout the thoracic spine. The patient had an uneventful inpatient stay and stayed in an inpatient rehabilitation unit for 4 days before being discharged to a subacute rehabilitation facility. At 3 months postoperative, the patient had significant improvement in her thoracic spine alignment (Fig. 44.3e) and complete relief of her mid-thoracic spine pain.

Cement Augmentation: Vertebroplasty and Kyphoplasty

For patients too ill for surgical intervention or unwilling to accept the morbidity of surgical intervention, vertebral body augmentation – vertebroplasty and kyphoplasty – may be an option to reinforce unstable segments. It is performed percutaneously and can be executed on an outpatient basis, meaning that patients need not stop their adjuvant chemotherapy regimens to undergo these procedures. Ideal candidates are patients

with predominately mechanical axial pain relieved in recumbency, who are neurologically intact and have no evidence of (1) compromise of the posterior vertebral body cortex or (2) epidural cord compression [117, 118]. In these patients, pain relief has been reported in ≥80% [118–134].

Models of cementoplasty for vertebral metastases have demonstrated its ability to stabilize the metastatic spine. Recent finite element analysis by Berton et al. demonstrated that prophylactic vertebroplasty was able to completely prevent vertebral height collapse and circumferential bulging that occur secondary to axial compression of a vertebral body [135]. The augmented vertebrae were also found to increase forces exerted on the endplate of adjacent vertebrae in the osteoporotic model though, suggesting that vertebroplasty may increase the risk of adjacent segment breakdown in those with osteoporotic spines. Studies in cadaveric spine have echoed these results [136, 137], and other computerized models have suggested that posterior placement of the cement within the vertebral body decreases the risk of burst fracture [138].

Contraindications to cementoplasty include a history of coagulation disorders, significant neural element compression, and complete or near-complete vertebral body collapse [139], though recent evidence suggests that it may be possible to safely treat patients with either vertebral body collapse [140] or posterior cortex compromise [141]. Vertebroplasty is also of limited utility in patients with focal kyphosis. In these patients, balloon kyphoplasty may be able to provide some correction or at least stabilization of the deformity. Kyphoplasty balloons increase vertebral body height [135] and in doing so create a cavity in the vertebral body capable of receiving the injected cement. The vertebral height correction addresses the deformity, and the formation of a receiving cavity may decrease the likelihood of cement leakage from the vertebral body [142, 143], which is the precipitating event of the most significant complications of vertebral augmentation [133], namely, pulmonary embolism and nerve compression [144]. The reported correction with kyphoplasty is 3–8° per level though the durability of this correction is unclear.

Prophylaxis Against Mechanical Instability

Radiation

Radiation is a commonly employed intervention for the treatment of symptomatic spinal metastases. It can lead to good local control and relief of pain in the majority of patients [145–147], and for those with epidural compression without acute neurological findings or mechanical instability, it is the treatment of choice. However, radiation cannot be used to remedy mechanical instability, limiting its role to prophylaxis.

Though radiation provides good local tumor control, it is not without costs though. In addition to damage to non-oncologic tissues involved in the treatment field, radiation destroys collagen fibers within the irradiated bone [71]. These fibers help impart much of the tensile strength to bone that is responsible for its durability. Their destruction then increases the fracture susceptibility of the irradiated bone. Previous animal work finds this effect to be greatest for hypofractionated regimens, which decrease maximum axial loading in rodent long bones without changing the bone mineral content, consistent with collagenous damage [148]. Radiation may also catalyze the formation of pathological cross-links between adjacent collagen fibrils that prevent remodeling and increase bone brittleness, predisposing bone to fracture [149]. The most recent research though has suggested that non-collagenous injury may also characterize irradiated bone, with decreases in both trabecular bone density and cortical bone thickness being noted in the limbs of irradiated rodents [150–152]. Many of these changes may be reversible with ambulation and other weight-bearing exercises, though evidence is currently limited [150]. Lastly, there is some suggestion that even focal irradiation may produce systemic

decreases in bone mineral density [152], supporting the notion that irradiation of one spine metastasis may destabilize other, remote bony areas.

Anti-osteolysis Drugs: The Bisphosphonates and Denosumab

As stated numerous time in this chapter, one of the goals with metastatic disease of the spine is to stop or delay mechanical destabilization of the vertebral column prior to the onset of *de novo* deformity. Radiation, while relatively focal in the context of SBRT, fails to address the underlying metabolic changes mediating osteolysis in the affected segments. For this reason, it fails to treat any lesions not within the irradiated field, and in many cases, widespread irradiation is an unrealistic option due to the side effects caused by irradiation of healthy tissues. A commonly used alternative is anti-osteolytic class of medications, namely, denosumab (an anti-RANKL ligand monoclonal antibody) and the bisphosphonates (a group of small phosphorous-based salts that encourage osteoclast death). The two medications work through complementary pathways. Denosumab (trade names Xgeva® and Prolia®) increases the osteoprotegerin-to-RANKL ratio, thus favoring osteoblastic over osteoclastic activity and stalling progressive osteolysis. Research in women with aging-related osteoporosis has demonstrated that it decreases the risk of vertebral compression fracture by over threefold [153]. Though the response in patients with osteolytic lesions is likely to be less owing to accessory RANKL-independent mechanisms of bone resorption, it has also been demonstrated to reduce the rate of skeletal events in this population [53, 56] presumably through an attenuation of bone resorption. Class I evidence evaluating its effect on patient survival have recently been published (NCT01077154), demonstrating no influence on disease recurrence or overall survival in patients already being treated with standard of care locoregional and systemic therapies [154].

Bisphosphonates, including zoledronic acid/zoledronate, ibandronate, risedronate, and alendronate, function to inhibit metastasis in a completely different fashion. After absorption into the systemic circulation, these pyrophosphate analogs [155] enter bone matrix and bind to hydroxyapatite within the matrix [47]. The bisphosphonate is then phagocytosed by osteoclasts along with the bony matrix. Once inside osteoclasts, they bind to farnesyl diphosphate synthase, a key regulator of cholesterol synthesis and protein prenylation, resulting in improper intracellular protein localization and osteoclast apoptosis [155]. They may also promote accumulation of the ATP analogue triphosphoric acid 1-adenosin-5-yl ester 3-(3-methylbut-3-enyl ester), which inhibits the mitochondrial ADP/ATP translocase, impairing cellular metabolism and inducing apoptosis. Combined, these proapoptotic effects have been demonstrated to reduce progressive osteolysis and formation of bony metastases [155]. Additionally, recent systematic reviews demonstrated that they may improve survival [156, 157] and lower skeletal-related events (e.g., compression fracture) [157] in select populations. Most of the studies considered focused on zoledronic acid administration, which is the most potent of the nitrogen-containing bisphosphonates and is currently standard of care for skeletal-related event prophylaxis in patients with metastatic disease (4 mg q3–4wk) [155].

Conclusions

Metastatic involvement of the vertebral column – most notably osteolytic lesions – is characterized by progressive destabilization that can result in debilitating *de novo* spinal deformity. As with neoplastic disease itself, the best intervention is prophylaxis against the formation of osteolytic lesions using adequate systemic therapy with concomitant bisphosphonates or denosumab administration. Once formed, lesions lead to decreases in axial loading and sheer strength of involved vertebrae secondary to destruction of both trabecular and cortical bone. When stresses exceed the strength of these segments, compres-

sion and/or burst fractures develop that can generate de novo deformity. The most effective means of correcting this deformity at present is surgical intervention; though there is some suggestion that kyphoplasty may adequately address minor deformity, especially in patients too moribund to undergo surgical management. Current literature evaluating standard alignment parameters in patients with metastatic spine disease is sparse (e.g., sagittal vertical axis and lumbar lordosis-pelvic incidence mismatch), given the historical poor survival of patients with metastatic disease and subsequent reluctance to perform significant deformity correction in these patients. However, with increasing numbers of long-term survivors, this viewpoint may need to be reexamined in an effort to reduce mechnical complications in patients with spinal metastases who undergo surgical instrumentation. Accordingly, future directions should focus on establishing interventions to prevent spinal destabilization and deformity, surgical strategies to improve construct stability that can overcome compromised bone, and guidelines describing the impact of alignment on quality of life in those with deformity-inducing fractures.

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45 Postoperative Complications and Spinal Metastases

Bushra Yasin and Michael S. Virk

Background

The vertebral column is the leading site of skeletal metastasis making spinal metastases the most common spinal malignancy. As many as 30% of patients with solid organ malignancies will develop spinal metastatic disease [1], and this rate continues to increase as multimodality therapy is extending life expectancy of cancer patients. Patients frequently present with neck or back pain. Pain can result from inflammatory mediators associated with tumor growth that is often responsive to steroids or due to spinal mechanical instability that is provoked by axial loading and/or movement. Pathologic fractures in the vertebral bodies or posterior elements can further contribute to pain. Tumor extension into the epidural compartment may cause compression of neural elements resulting in radicular pain, numbness, weakness and, in the most severe settings, myelopathy or cauda equina syndrome.

Management of spinal metastasis requires an increasingly multidisciplinary approach. Enhanced diagnostic imaging modalities, CT-guided biopsy, chemotherapeutics, radiation therapy, and spine surgery may all play a role thus incorporating five specialty services into the treatment team. Operative indications for metastatic spine tumors are directed at stabilization of the vertebral column, decompression of the neural elements and optimizing targets for radiation therapy. Because these patients have metastatic disease, such procedures are palliative with the ultimate goal of treating pain, optimizing function and ambulation, improving quality of life and preserving continence of bowel and bladder. Such procedures can range from vertebro- or kyphoplasty to percutaneous instrumentation for stabilization of the posterior tension band to open procedures for separation surgery or en-bloc resection with spinal reconstruction.

Postoperative complications after spinal surgery have been reported to fluctuate widely in the literature, from 10% to 52% [2, 3]. Complications may be medical or surgical and occur intraoperatively or postoperatively. Common medical complications include deep vein thrombosis and pulmonary embolism, pneumonia, stroke, myocardial infarction, pressure ulcers, urinary tract infection, sepsis or septicemia and persistent pain. Surgical-related complications include postoperative hematoma, surgical site infection, wound dehiscence, dural tear with persistent CSF leak, hardware failure, and neurological injury (Table 45.1). Risk factors for postoperative complications are associated with advanced age, preoperative radiotherapy, multilevel spinal metastasis, and the burden of comorbidities. Proper risk stratification involves evaluation of

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Table 45.1 Common postoperative complications and management

Adverse event	Risk factors	Management strategy
Surgical:		
Hardware failure	Preoperative radiation, osteopenia/osteoporosis, rib resection, >6 instrumented segments	Identify high risk patients, use of fenestrated screws, PMMA vertebral augmentation, increase number of instrumented levels
Durotomy and persistent CSF leak	Previous surgery or irradiation, size and location of durotomy	Repair primarily with autologous graft, dural substitute, fibrin glue; place lumbar drain, subfascial epidural drain management, positioning; local vascularized, myocutaneous flap closures
Wound complications	Previous surgery or irradiation, instrumentation, DM, smoking, chronic steroids, low serum albumin, obesity, age, neurological disability	Modify preoperative risk factors, *Infection prevention*: Preoperative antibiotics, application of intrawound vancomycin powder, treatment: Systemic antibiotics, packing or wound VAC, reoperation with local vascularized, myocutaneous flap closures
Neurologic deficit	Coagulopathy, multilevel spinal surgery	Identify etiology, imaging, critical care setting, epidural hematoma evacuation, blood pressure augmentation, possible steroids
Intra−/postoperative hemorrhage	Thombocytopenia, coagulopathy, bone marrow suppression, highly vascularized tumor	Preop risk assessment: Thrombocytopenia/coagulopathy, use of anti-thrombotic, preop angiography +/− embolization
Medical:		
Thromboembolism: PE DVT	Immobility, vasculopathy, coagulopathy	*Prevention*: Patient assessment for coagulation test and reviewing medical history, placement of IVC filter, pneumatic intermittent compression and compression stockings, postoperative pharmacological prophylaxis. *Treatment*: Observation and thrombolytic therapy LMWH. Thrombectomy in massive PE

CSF cerebrovascular fluid, *PMMA* polymethylmethacrylate, *DM* diabetes mellitus, *VAC* vacuum-assisted closure, *PE* pulmonary embolism, *DVT* deep venous thrombosis, *IVC* inferior vena cava, *LMWH* low molecular weight heparin

each individual patient's medical and surgical history, co morbidities, and physical exam prior to offering surgical intervention.

Intraoperative and Postoperative Hemorrhage

Multiple factors affecting intraoperative tumor bleeding must be carefully considered prior to proceeding with surgical management of metastatic spine tumors. Among these are thrombocytopenia, coagulopathy, bone marrow suppression, and factor deficiencies. These same risk factors contribute to the likelihood of postoperative hematomas. Effectively addressing these concerns requires a multidisciplinary approach with hematology and oncology among others. Coagulopathies can result from factor deficiencies, clotting disorders, hepatocellular carcinoma, or large metastatic tumor burden in the liver. Thrombocytopenia due to blood count nadirs following treatment with certain chemotherapeutics or bone marrow suppression secondary to wide-field radiation or significant metastatic disease should be identified and remedied prior to surgery. While medications that cause thrombocytopenia can often be held until counts return, marrow suppression may ultimately be a contraindication to surgery. Bone marrow biopsy may be a helpful diagnostic adjunct to determine the etiology, severity, and implications of failed synthesis.

Certain metastatic tumors pose increased risk of intraoperative hemorrhage that may prove challenging to control or result in high blood loss during surgery. Tumor histologies incorporating "angio" or originating from vascular organs such as the thyroid, liver, or kidney are often highly vascular. Performing preoperative digital subtraction angiography assists with determining the extent of tumor vascularization, identifying

vascular anatomy including significant feeding vessels, and potentially embolizing the tumor to decrease intraoperative hemorrhage [4, 5]. Tumors with deep contrast blushes are more vascular and should be considered for embolization with particles (polyvinyl alcohol), liquid embolics (NBCA) and/or platinum coils. Vascular anatomy should be considered carefully during the diagnostic phase in order to avoid the artery of Adamkiewicz or radiculomedullary feeders prior to making the decision to embolize. Reductions in intraoperative blood loss of 50% have been demonstrated following effective embolization [6, 7]. Patients should undergo surgery between 24 and 72 hours following embolization or there is risk of tumor revascularization [8]. By identifying risk factors for hemorrhage and performing tumor embolization, surgeons may reduce blood loss, decrease surgical time, prevent transfusions, and avoid hypotensive episodes.

Postoperative hemorrhage is an additional worry in patients with metastatic spine disease. In patients who undergo large decompressions and reconstructions, there is significant potential space. As such, hematoma development can cause new neurologic injury given the now-decompressed thecal sac. This complication can be minimized by preoperative and intraoperative techniques. Preoperatively, the patient should be optimized hematologically and poor surgical candidates should not be offered surgery. Intraoperatively, meticulous hemostasis, drain use, and closure of dead space (see later chapters in this book related to complex wound closure) represent important surgical techniques.

Wound Infection and Dehiscence

Reported complication rates for patients undergoing surgery for spinal metastases are higher than for equivalent surgeries for nontumor indications [9, 10]. Surgical site infections (SSI) are the most common complication after instrumented spinal metastasis surgery and are associated with prolonged hospital stay as well as increased morbidity and mortality [9–11]. Risk factors contributing to SSI include spinal instrumentation, previous radiation, reoperation, diabetes, smoking, systemic therapy (e.g., steroids, immunosuppressive adjuvant therapy), neutropenia, low serum albumin level, higher number of fused vertebrae, intraoperative bleeding in excess of 2000 ml, obesity, age, neurological disability and ASA >3 [11–14]. *Staphylococcus aureus*, including methicillin-resistant organisms (MRSA), is the leading isolated pathogen causing infection in these patients and is estimated to account for 50% of cases [10]. Additional common pathogens include Streptococci, *Enterococcus faecalis*, *Psuedomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae* [10]. *Propionibacterium acnes* is a low virulence, anaerobic bacteria, comprising skin flora, however, is an underestimated cause of SSI. It may be the most common cause of *late* postoperative infections in implantable devices and has been reportedly involved in up to 45% of spinal implant infections [15]. The management of severe SSI caused by *P. acnes* generally involves antimicrobial treatment including long-term suppression. The treatment of spinal implant infection is variable. While debridement, washout, and local flap closure with well-vascularized muscle are generally the treatment of choice, there may be cases where implant removal is necessary [16, 17]. Preventing SSIs during the index procedure is the preferred strategy. Prophylactic antibiotic dosing within 1 hour of incision, in addition to applying vancomycin powder directly into the wound prior to closure have proven to be effective in SSI prevention [18, 19]. Regional application of Vancomycin powder before wound closure has been shown to decrease the rate of SSI [18, 20]. Several cohort studies have demonstrated the effect of vancomycin in SSI reduction in thoracolumbar fusion surgery [20, 21], posterior fusion after trauma [18], and posterior surgical decompression and fusion surgeries [22]. Godil et al. [23] found a significant improvement in the rates of SSI by using intrawound vancomycin (13% vs. 0%). In addition, this study also showed that the cost of treating postoperative infections was significantly reduced by the use of vancomycin powder.

One approach to address wound complications prophylactically is the use of soft tissue reconstruction techniques during the index

surgery. Patients with spinal instrumentation undergoing revision surgery, those undergoing surgery in a previously irradiated field, smokers and those with diabetes may be appropriate candidates. The strategy, often coordinated with plastic surgery, is to mobilize well-vascularized local muscle flaps to close potential dead space and provide vascularized coverage to spinal instrumentation. Chang et al. demonstrated a decreased incidence of wound complications from 45% to 20% with such an approach [24]. A group from MD Anderson compared their rate of major wound complications when using this prophylactic strategy and found a decrease from 38% to 12% [25].

For patients returning with suspected SSI, it is important to determine whether it is located in a superficial or deep (to the paraspinal muscle fascia) compartment. While superficial infections may be effectively managed with a course of antibiotics, wound packing or wound vacuums, deep infections can require more aggressive treatment. Moreover, deep infections can cause osteomyelitis, discitis, epidural abscesses with compression of the neural elements and colonization of the hardware. Patients presenting with high suspicion for infection based on pain, erythema, tenderness to palpation, fluid collection, or drainage from wound should have a vitals and labs including complete blood count, ESR, CRP, pro-calcitonin, and cultures sent. High suspicion should prompt an MRI with gadolinium contrast. Contrast enhancing collections can be aspirated under image guidance in order to obtain gram stain and culture. Based on these results, surgical intervention including drainage, wound debridement, placement of drains and plastics-assisted closure should be considered (Fig. 45.1), [26–28]. The selection of antibiotic agents and duration of treatment should be determined by an infectious disease specialist. Patients are generally treated with intravenous broad-spectrum antibiotics until a pathogen is identified from culture and then treatment is narrowed.

Patients that have had prior radiation, particularly conventional, and/or treatment with certain chemotherapeutic agents, such as bevacizumab, may develop wound complications in a more delayed fashion [24, 27]. For complex failures where local tissue is of questionable viability, specialized closure techniques including local muscle advancement, rotational or transpositional tissue flaps may be necessary in order to increase the vascularity and tissue coverage over the defect. In addition to reducing dead space and preventing seroma cavities, procedures that relocate vascularized tissue can provide necessary hardware coverage, facilitate wound healing, and accelerate bacterial clearance [29]. Flap closure has been shown to decrease both the number of debridements as well as to decrease the need to remove hardware [30].

CSF Leak

Surgical approaches to spinal metastases frequently involve resecting tumor in a circumferential fashion from the epidural space with the potential need to sacrifice a nerve root. These maneuvers can result in unintended durotomy with subsequent cerebrospinal fluid (CSF) egress. CSF leaks occur in spine surgery at a reported incidence of 0.3–35% [31–33]. Complications resulting from CSF leak include positional headache, pseudomeningoceles, meningitis, arachnoiditis, CSF fistula through the dermis, neurological symptoms resulting from nerve root or spinal cord compression, failed wound healing, and surgical site infection [34, 35].

Successful management of durotomies is related to both the size and early detection of the defect. Small durotomies detected intraoperatively should be closed primarily and may be augmented with fibrin sealants, fat, muscle or fascial grafts or gelatin sponges. When sacrificing a nerve root, it should be performed proximal to the dorsal root ganglion and ligated with silk suture or vessel clips where the root diverges from the common dural sac. Closures can be challenged intraoperatively by requesting a Valsava maneuver from the anesthesiologist to determine whether they are water tight and durable.

Larger durotomies may require dural grafts to be sutured to native dural margins to form a

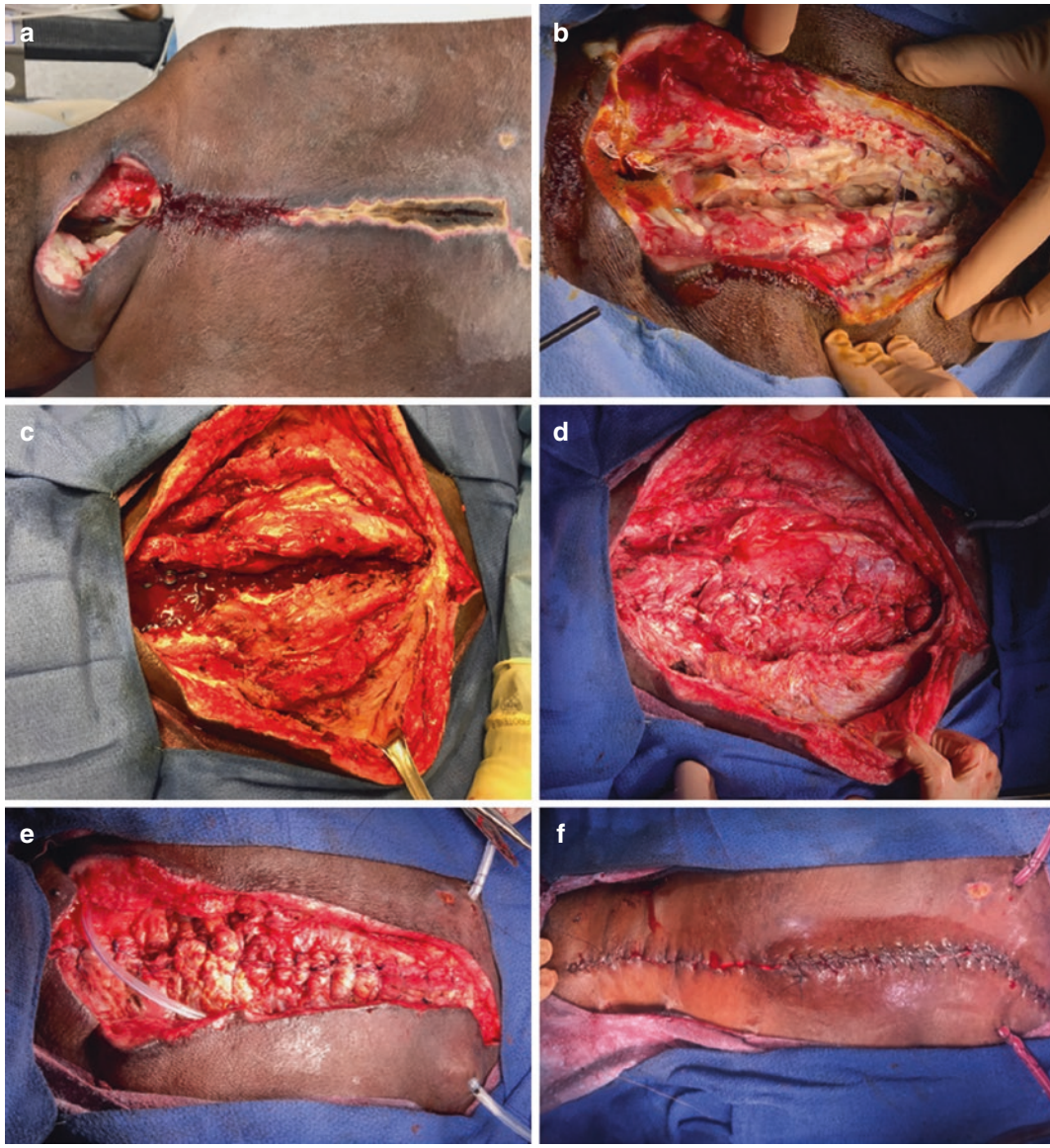

Fig. 45.1 Wound reconstruction with local muscle flap. (**a**) Wound infection at the cervicothoracic junction with dehiscence and exposed hardware. (**b**) Incision is reopened prior to debridement of necrotic tissue. (**c**) Paraspinous musculature and trapezius are dissected and elevated bilaterally. (**d**) Paraspinous muscles are advanced toward the midline and imbricated to cover the overlying dead space between vertebrae and instrumentation. (**e**) Subcutaneous drains are placed between the paraspinous muscle layers and in the epidural subfacial space. The trapezius muscles are approximated. (**f**) Skin is closed and drains are secured

patch. Dural substitutes are made of a variety of materials including bovine pericardium, porcine intestinal mucosa or processed collagen matrices. The suture line can then be covered with fibrin glue. In difficult-to-access regions, such as anterior defects encountered during posterior approaches, other onlay strategies may be employed. These consist of dural slings made of dural substitutes, fascia lata, muscle, gelatin sponges, fibrin sealants with or without buttressing by hardware, interbody grafts, or other implants. Location of drains and whether or not

they are placed to suction is a matter of debate. In a series of 25 patients undergoing intentional durotomy and placement of subfascial epidural drain, no patient developed postoperative CSF cutaneous leak, symptomatic pseudomeningocele, or complication associated with closed suction drains [36]. Alternatively, epidural drains can be placed to passive or gravity drainage if there is concern for the integrity of the dural repair. Tenuous dural closures may benefit from placement of a lumbar drain intraoperatively with postoperative drainage and positional restrictions. This is discussed in greater detail below.

Postoperative detection of CSF leaks is of equal importance. Patients presenting with postural symptoms of headache, dizziness, nausea and vomiting that resolve when recumbent should be approached with suspicion. Further indicators include persistent high output clear drainage from wound drains, clear fluid from the wound or blottable collection. More severe intrathecal hypotension may result in hygromas, subdural hematomas, and cerebellar tonsillar descent to the foramen magnum. Postoperative neurological symptoms resulting from compression secondary to pseudomeningocele and meningitis should also be ruled out. MRI may be useful to detect CSF collections, determine if they are exerting mass effect, and whether they are communicating with the intrathecal space. MRI studies of the brain will demonstrate pachymeningeal enhancement in the setting of intracranial hypotension [37].

With symptomatic CSF leaks, placement of lumbar drains and positional restrictions with bed rest should be considered. If CSF is draining through the wound, the wound can be oversewn [38]. The decision to put a patient on bed rest generally remains surgeon preference. Indeed, Gautschi et al. demonstrated that in a mixed population 175 spine surgeons, 14.9% do not use bed rest, 35% endorse 24-hr bed rest, 28% endorse 48-hr bed rest and 6.3% use 72-hr bed rest [39, 40]. Drainage parameters range from 5 to 15 cc/hr for 4–5 days. This was reported to be effective in 83–100% of cases [41–44]. While patients with leaks occurring in the distal thoracic or lumbar spine are generally placed flat while on bed rest, patients with proximal thoracic or cervical leaks are kept upright [31]. In complex cases refractory to conservative treatment, revision surgery may be the necessary management strategy in order to prevent postentially severe delayed sequelae: the formation of chronic fistula, pseudomeningocele, and delayed wound healing [45].

Hardware Failure

Hardware failure is the second most common adverse event that necessitates reoperation [46]. This complication is characterized by broken rods, cage migration, loosened or pulled out screws, and displacement of implanted hardware requiring revision surgery. Previous radiation therapy is the most significant risk factor associated with hardware failure [47]. Other risk factors include extensive tumor involvement of the pedicle and vertebral body, prior or concomitant rib resection leading to chest wall instability, instrumentation construct involving more than six vertebral segments [48], poor bone quality associated with metastatic involvement, and postmenopausal or androgen-blockade-induced osteoporosis [49]. Metastatic tumor histology also contributes to the risk of hardware failure. Among symptomatic hardware failure patients, breast, and prostate cancer represent the most common source of primary tumors, while lung cancer was the most common in the group of patients who did not suffer from hardware failure [47]. Of note, the same study revealed that survival time for patients without hardware failure is twice as long as for patients with hardware failure.

Hardware failure requires revision surgery if the patient becomes symptomatic. Strategies to prevent screw loosening (Fig. 45.2a, b) or pullout include cement augmentation of pedicle screws with polymethyl methacrylate (PMMA) in the thoracic and lumbar spine (Fig. 45.2b, c) [50–52]. Recently, fenestrated screws through which cement can be injected into the vertebral body have been approved by the US Food and Drug Administration (FDA) [53]. This technique can serve as an anchor to increase screw pull out strength and may also ward off vertebral body compression fractures. Additionally, extending

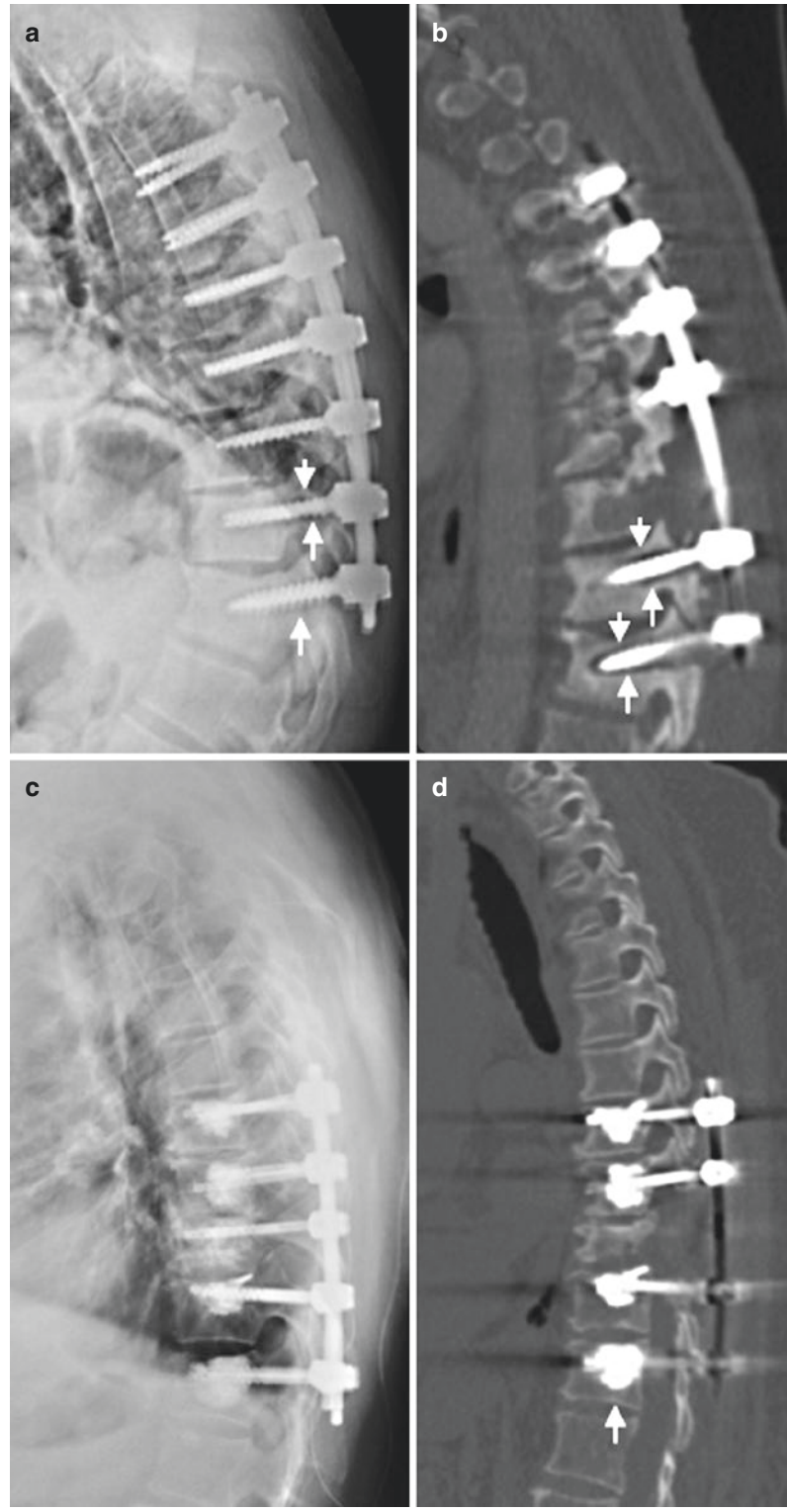

Fig. 45.2 Hardware failure and cement augmentation via fenestrated pedicle screws. (**a**, **b**) T5 – T11 posterior spinal fusion with T9 transpedicular decompression for metastatic renal cell carcinoma. (**a**) Lateral radiograph obtained on routine follow up demonstrates regions of lucency around right T10 and T11 pedicle screws (*arrowheads*) prompting follow up CT. (**b**) Sagittal CT confirms osteolysis around right T10 and T11 pedicle screws. (**c**, **d**) T8 – T12 posterior spinal fusion with T10 transpedicular decompression for metastatic lung adenocarcinoma in osteoporotic patient with metastases at adjacent segments. (**c**) Lateral radiograph showing multi-level cement augmentation through fenestrated pedicle screws. (**d**) Sagittal CT demonstrates extent of PMMA cement around the tip of pedicle screw in attempt to prevent screw loosening as well as vertebral body compression fracture (*arrow*)

construct length to two or more levels below and above vertebrae infiltrated with tumor for posterior-only approaches may mitigate the risk of future hardware failure. Where possible, inclusion of anterior column support in the reconstruction process may be useful as 360-degree stabilization distributes axial loading forces and decreases the likelihood of future hardware failure.

Venous Thromboembolism (VTE)

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), represents one of the most significant causes of morbidity and mortality in cancer patients with a prevalence ranging from 0.3% to 15.5% [54]. The preoperative prevention and early detection of thrombosis including, screening and assessment of coagulation cascade is necessary for early intervention and risk stratification. Placement of inferior vena cava (IVC) filter in spinal metastasis patients with positive ultrasonographic screening for DVT has significantly reduced the incidence of postoperative PE associated with DVT [55]. In addition to IVC filter, placement of mechanical devices such as pneumatic intermittent compression boots and compression stockings has also reduced the rate of postoperative DVT [55, 56]. Postoperative prophylactic subcutaneous unfractionated heparin is critical in this population and can be used safely without significantly increased risk of postoperative hemorrhage [57]. In patients diagnosed with acute postoperative PE who are hemodynamically stable, clinical observation may be sufficient. However, should patient become hemodynamically unstable, thrombolytic therapy or mechanical pulmonary thrombectomy should be considered to prevent complications such as cardiopulmonary arrest [58].

Neurological Deterioration

Neurologic deterioration after spinal surgery is a potential complication and has an incidence of 2–4% [59]. Epidural hematoma should be suspected in patients with a rapidly declining neurological examination and can be confirmed with imaging. This is an operative emergency and the patient should be taken for evacuation and decompression immediately to optimize neurologic recovery [60]. In patients who emerge from anesthesia with radicular pain or neurologic deficit, imaging should be acquired immediately to rule out misplaced hardware, compressive lesion, overcorrection, or malalignment. Spinal cord infarcts are rare in this patient population but if suspected, MRI with perfusion and diffusion imaging can be used for diagnosis with subsequent blood pressure management in the ICU setting. Finally, in patients who sustained a change in intraoperative neurophysiological monitoring and wake with a neurological deficit that has no other etiology confirmed with imaging, intensive care should be pursued. Mean arterial pressure goals greater than 85 mm Hg and possible steroid administration can be considered for 5–7 days [61–63].

Conclusion

The high incidence of spinal metastatic lesions calls for a thorough understanding of surgical treatment strategies as well as complication recognition and management in order to optimize patient outcomes. Surgical treatment is employed as a palliative measure to alleviate pain, improve function, and optimize quality of life in symptomatic patients. Minimizing morbidity associated with complications is critical in this patient population. Complications can be categorized into medical such as DVT, pneumonia, and wound infection. Surgical complications include excess intraoperative bleeding, postoperative hematoma, wound dehiscence, CSF leak, and hardware failure. Individual patient risk profiles should be constructed based on comorbidities and prognosis should be carefully considered prior to offering surgery. Based on risk assessment, some patients may benefit from open surgery while others may be more appropriate for minimally invasive or percutaneous approaches. Still others may not be appropriate

surgical candidates and most appropriately treated with chemotherapy and/or radiation alone. Careful preoperative optimization with attention to risk mitigation facilitates desirable postoperative outcomes. Finally, early recognition of postoperative complications is the first step in effective management and will serve to minimize long-term morbidity in this vulnerable patient population.

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46 Vertebral Augmentation Procedures for Treatment of Pathologic Vertebral Body Fractures

Justin Schwarz, Alejandro Santillan, Adham Mushtak, and Athos Patsalides

Introduction

The spine is a common site for metastasis in cancer patients, and spinal metastases are observed in approximately 60–70% of patients with systemic cancer [1]. In the United States alone, more than 350,000 cases of bony spinal metastasis are reported each year due to prostate, breast, kidney, lung, and thyroid cancers [2]. Symptomatic pathologic vertebral compression fractures (VCF) can be debilitating for patients, causing pain that significantly affects quality of life. As with osteoporotic compression fractures, pathologic fractures historically have been treated conservatively with pain medication and bracing [3]. While conservative treatment is adequate for some patients, others continue to suffer from debilitating pain that affects their ability to care for themselves, live independently, and significantly decreases their quality of life. Depending on the degree of tumor invasion of the vertebral body, these malignant fractures can significantly worsen with conservative measures alone, leading to fracture progression, exacerbation of pain, or compression of neural elements that can cause neurologic deficits. Vertebral augmentation procedures (VAP) are minimally invasive treatment options which have been shown to reduce pain, improve mobility, and stabilize vertebral bodies in patients with refractory back pain from pathologic compression fractures [4].

Procedural Details

Vertebroplasty and kyphoplasty are effective percutaneous minimally invasive techniques for treating pathologic VCF and ameliorating symptoms [4]. In both procedures, polymethylmethacrylate (PMMA) is injected into the fractured bone where it hardens and congeals the fracture fragments, providing immediate stability and pain relief [5–7]. Kyphoplasty includes an additional step prior to PMMA injection where a balloon is gently inflated within the fractured vertebral body to create a cavity for the PMMA and restore vertebral body height [8].

VAP is most efficiently performed using biplane fluoroscopy but can also be performed using single-plane fluoroscopy in either an interventional procedure room or a traditional operating room. Patients are placed in the prone position on the procedure table prior to the administration of moderate sedation or following endotracheal intubation and administration of general anesthesia. Pressure points including the forearms,

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elbows, knees, and abdomen are appropriately secured and supported (Fig. 46.1a). Patients are sterilely prepped in typical fashion, and a single dose of perioperative intravenous antibiotics is administered just prior to the procedure (Fig. 46.1b).

VAP are minimally invasive percutaneous procedures that only require one or two small skin incisions per treated vertebral body level, depending upon if a unilateral or bilateral approach is utilized (Fig. 46.1c). Intermittent fluoroscopy is used to direct a narrow cannula (10-gauge) from a posterior approach through the skin and soft tissues and into the fractured vertebral body. The cannula is directed through or just lateral to the corresponding vertebral body's pedicle so that the center of fractured vertebral body is ultimately reached (Figs. 46.2d, e and 46.3e). The trajectory of the cannula is carefully chosen to ensure that the neural elements, neuroforamen, and spinal canal are not encountered. This minimizes the risk of direct neural element injury or cerebrospinal fluid leak, both of which are exceedingly rare but potential complications. Once the cannulas are appropriately positioned, core biopsies of the fractured vertebral body are collected so that tissue can be sent for pathologic and histologic analysis, especially for patients with questionable cancer recurrence or a new cancer diagnosis (Fig. 46.2e). Then, for patients undergoing kyphoplasty, balloons are placed into the vertebral body and carefully inflated under fluoroscopy (Fig. 46.2f). After balloon inflation for kyphoplasty or just after cannula placement for vertebroplasty, PMMA is injected into the fractured vertebral body (Figs. 46.2g and 46.3f). PMMA injection proceeds under fluoroscopy to prevent an inadvertent leakage of cement out of the vertebral body, either into venous structures or into the spinal canal. If this situation is encountered, cement injection is stopped immediately. Following the successful injection of PMMA, the cannulas are removed and sterile dressings are applied.

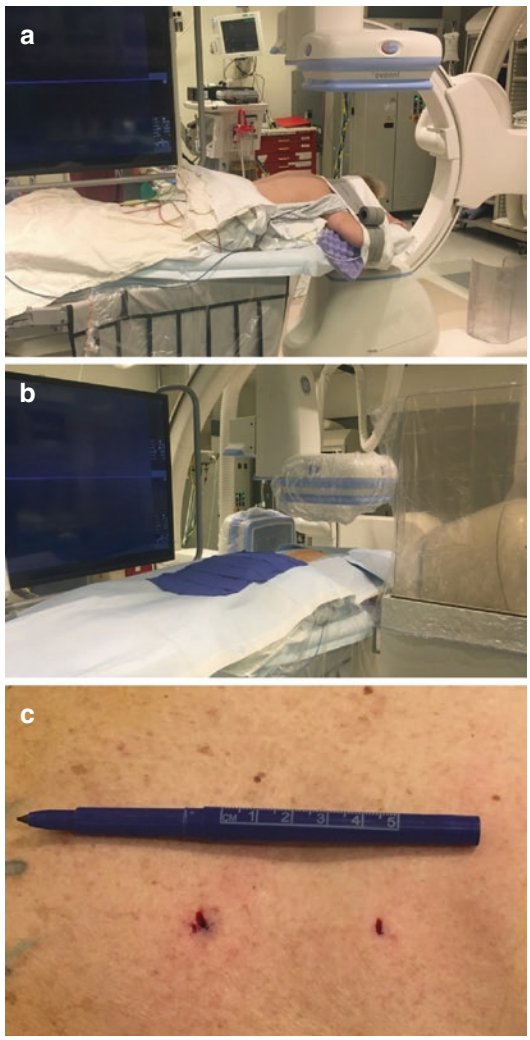

Fig. 46.1 (**a**) Prone positioning for VAP with pressure points adequately padded. (**b**) Sterilely prepped and draped patient. (**c**) VAPs require small incisions

Post-Procedural Care

The postoperative care for VAP is limited, and an emphasis is placed on early mobilization. Patients are encouraged to ambulate as much as reasonably possible in order to prevent complications from inactivity, such as pneumonia and deep venous thromboses. However, patients are counseled to avoid strenuous activity, lifting objects over 5–10 pounds, and excessive bending or twisting until they are seen at their follow-up appointment 2 weeks following VAP. Patients with lower thoracic and lumbar VCF are encouraged to use a thoracic lumbar sacral orthosis

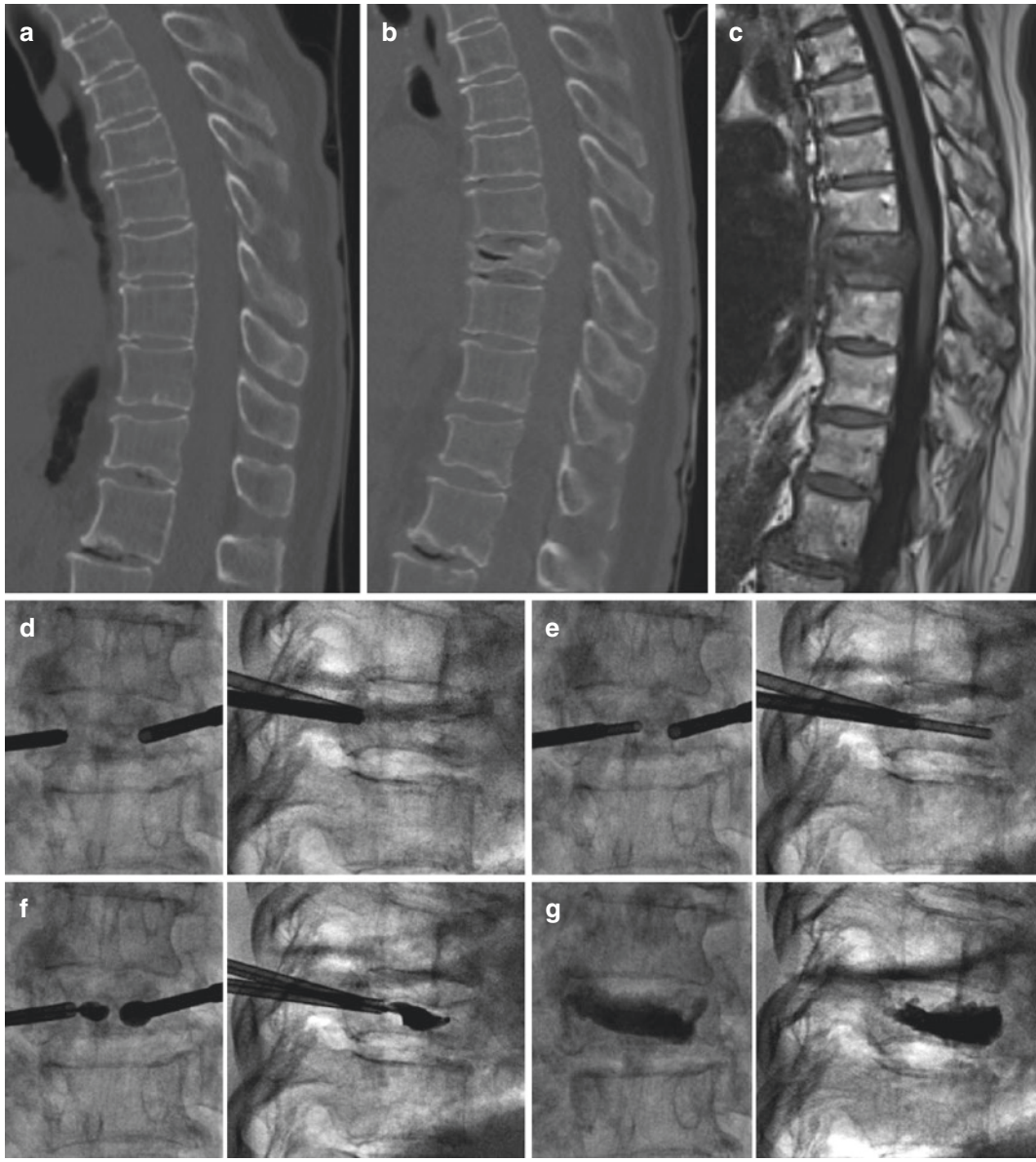

Fig. 46.2 Pathologic T8 VCF from lung adenocarcinoma. (**a**) Non-contrast CT sagittal pre-VCF. (**b**) Non-contrast CT sagittal post-VCF. (**c**) MRI sagittal T1 without contrast demonstrates T8 tumor infiltration. (**d**) Bilateral transpedicular VAP approach to T8 VCF with 10-gauge cannulas. (**e**) Left unilateral core biopsy needle in place in T8 vertebral body. (**f**) Bilateral balloon inflation for T8 kyphoplasty. (**g**) T8 post-kyphoplasty

(TLSO) for 2 weeks following vertebroplasty or kyphoplasty when ambulating, but not while sitting or lying down. These procedures do not require an extensive hospital stay and are usually performed as an outpatient, with patients leaving 1–2 hours after the completion of the procedure. There is also minimal postoperative incisional care required. The procedural sterile dressings are typically removed 24–48 hours after the VAP, and the small incisions can remain uncovered after that time. Patients are instructed to avoid any submerging of the incisions, but they are encouraged to shower normally after the dressings are removed. VAP also minimizes the time

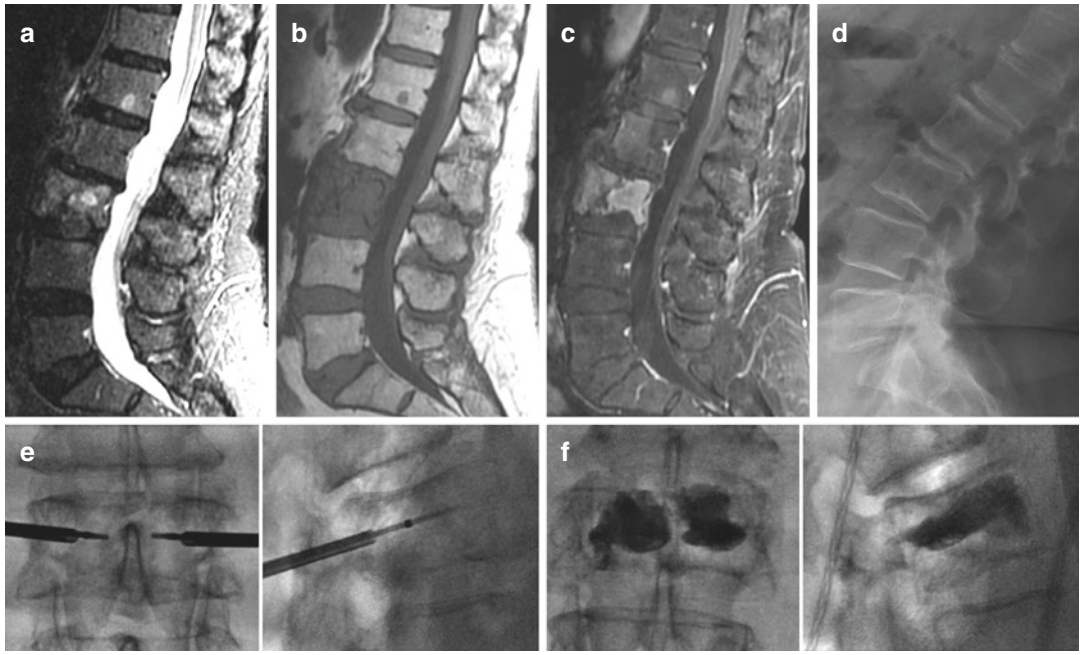

Fig. 46.3 Pathologic L3 VCF from breast adenocarcinoma. (**a**) MRI sagittal T2 STIR hyperintensity within L3 suggests an acute to subacute fracture. (**b**) MRI sagittal T1 without contrast demonstrates L3 tumor infiltration. (**c**) MRI sagittal T1 with contrast demonstrates typical tumor enhancement. (**d**) Frontal and lateral X-rays are inadequate to demonstrate VCF or tumor infiltration. (**e**) Frontal and lateral fluoroscopy demonstrates bilateral transpedicular approach with bilateral radiofrequency ablation probes. (**f**) Post-vertebroplasty of L3 pathologic VCF

that patients need to be off of their antiplatelet or anticoagulation medication. These procedures can be performed while patients are on single antiplatelet therapy, such as aspirin. Dual antiplatelet therapy and anticoagulation are typically held prior to the procedure but can be resumed on postoperative day 1.

Anesthesia Care

VAP is performed with the assistance of an anesthesiologist and is typically performed under monitored anesthesia care (MAC) with generous use of local anesthetic to minimize the amount of sedative medications required. Endotracheal intubation with general anesthesia is used in select patients where MAC is not appropriate. MAC is used for relatively healthy and cooperative patients undergoing a one- or two-level kyphoplasty or vertebroplasty. General anesthesia is used if three or more vertebral levels are being treated, the patient is unable to cooperate, or systemic medical issues necessitate endotracheal intubation with general anesthesia.

Patient Selection

As with any other invasive treatment, patient selection is important. VCF with symptoms that are not adequately controlled on oral pain medications are considered for kyphoplasty or vertebroplasty. The typical presentation of a symptomatic pathologic compression fracture is an acute onset of mechanical back pain that roughly correlates with the vertebral level of the VCF.

Pain Quality and Characteristics

Pathologic compression fractures cause significant pain due to the relative instability of the fractured vertebral body. This pain is often intensified

with any axial loading of the compression fracture and brought on by movement. VCF pain is typically experienced in the region of the fracture. For instance, a lower thoracic pathologic compression fracture will cause pain in the lower thoracic region corresponding to the fractured level. Sometimes this pain can be reproduced on physical examination by palpation of the midline at the level of suspected fracture. It is common for patient with pathologic VCF to also have significant pain from spasm of the paraspinal muscles. This pain is often described as sharp and episodic and travels rostrally and caudally just lateral to midline. It does not directly improve following VAP because it is muscular in etiology. Muscle spasm pain is typically improved by muscle relaxant medications and by increasing physical activity. Patients with symptomatic compression fractures may also experience radicular pain at the associated level, especially for thoracic compression fractures. The loss of vertebral body height can cause irritation of the associated nerve roots leading to pain that can radiate in a radicular distribution to the anterior chest wall. Less frequently, this can occur in the lumbar spine, leading to radicular pain in the corresponding nerve root distribution into the legs.

Diagnosis

Many patients who suffer from pathologic VCF have multiple medical comorbidities, such as arthritis, spinal stenosis, or other bony or visceral metastases that may make the assessment of pain difficult. In such cases, it may be difficult to determine if a newly diagnosed compression fracture is truly symptomatic. A thorough clinical history is necessary to determine if a VCF is the etiology of a patient's pain. Determining the chronicity of symptoms and correlating the clinical history with physical exam and radiographic findings are important. A dedicated spinal CT or MRI is preferred for diagnosis (Figs. 46.2a–c and 46.3a–c). Plain X-rays are inadequate for proper diagnosis but have limited utility as an initial screening tool (Fig. 46.3d). The chronicity of injury can be determined by comparing current imaging with past radiologic studies, including previous X-rays, CT, or MRI (Fig. 46.2a–c). If no comparison imaging is available, an MRI is obtained to determine acuity of the fracture. Short tau inversion recovery (STIR) hyperintensity within the vertebral body of interest suggests a relatively recent fracture and identifies a vertebral body that is amenable to intervention (Fig. 46.3a). Subacute and acute compression fractures respond well to VAP, whereas chronic fractures are unlikely to have a favorable response. Pathologic fractures or at risk vertebral levels can be identified by regions of T1 hypointensity, which is typically exceptionally sensitive at identifying tumor infiltration (Figs. 46.2c and 46.3b).

Contraindications

Vertebroplasty and kyphoplasty are typically reserved for patients with pathologic VCF that are mechanically stable and are not causing symptomatic spinal cord or nerve root compression. Patients with unstable fractures do not have significant pain relief following VAP and usually require surgical stabilization. A qualified practitioner, such as a neurosurgeon or an orthopedic spine surgeon, should be consulted if there is any uncertainty about the mechanical stability of a VCF. Retropulsion with symptomatic cord, conus medullaris, cauda equina, or nerve root compression is an absolute contraindication to VAP. These patients require open surgical intervention for decompression of the neural elements and possible stabilization. VAP in these circumstances may worsen the compression of neuronal structures in these patients and worsen their neurologic status. Asymptomatic patients with retropulsion are still candidates for vertebroplasty. In this patient population, PMMA injection is performed cautiously to avoid any worsening of retropulsion into the spinal canal and prevent any neurologic deterioration. Other absolute contraindications to VAP include active osteomyelitis at the fracture area or an allergy to polymethylmethacrylate. Patients being considered for VAP should not be thrombocytopenic, leukopenic, or coagulopathic at the time of the

procedure because these clinical scenarios increase the risk of post-procedural hematoma or infection. Typically, these situations can be addressed by waiting for the patient's leukopenia or thrombocytopenia to resolve following chemotherapy administration. If this is not possible, transfusion or administration of bone marrow stimulant medications can be considered. These situations require direct communication between the interventionist, primary care team, and oncologist to determine the best course of action.

Potential Complications

The risk of VAP is exceptionally low, and the potential benefit of these procedures is significant [4]. There is a risk of infection in VAP, as with any surgical procedure, but the risk of infection in VAP has consistently been reported to be less than 1% [9]. While the rate of infection is low, an infection involving PMMA can result in substantial morbidity and necessitate extensive surgical procedures, including laminectomies, corpectomies, and spinal fusions [10]. The majority of patients with post-VAP infections have a recent preoperative history of infection, including osteomyelitis, discitis, or urinary tract infections [11]. Therefore, patients must be carefully evaluated preoperatively to rule out any active infective processes prior to consideration of VAP. The leakage of PMMA outside of the vertebral body is not uncommon, but it is usually not of clinical significance [12]. Leakage of PMMA into the surrounding soft tissues or the intervertebral disc space is typically asymptomatic [13]. PMMA can travel into venous structures and lead to pulmonary embolism, but the risk of a symptomatic PMMA pulmonary embolism is exceedingly low [14]. Post-procedural hematoma or PMMA leakage into the neuroforamina or spinal canal can also occur, but these are rarely symptomatic [15, 16].

Treatable Vertebral Levels

Fractures involving T5 through the lumbar spine are amenable to VAP because the vertebral anatomy is easily visualized using frontal and lateral fluoroscopy for these levels. In certain situations, T3 and T4 can be visualized well enough to attempt VAP, but this is dependent upon the patient's body habitus and anatomy. In these situations, the operator will often not know if the T3 or T4 level can be successfully visualized to perform VAP until the patient is positioned. Pathologic cervical fractures are usually not treated with VAP, but these procedures can be utilized in certain situations, especially for pathologic fractures of C2 [17–19]. Symptomatic sacral metastases can also be treated with VAP, but it is much less common than treatment for lumbar and thoracic spine metastases [20].

Kyphoplasty and Vertebroplasty Results

Multiple studies have demonstrated that vertebroplasty and kyphoplasty are well tolerated, provide pain relief, and improve functional outcomes in patients with painful neoplastic spinal fractures. A single randomized study of 134 patients with bone metastases resulting from solid tumors and multiple myeloma demonstrated that treatment of VCF with kyphoplasty was associated with durable and clinically meaningful improvements in physical functioning, back pain, and quality of life when compared to nonsurgical management [21]. A meta-analysis of seven nonrandomized studies of patients with multiple myeloma or osteolytic metastasis revealed that kyphoplasty was associated with reduced pain and improved functional outcomes, which were maintained up to 2 years postprocedure. Kyphoplasty also improved early vertebral height loss, but these effects were not long term [22]. Similarly, a retrospective review of 67 patients with multiple myeloma-related VCF demonstrated that vertebroplasty provided clinically meaningful improvements in physical functioning, pain, and mobility throughout a year of follow-up [23]. Several small nonrandomized studies of VAP including kyphoplasty and vertebroplasty have generated comparable results [24–26]. The role of vertebroplasty for patients with myeloma, however, remains debatable in the absence of prospective data because two random-

ized trials failed to show any benefit with vertebroplasty in patients with osteoporotic fractures versus conservative therapy [27–29]. Furthermore, a meta-analysis of 59 studies, including 56 case series, showed that kyphoplasty seemed to be more effective than vertebroplasty in relieving pain secondary to cancer-related VCF [30]. These results taken in aggregate suggest that kyphoplasty should be performed for symptomatic pathologic VCF when possible. Vertebroplasty is potentially useful in situations where kyphoplasty is contraindicated, such as in patients with VCFs associated with significant retropulsion or neural element compression.

Radiofrequency Ablation

Radiofrequency ablation has been proposed as a stand-alone and adjuvant therapy to vertebroplasty and kyphoplasty. RFA utilizes a high-frequency alternating current that is passed from a needle electrode into the surrounding tissue, resulting in heating and eventual coagulative tissue necrosis [31]. Some reports have suggested that combined RFA and vertebroplasty is a safe and efficacious procedure for not only pain management but also local tumor control in spinal metastasis [32]. While RFA and vertebroplasty are independently effective in pain palliation in spinal metastasis, some studies suggest that the combination of RFA and vertebroplasty may have a synergistic effect on pain management [33–41]. The majority of these studies are single-arm observational studies, and there is a need for additional studies evaluating combined RFA and VAPs for efficacy in regard to pain relief and local tumor control.

Conclusion

Pathologic VCFs are relatively common in cancer patients and are often painful and potentially debilitating for patients. Their prompt diagnosis and treatment is essential. Vertebroplasty and kyphoplasty are minimally invasive procedures that can significantly improve the quality of life and functional status of patients suffering from pathologic VCFs with minimal risk. Radiofrequency ablation is a promising adjuvant or stand-alone therapy for pathologic VCFs for pain control and local tumor control, but this treatment modality needs additional prospective studies to confirm its efficacy.

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Spinal Laser Interstitial Thermal Therapy for Metastatic Tumors

47

Linton T. Evans, Rafael A. Vega, and Claudio E. Tatsui

Introduction

Metastatic epidural spinal cord compression (MESCC) is a significant source of morbidity and impairment in quality of life in individuals with cancer [1]. Approximately 40% of patients with a systemic malignancy will develop spinal osseous metastases, and up to 10% present with symptomatic spinal cord compression [2]. Not all tumors exhibit the same predilection or tropism for bone; frequent offenders include prostate, lung, and breast carcinoma followed by lymphoma, renal cell carcinoma, and multiple myeloma. The distribution of metastases along the spinal axis reflects the relative bone mass of each segment and the regional blood flow. Most spine metastases are found within the thoracic spine (60%) followed by the lumbosacral (25%) and cervical spine (15%). Multiple synchronous sites of disease in the spine are common, an important fact to consider during evaluation and treatment of these patients. The burden of spinal metastases continues to grow as advancements in radiation and systemic therapy have prolonged survival in individuals with metastatic cancer. Treatment is fundamentally palliative, focused on neurologic preservation, restoration of spinal stability, pain relief, and durable local tumor control [3]. Due to the palliative intent of therapy, however, any intervention must minimize treatment-related morbidity or complications, leading to a relatively narrow therapeutic window. The practice of spinal oncology is becoming increasingly complex as innovations in surgical technology, immunotherapy, targeted chemotherapies, and radiation therapy change the therapeutic landscape. Furthermore, patients with metastatic disease frequently have multiple medical comorbidities in the face of progressive systemic disease. The clinical management of these patients is multidisciplinary at its core, requiring discussions between surgeons, medical oncologists, and radiation oncologists. The demands on the surgeon are to provide effective surgical intervention associated with minimal morbidity, shortest hospitalization, and least disruption to systemic therapy.

Historically patients with MESCC were treated with high-dose glucocorticoids and fractionated radiation therapy [4]. Initial efforts at surgical intervention were focused on posterior-only decompression of the spinal canal and were commonly associated with worsened neurologic and functional outcomes compared with radiation

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alone. In retrospect this surgical strategy led to further destabilization of an already compromised spine by removal of the intact posterior elements. Furthermore, the site of epidural compression and spinal metastases is typically anterior or ventral to the spinal canal. Later developments in spine stabilization and instrumentation, as well as methods of circumferential decompression of the spinal canal, revitalized the role of surgery in the management of spine metastases. In a pivotal study by Patchell et al. [5], individuals with solitary and symptomatic MESCC were randomized to circumferential decompression/stabilization followed by conventional external beam radiation therapy (cEBRT) or cEBRT alone. Patients in the surgical cohort experienced significant improvement in rates of ambulation, functional ability, pain control, urinary continence, and survival. This study established that appropriately selected surgery offers a meaningful improvement in quality of life with acceptable morbidity when added to radiation therapy. The aim of surgery is to provide surgical stabilization and decompression of the neural elements. Ultimately radiotherapy is the source of local tumor control.

Tumor histology has an impact on the efficacy of radiation therapy, measured as the rate of local control. Traditionally, tumors were classified as either radiation sensitive or resistant based on their response to conventional fractionated radiation therapy [6]. Radiosensitive histologies include lymphoma, plasmacytoma, multiple myeloma, small cell lung carcinoma, germ cell tumors, breast carcinoma, and prostate carcinoma. In response to cEBRT, these tumors have a reported 2-year local control rate of up to 80–90%. In contrast, radioresistant malignancies such as lung, thyroid, hepatocellular, colorectal, and renal cell carcinoma, melanoma, and sarcomas exhibit much poorer 2-year local control – as low as 30% following radiation therapy. Furthermore, symptomatic and neurologic improvement is often limited to several months in these patients. Developments in image-guided stereotaxy and radiation therapy have enabled the delivery of highly conformal and tumoricidal doses of radiation as either a single treatment or hypofractionated (2–5) regimen. Spinal stereotactic radiosurgery (SSRS), or stereotactic body radiation therapy (SBRT), delivers radiation to a contoured volume with a steep dose gradient that spares surrounding tissues such as the spinal cord, nerves, or esophagus. The biologically effective dose of radiation delivered with SSRS is estimated to be approximately three times greater than with cEBRT, leading to more extensive DNA damage, irrecoverable endothelial damage, and potentially enhanced immune environment with T-cell activation and pro-inflammatory cytokines [7]. Radiosurgery effectively overcomes the previously held histology-specific radioresistance, with 12-month local control rates of 85% in even notoriously difficult tumor types such as RCC [8]. Furthermore, due to the conformality of SSRS and relative sparing of surrounding tissues, it is possible to use as a salvage therapy in the setting of prior radiation failures for local recurrence [9, 10].

While SSRS is an effective and reliable treatment for spine metastases, radiation-induced spinal cord injury remains a concern [11]. A widely accepted dose maximum to the spinal cord is 14 Gy. Using this parameter, a large multicenter study following over 1000 individuals treated with SSRS found only 6 patients that developed radiation-induced myelopathy. In the setting of high-grade epidural compression, the toxicity-limiting dose of the spinal cord or cauda equina requires adjustment to the prescribed treatment dose, potentially under treating the tumor margin and compromising local tumor control. Lovelock et al. [12] found that local treatment failure was associated with tumors that received less than 15 Gy to any point in the treatment planning volume. A surgical strategy designed to create separation between the tumor and spinal cord has emerged to facilitate the use of radiosurgery in the setting of epidural compression [13, 14]. Surgery involves resection of epidural tumor with reconstitution of the thecal sac, followed by spinal stabilization as indicated. The aim of surgery applied in conjunction to SSRS is (i) decompression of the spinal cord in cases of compressive myelopathy; (ii) to create separation between tumor and the spinal cord; (iii) and to provide spinal stabilization. The extent of tumor resection is not crucial to local control as long as there is an adequate distance between the tumor margin

and spinal cord to deliver tumoricidal doses of SSRS. Separation surgery followed by SSRS represents a paradigm shift in spinal oncology and has dramatically improved treatment of oligometastatic disease.

Rationale for Laser Interstitial Thermal Therapy (LITT)

Individuals with metastatic cancer are frequently deconditioned and harbor a number of medical comorbidities. Malnutrition, chronic anemia, chronic steroid use, systemic thromboses (DVT or PE), and/or prior radiation complicate surgical intervention. Furthermore, these patients commonly have rapidly progressive disease at other sites in addition to their spine requiring concurrent and systemic therapy with cytotoxic or targeted agents. For these individuals separation surgery may lead to significant morbidity and delays systemic therapy until the patient has adequately recovered. Percutaneous techniques have been developed as an alternative to open surgical procedures in certain scenarios to decrease morbidity, limit disruption of systemic therapy or anticoagulation, shorten hospital admissions, decrease pain, and minimize blood loss or transfusions. Currently used methods include CT-guided cryo- or radiofrequency ablation of vertebral tumors [15–17]. Injury to the spinal cord or nerve roots has been documented with radiofrequency ablation, and in animal studies, placement of the electrode immediately adjacent to the posterior cortex of the vertebral body or pedicle leads to neural injury [18, 19]. Concern for neurologic injury and the inability to monitor tissue injury in real time has limited the adoption of these techniques for the ablation of epidural tumor in close proximity to the neural elements. Laser interstitial thermal therapy is an alternative method of percutaneous ablation that has seen widespread adoption in the treatment of intracranial tumors and other pathology [20, 21]. Using this technique, a small laser probe is inserted into the lesion using stereotactic guidance. Energy is transferred from the laser into the surrounding tissue producing a thermal injury sufficient to lead to tumor cell death and coagulative necrosis. The amount of tissue damage is based on a thermal response model in which there is a correlation between temperature, duration of exposure, and the ensuing damage. An advantage of this technology over others is that an intraoperative MRI is used to monitor in real time the heat generation within a particular region. Using spinal LITT (sLITT), epidural tumor in close proximity to the thecal sac and spinal cord can be ablated while ensuring that there is no thermal injury to

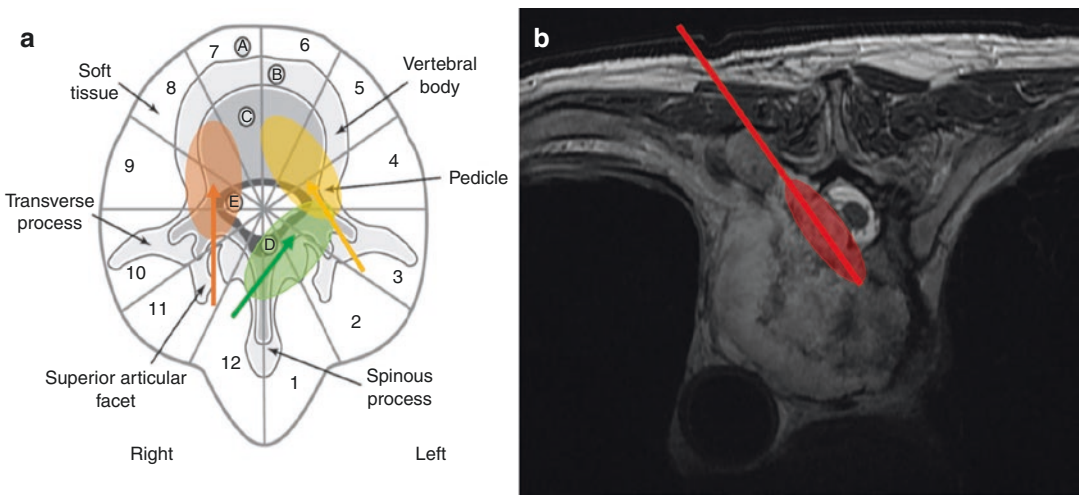

Fig. 47.1 Diagram demonstrating the typical approaches (i.e., oblique transpedicular, *yellow arrow*) based on the location of the metastatic lesion in relation to the spinal cord (**a**). The ideal distance between the fiber and dura is 5–7 mm, while each fiber covers a 10–12 mm radius (**b**)

the spinal cord (Fig. 47.1) [22–24]. As an additional source of protection, the CSF surrounding the spinal cord and epidural venous plexus serve as a heat-sink limiting the generation of heat in close proximity to the spinal cord. Regions of high-grade epidural compression can safely be ablated using sLITT. This treatment paradigm, similar to separation surgery, requires adjuvant SSRS for effective tumor control. Similar to circumferential decompression, the region of necrotic tissue following thermal ablation creates a separation between viable tumor and the spinal cord facilitating effective doses of SSRS. For individuals that also have spinal instability, a percutaneous stabilization can be performed following LITT in the same setting [25].

Patient Selection

Spinal laser interstitial thermal therapy is an effective and safe procedure in properly selected patients. sLITT is a minimally invasive alternative to open circumferential decompression for patients with epidural compression that are candidates for radiosurgery [22, 23]. High-grade epidural compression is typically defined using the Bilsky scale [13] and classified as grade 1c or higher. In these individuals the degree of epidural compression would limit treatment with an effective radiosurgery dose. Additional considerations for patient selection include (i) medical comorbidities; (ii) need to continue or rapidly resume systemic therapy; (iii) normal neurologic exam; (iv) thoracic spine; and (v) no contraindications to MRI (e.g., pacemaker or neurostimulator). For patients in which MRI is contraindicated, sLITT cannot be performed without MRI thermography. Similarly, existing instrumentation at the level of ablation typically creates metallic artifact that impairs the accuracy of MRI thermography and precludes its use. Individuals presenting with a neurologic deficit require surgical decompression and are not candidates for a percutaneous procedure such as LITT or radiosurgery alone. Individuals with debilitating thoracic radiculopathy due to foraminal tumor involvement are ideal candidates for laser ablation [24]. The ablation and destruction of tumor within the foramina and associated nerve typically provides complete resolution of the pain. For the same reason, we restrict the use of LITT to the thoracic spinal segments to avoid unintentional injury to functional nerve roots of the cervical and lumbosacral plexus. For lesions of the cervical and lumbar spine, surgical decompression with visualization and complete decompression of the functional roots is preferred. As previously discussed, prior conventional radiation therapy and spinal instability are not contraindications to sLITT. In the case of prior radiation, a percutaneous technique such as LITT is desirable to avoid wound complications. If there is spinal instability, a percutaneous stabilization is frequently performed following the laser ablation [25]. This can be done during the same anesthetic or as a staged procedure.

A number of metastatic tumors are notoriously vascular. These include renal cell carcinoma, hepatocellular carcinoma, and thyroid carcinoma. Prior to a circumferential decompression, these tumors are typically embolized preoperatively in an effort to decrease the amount of blood loss. Percutaneous laser interstitial thermal ablation is associated with only minimal blood loss. Furthermore, an endovascular embolization is unnecessary and avoids an additional procedure in this patient cohort.

Technical Description

At our institution sLITT is performed within an operating room suite equipped with an intraoperative MRI (iMRI) (BrainLab Inc., Feldkirchen, Germany). Following induction of general anesthesia, the patient is placed in the prone position with the upper extremities parallel to the body in a manner that is ergonomic to the surgeon and does not interfere with the use of the C-arm fluoroscope or iMRI [26]. Initially, we used a CT scan of the spine and C-arm for localization and stereotactic placement of the laser fibers [22, 23]. Currently, we are using MRI for coregistration and spinal navigation and have found that this can be accomplished with submillimeter accu-

racy. Additionally, the MRI provides better spatial resolution of the tumor and its relation to the neural elements for trajectory planning and insertion of the fibers. After final positioning, but prior to the iMRI, skin fiducials (Izi Medical Products, Owing Mills, MD, USA) are placed on the region of interest in a unique pattern that distinguishes right-left and rostral-caudal (Fig. 47.2a). The surgical site is prepped and draped, and a small incision is made with dissection proceeding to the level of the spinous process. Using subperiosteal dissection the soft tissues are reflected away from the spinous process, and a MRI-compatible clamp and reference array (Medtronic, Minneapolis, MN) are secured to the bone (Fig. 47.2b, c). Without disrupting or displacing the reference array and fiducials, a Siemens body matrix coil is placed over the region of interest and the patient is positioned within the MRI (Fig. 47.2d). A high-resolution T2WI is used for coregistration and navigation. Following image acquisition, the series is transferred to a Stealth S7 workstation (Medtronic, Minneapolis, MN), and coregistration is performed using a point matching registration with the fiducial markers (Fig. 47.3). The accuracy is confirmed prior to proceeding with insertion of the epidural cannulas and laser fibers.

Spine navigation allows for meticulous trajectory and entry point planning. In our experience we have relied on the Weinstein-Boriani-Biagini tumor classification to select the optimal probe trajectory [27]. Typically one of three trajectories is used based on the location of the epidural disease that is being treated. The most common trajectory is an oblique transpedicular or transforaminal trajectory. This is well suited to treat disease that is ventral to the spinal cord or canal (zones 4–6 or 7–9). Orthogonal transpedicular or translaminar trajectories can also be used to access different sites of disease intended for treatment. In general the selected trajectory places the laser fiber approximately 6 mm from the dura or thecal sac, and it is assumed that each fiber can achieve a 10 mm diameter of thermal injury. Depending on the extent of disease in the rostral-caudal plane, multiple trajectories may be required to achieve an adequate ablation (Fig. 47.4). We have used up to nine trajectories in a single patient. When planning multiple trajectories, they are placed within 10 mm of one another to ensure that there are no untreated segments between successive ablations. Similarly, bilateral trajectories may be needed to completely treat ventral or lateral epidural disease.

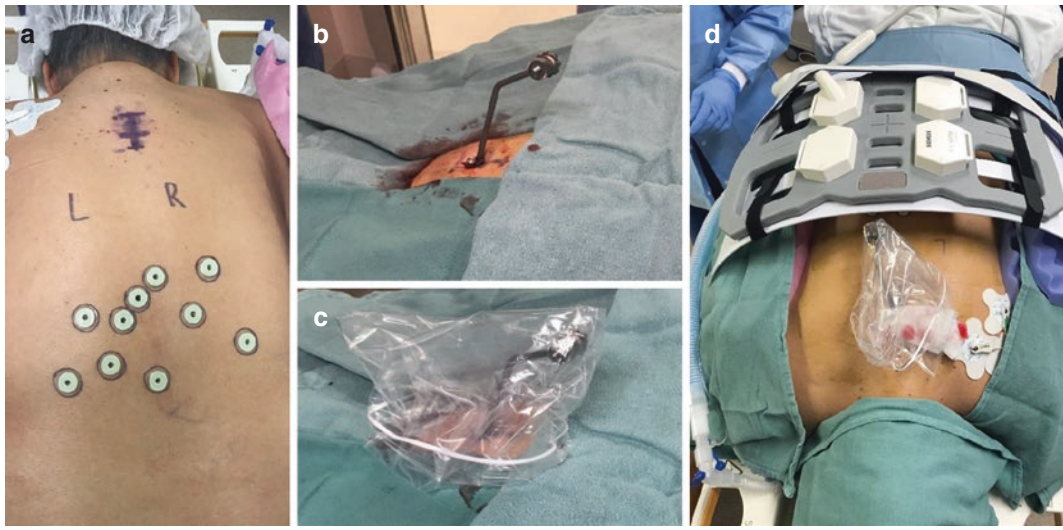

Fig. 47.2 Patient in prone position on the iMRI transfer table, with fiducial markers applied in the dorsal region overlying the tumor (**a**). The skin is prepped and the spinous process clamp is secured (**b**). Spinal clamp is covered with a sterile plastic bag (**c**). MRI coil placed over the plastic fiducial held by a plastic cradle to avoid fiducial displacement (**d**)

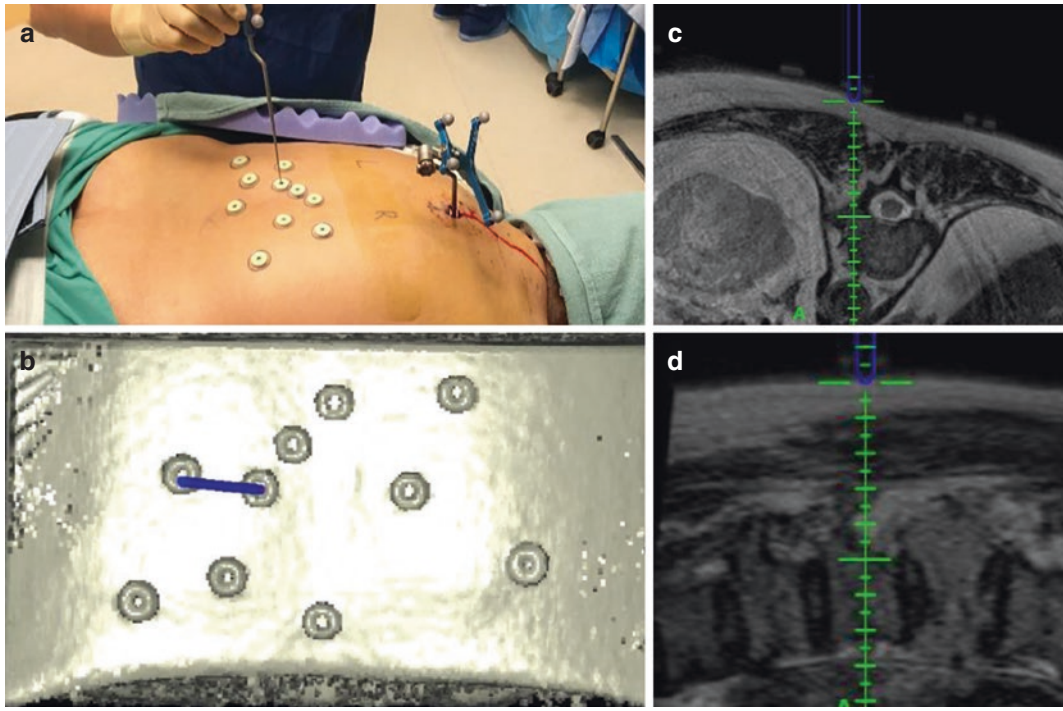

Fig. 47.3 (**a**) Sterile reference array is attached to clamp under sterile conditions. A non sterile probe is used to perform surface matching of fiducials. (**b**). MRI 1mm acial cuts are obtained and transferred to standard navigation system for registration, accuracy of the image guidance is tested inside the fiducials, midline and easily palpable spinous processes. (**c**) Axial (**d**) sagital navigated inline images are used for planing trajectories for placement of laser catheter and pedicle screws.

Following selection of the appropriate trajectory(s) and entry point(s), a navigated Jamshidi needle is introduced and the navigation accuracy is confirmed. Small incisions are made at the entry sites, and a Jamshidi needle (DePuy Synthes, Raynham, MA, USA) is advanced until it contacts the lamina or other bone surface. The C-arm is then used to confirm the location of the Jamshidi needle and verify that the fluoroscopy and spine navigation are commensurate with one another. Next, the Jamshidi is advanced to target depth using navigation (Fig. 47.4). A K-wire is introduced through the Jamshidi needle and exchanged with a 1.65 mm-diameter plastic catheter and stylet (Fig. 47.5). This is repeated in succession for each trajectory. Once all of the cannulas have been inserted, the surgical field is covered, and another MRI is obtained to confirm the locations (Fig. 47.6).

The laser fiber consists of a 980-nm diode encased in a catheter that is connected to a 15-W power source. A single fiber is introduced to the cannula and advanced to depth. MR thermography is based on gradient-echo acquisition and used throughout the ablation to monitor the heat generated within the tissue. Proton resonance within the tissue is sensitive to temperature, and the difference in phases allows for modeling of the temperature within the exposed tissue. 3-mm slices are acquired every 5–6 seconds while the laser is activated. The laser is deactivated when one of two temperature thresholds are reached. The boundary between dura and tumor is identified and set to an upper temperature limit of 48–50° (Fig. 47.7). A second threshold is set to 90° in the tissue adjacent to the laser fiber to prevent excessive heating of the tumor and tissue carbonization. The

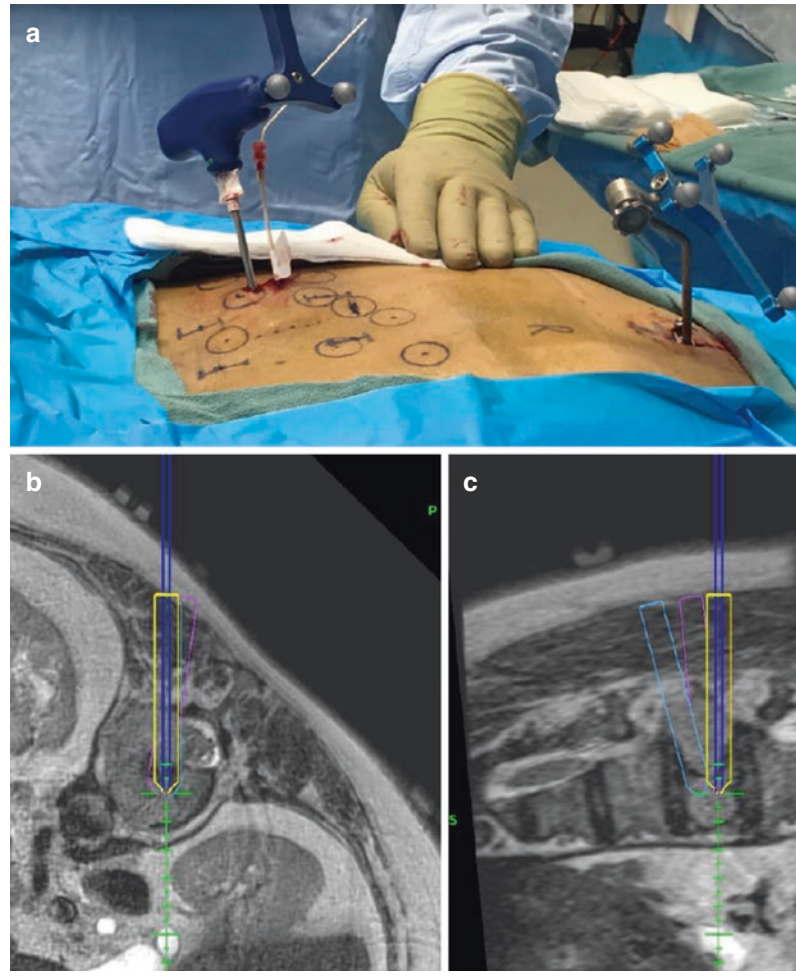

Fig. 47.4 Fiducials are removed; the rest of the skin is prepped and draped in the usual sterile fashion (**a**). Navigated Jamshidi needle is inserted using image guidance, where the diameter of the needle (*yellow*) is increased to position the needle (*blue*) 5–7 mm lateral to the dura (**b**). This is repeated to with multiple trajectories, as needed, to achieve an adequate ablation (**c**)

thermal maps are sensitive to and degraded by motion. The spine is vulnerable to respiophasic motion and demands that a breath hold be completed during the ablation. Thus, the ablation is performed in cycles in which the laser is active for up to 120 seconds during a breath hold, interrupted by periods of ventilation to allow for adequate oxygenation and recovery from hypercapnia. Typically, the ablation time in total is up to 4 minutes at a single site. The laser fiber is manually advanced or withdrawn as needed to ensure that there is ablation of the entire intended epidural tumor.

After the ablation is complete, the laser fiber and cannulas are removed, and the incisions are closed with an absorbable suture. To visualize the extent of ablation, a pre- and post-contrast T1WI is acquired, again with breath holding. The region of coagulative necrosis will lack contrast enhancement, and it appears as a hypointense or dark area post-contrast sequence (Fig. 47.8). In our experience this has been an accurate estimation of the ablated volume. For individuals with concomitant spinal instability, a stabilization procedure can be performed under the same anesthetic or as a separate staged surgery (Fig. 47.9). Typically, a percutaneous instrumentation with cement augmentation is performed using spinal navigation and the reference array from the sLITT, or standard fluoroscopic techniques. Generally, our practice is to repeat a MRI of the spine in 6–12 weeks. If instrumentation is used, a CT myelogram is obtained postoperatively for radiosurgery planning.

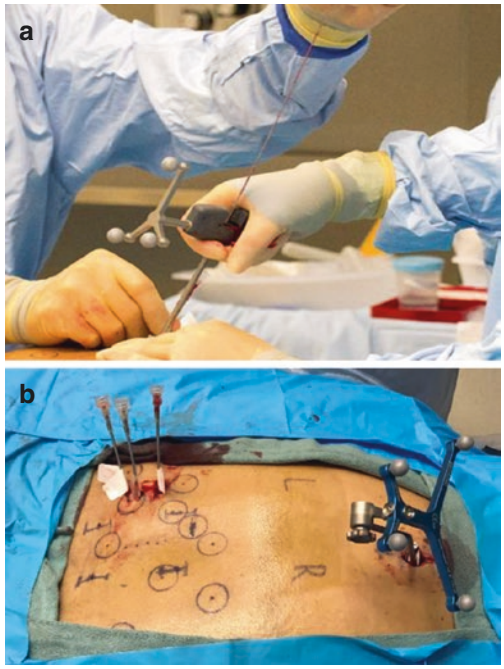

Fig. 47.5 K-wires are inserted through the Jamshidi, which is exchanged to a plastic access cannula (**a**). A modified plastic introducer is inserted into the plastic cannula to maintain the trajectories, and additional needles are inserted in tandem to cover the craniocaudal extension of the epidural mass (**b**)

Clinical Outcomes and Results

In conjunction with radiosurgery, spinal laser interstitial thermal therapy provides effective and durable local tumor control with minimal morbidity. From our initial experience, we reported outcomes of sLITT and SSRS in 19 individuals presenting with radioresistant tumors, the majority of which had progressed despite systemic therapy [22]. Within this cohort seven patients had Bilsky 1c epidural compression, eight had grade 2 compression, and four exhibited grade 3 compression. SSRS was indicated in all subjects for oncologic control, but the degree of epidural compression would have restricted effective dose to the planned treatment volume. sLITT provided a percutaneous alternative to open surgery with the benefit of an abbreviated hospital admission (median of 2 days) and durable tumor control. Progression was documented in only two patients at 16 and 33 weeks and was ultimately retreated with a subsequent sLITT. Furthermore, there was a statistically significant reduction (22%) in the dimensions of epidural tumor seen at 2 months and improvement in the degree of epidural com-

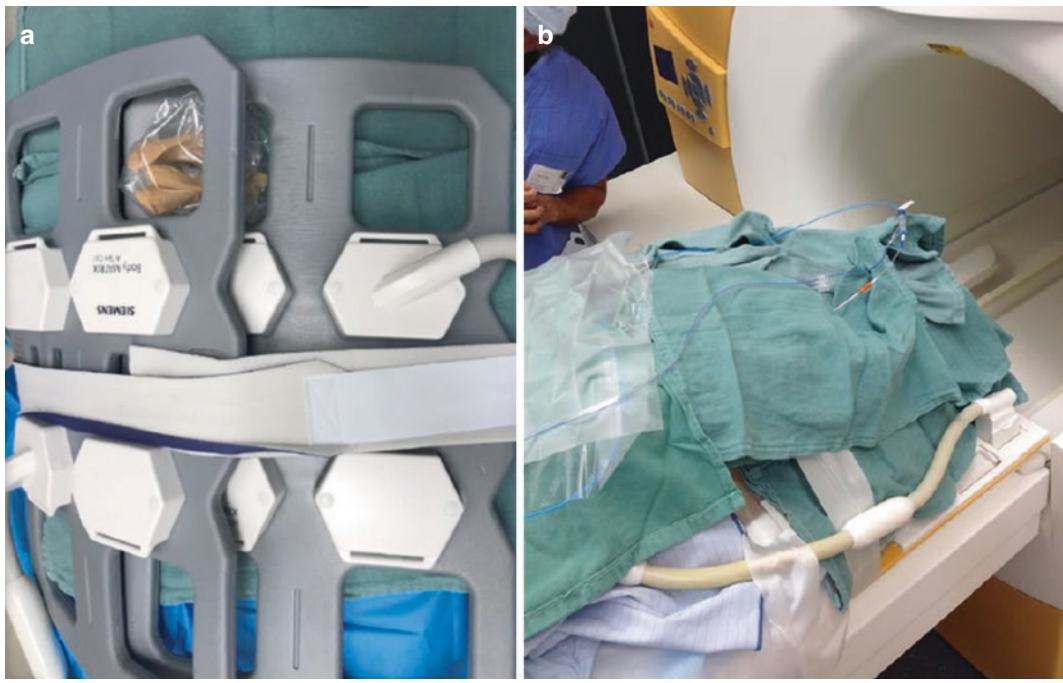

Fig. 47.6 The access cannulas are covered with sterile technique and the MRI coil placed over the region of interest, followed by transferring the patient to the MRI magnet for fiber localization (**a**). Sterile towels are placed over the MRI coils, and the laser catheter is inserted into the access cannulas (**b**)

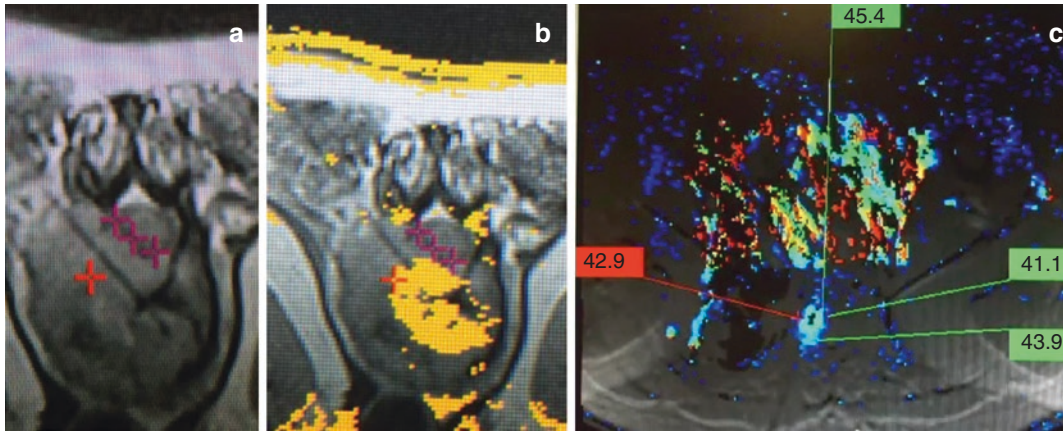

Fig. 47.7 MRI T2 sequence is utilized to localize the exact axial plane for the fiber, and a high limit is placed lateral to the fiber and set to 90 °C (*red cross*), and a lower limit is placed in the interface between the tumor and dura mater and set to 50 °C (*purple cross*) (**a**). Mathematical model of thermal damage monitored in real time, attained with our imaging software (**b**). A monitored ventilator pause is performed by the anesthesiologist during the acquisition of thermal images, where a total of 2 minutes is allowed for each ablation cycle (**c**)

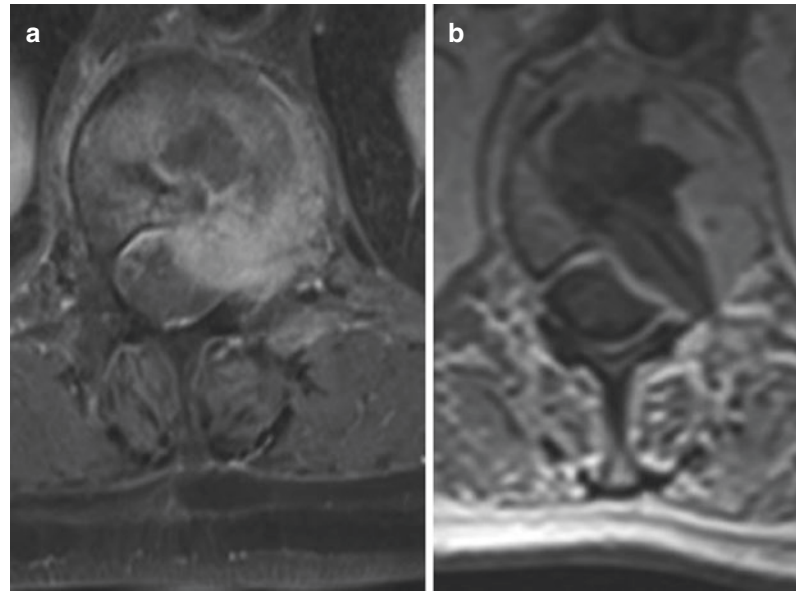

Fig. 47.8 MR images are obtained and demonstrate the immediate thermal damage. Preoperative T1 with contrast (**a**), postoperative T1 without contrast (**b**)

pression. Pain scores (VAS) were also significantly improved following sLITT. Complications in this series included a transient monoparesis in one patient, a wound dehiscence requiring reoperation, and a delayed compression fracture. To date, we have performed more than 100 procedures to treat a variety of tumor histologies. Local tumor progression has been documented at a total of 17 treated sites – 15 were in-field recurrences, while 2 were at the treatment margins (unpublished analysis). Median follow-up was 35 weeks for the entire cohort, with time to recurrence measuring a mean of 26 weeks. Approximately one-third of patients also underwent a subsequent stabilization procedure.

From this larger experience, several lessons have emerged. In our current practice, we limit treatment to lesions within the thoracic spine located between T2 and T12 to avoid injury to the cervical or lumbosacral plexus. Based on the

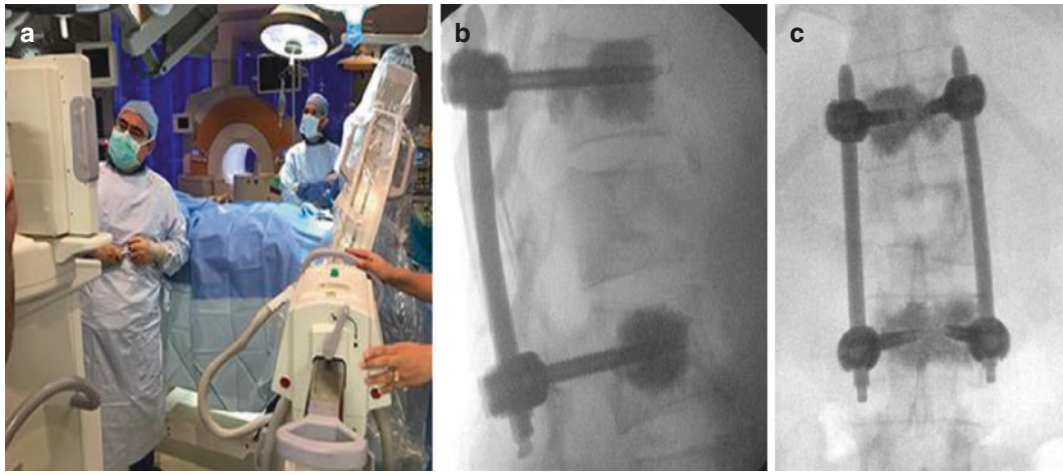

Fig. 47.9 Cases associated with spinal instability are treated in the same day directly after the ablation is completed (**a**). The patient is positioned away from the MRI scanner and standard percutaneous pedicle screws with cement augmentation can be placed using either fluoroscopy or image guidance; lateral (**b**) and AP views (**c**)

percutaneous nature of the procedure, traversing nerve roots cannot be identified and protected. Initial efforts to treat lesions in the upper lumbar spine were complicated by injury to roots at the corresponding level. In addition to spinal level, the presence of a neurologic deficit prior to surgery, even if subtle, is an absolute contraindication. Individuals with preexisting deficits have increased potential for neurologic worsening post-ablation. Our series includes a patient treated with mild motor weakness preoperatively and renal cell carcinoma. The procedure itself was uncomplicated and initially well tolerated, but unfortunately, the patient had a delayed neurologic decline requiring surgical decompression. Interestingly, review of the pathology obtained from the ablated level at the time of reoperation consisted of necrotic tissue with no viable tumor. A second subject included in this series required an urgent decompression in the setting of a delayed neurologic deficit. In this case the patient was neurologically intact prior to laser ablation but subsequently declined. The patient had received concurrent immunotherapy for RCC, and it was hypothesized that the combination of LITT and immunotherapy led to a significant immune reaction and edema. Individuals treated with sLITT and immunomodulatory agents may require special consideration. Similar observations have been made in patients on immunotherapy undergoing LITT for cranial tumors that subsequently develop severe edema and inflammation.

Although the zone of thermal injury typically measures up to 10 mm in diameter, the ablation is not universally homogenous or predictable. Regions of tumor that are adjacent to spinal fluid, large vessels, or cystic areas are more difficult to treat due to the ability for these structures to dissipate heat and function as a heat sink. Similarly, vascular tumors such as renal cell carcinoma may require longer treatment times and multiple trajectories to adequately treat an area. The area of ablation is often less homogenous compared to other tumor types such as chordoma or lung carcinoma. Osteoblastic tumors present additional challenges when using sLITT, as highly calcified tissue presents a low MRI signal interfering or decreasing the quality of temperature monitoring by MRI thermography.

Conclusion

Spine laser interstitial therapy is an emerging and minimally invasive method to treat spine metastases. It provides effective and durable local control with minimal morbidity. Compared to other percutaneous techniques, sLITT is unique in offering real-time monitoring of thermal injury.

Additional benefits over conventional separation surgery include limited hospital admissions, improved pain control, and minimal blood loss. Furthermore, vascular tumors do not require preoperative embolization, and patients with significant medical comorbidities or need for continued systemic therapy can safely be treated. The technology is still early in its development and not stand-alone therapy. Rather it is best used in conjunction with SSRS to provide symptom palliation and local oncologic control.

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Optimizing Wound Healing in Metastatic Spine Surgery

48

Jaime L. Bernstein, Matthew A. Wright, and Jason A. Spector

Introduction

Neoplasms involving the spine present a challenging and increasingly common problem for the spine surgeon. As treatment options for oncologic diagnoses have improved patient survival from primary malignancy, the incidence of spinal metastasis has inevitably increased. In fact, the axial skeleton is the third most common location of metastasis, and it is the most frequent site of bony metastasis [1]. The incidence of spinal metastasis has been predicted to range from 30% to 90% at the time of death depending on the primary cancer diagnosis (most commonly from the breast, prostate, and lung) [2]. Although treatment recommendations for metastasis of the spine have evolved over the last decade with a concomitant improvement in life expectancy, surgery remains an important component of the treatment algorithm as it reduces tumor burden/recurrence and stabilizes the spine which helps patients maintain an increased quality of life [3]. Current indications for surgical intervention in cases of metastatic disease of the spine include progressive neurologic deficit, intractable pain, spinal instability, and metastasis resistant to radiation therapy. To address these issues, surgery may involve decompression, debulking of the tumor, and stabilization of the spine [4].

Despite the treatment benefits that surgical interventions offer, wound-healing complications have traditionally been high in patients with spinal metastasis due to multiple factors including poor nutritional status, pre- and/or postoperative chemotherapy or radiation, and a history of previous operations/instrumentation. This leaves the surgeon to close within a suboptimal, atrophic wound bed following tumor extirpation and placement of instrumentation and/or avascular graft material. Moreover, this wound bed is then often subjected to adjuvant chemotherapy and/or radiation [5]. Not surprisingly, the historical rate of postoperative complications in these complex cases is reported in the literature to be as high as 30–40%, with surgical-site infection being the most common complication [5, 6].

When wound-healing issues arise in this patient population, the consequences can be profound and include reoperation, hardware removal, prolonged hospital stay, critical delay in the delivery of adjuvant therapy, decreased patient quality of life, and increased healthcare costs [4, 7–10]. The poor postoperative outcomes reported in the literature, combined with the limited lifespan remaining for many patients with metastatic disease of the spine, have traditionally tempered the desire for surgical treatment.

More recently, however, the literature has shifted toward supporting surgical intervention

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for a select cohort of patients with metastatic disease to the spine as data show declining complication rates and excellent functional outcomes after surgery. However, when compared with nononcologic spinal surgeries, the complication rate remains significantly higher [3]. Ultimately, the risk of complications must be weighed against the benefits of the surgery. If surgery is selected as a treatment modality, it is important that the surgical team focuses on measures to mitigate wound-healing complications beginning in the preoperative period.

Wound Healing

General Wound Healing

Healing of spinal surgical wounds follows the traditional model beginning with hemostasis via vasoconstriction and formation of a platelet plug. To briefly summarize, platelet cytokine release in addition to activation of the coagulation and complement cascades leads to chemotaxis of inflammatory cells. Neutrophils predominate within the first 48 hours, though macrophages become the dominant cell type driving the inflammatory response at 48–96 hours. Macrophages initially exhibit an "M1" phenotype, releasing cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)1, and IL6, resulting in a clearing of debris and pathogens from the wound. Macrophages then switch to an "M2" phenotype, commencing the fibroproliferative phase. During this phase, growth factors including transforming growth factor beta (TGF-β), epidermal growth factor (EGF), and vascular endothelial growth factor (VEGF) promote matrix formation, epithelization, and neoangiogenesis. Collagen production peaks during this time period, but net collagen deposition equilibrates by around week 3 due to concurrent resorption via collagenase. Over the following months, collagen maturation occurs and is characterized by collagen cross-linking and turnover of type 3 collagen to type 1 collagen. In a healthy patient, the wound achieves approximately 80% the prewound tensile strength by about 2 months and reaches its final plateau strength at around 6 months [11–15].

Concerns in the Spinal Metastasis Patient

Wound healing is a complex and multifactorial process, and there are numerous steps where it may become impaired in the patient with spinal metastases either as a direct consequence of the cancer or indirectly via the treatment modalities employed against the tumor with a resultant increased risk for the development of wound complications [4, 5, 16, 17]. Cancer is almost always associated with some degree of immune dysregulation regardless of the patient's primary tumor type. On a systemic level, tumor cells produce cytokines which lead to a decreased ability of the immune system to respond to either the tumor or other potential pathogens [18, 19]. Furthermore, high levels of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6 are frequently associated with adverse clinical consequences, including muscle wasting, cachexia, and malnutrition. Patients may also become hypoalbuminemic (likely due to TNF-α inhibition of albumin production from the liver), which is associated with postoperative mortality [20, 21].

Another factor to consider in the patient with spinal metastasis is whether he or she has a history of irradiation either for treatment of the primary tumor or for the metastasis. Irradiation results in scarring and tissue fibrosis, which may lead to fusion of tissue planes and loss of elasticity. Furthermore, patients who receive irradiation within the weeks or months following their spinal procedure face additional wound-healing challenges, given that irradiation inhibits the neoangiogenesis and fibroblast proliferation necessary for proper wound healing.

Finally, many patients with spinal metastasis will receive steroids to combat cord compression. Steroids dysregulate wound healing by multiple mechanisms, including decreased collagen deposition by fibroblasts, reduced inflammation, and decreased re-epithelization. Other comorbidities, which can inhibit proper wound healing that are not necessarily specific to this patient population but which must be assessed, include advanced age, very high or low BMI, tobacco use, diabetes mellitus, renal disease,

cardiac disease, peripheral vascular disease, vasculitis, and coagulation disorders.

Preoperative Optimization

Whenever appropriate, the patient should always be medically and nutritionally optimized prior to surgery. In addition to routine preoperative medical and cardiac clearance, nutritional optimization should be achieved, with a targeted albumin of >4 g/dL and prealbumin >16 mg/dL, with the addition of protein supplementation as necessary. Patients should also be counseled on smoking cessation, and nicotine products should be discontinued at least 6 weeks prior to surgery. Patients with a history of diabetes mellitus should have their blood glucose levels controlled as monitored by their hemoglobin A1c. Coagulopathies must be reversed, and any vasopressors must be discontinued as they decrease perfusion to the wound bed. Finally, steroids should be discontinued as rapidly as possible or supplemented with Vitamin A to counter steroid-induced negative wound-healing effects.

Multidisciplinary Approach

Traditionally, the plastic surgeon becomes involved with the complex spinal wound after complications have developed, with a resultant reconstructive need that has been associated with a high rate of spinal wound morbidity. Recent literature has demonstrated lower complication rates in patients who receive prophylactic coverage of the spine with muscle flaps at the time of the primary operation when compared against delayed reconstruction. Patients with decreased wound-healing capacity should be specifically identified so that wound-healing complications may be mitigated by providing well-vascularized soft-tissue coverage and a tension-free closure at the time of the index operation [4–6, 22]. Preoperatively, through this collaborative effort, the spine and reconstructive surgeon can discuss the location of planned surgical incisions and the anticipated soft-tissue approach to the spine in order to avoid compromising the blood supply to either the skin or underlying muscle. Such communication helps to ensure that the muscle flaps remain a viable reconstructive option.

Reconstructive Options

Although a wide array of reconstructive options of the spine exists, the most common approach utilizes local muscle flaps given the efficiency of harvest and minimal additional morbidity. Coverage with flaps supports wound healing in a multifaceted manner. First, flaps provide increased vascularity and perfusion to the surgical site, which facilitates wound healing, bone graft revascularization, and antibiotic delivery.

Muscle flaps also create a soft-tissue barrier between the skin and the spine, providing continual protection of the spine and any hardware that has been placed. In the event of a superficial dehiscence or even full-thickness skin loss, wounds have the potential to heal with nonoperative interventions, and salvage of the hardware is possible given the extra protection afforded by the layer(s) of muscle flaps from outside exposure and contamination (Fig. 48.1). In addition, local muscle flaps have the added benefit of obliterating dead space, which reduces the potential space for fluid accumulation. Finally, placing muscle tissue adjacent to the exposed spinal cord may also improve dural healing and decrease the potential for cerebrospinal fluid (CSF) leak.

Anatomically, there are superficial and deep layers of muscles near the spine available for soft-tissue coverage (Fig. 48.2). Closure of the wound with muscle flaps almost always includes the paraspinous muscles given their deep and longitudinal orientation to the spine. Depending on the wound and spinal levels involved, reconstruction may also call for a second layer of coverage from the superficial extrinsic muscles of the back, including the trapezius, latissimus dorsi, thoracolumbar fascia, and/or gluteus maximus [4, 22] (Fig. 48.3). All efforts should be made to preserve the perforators supplying the skin overlying these muscle flaps.

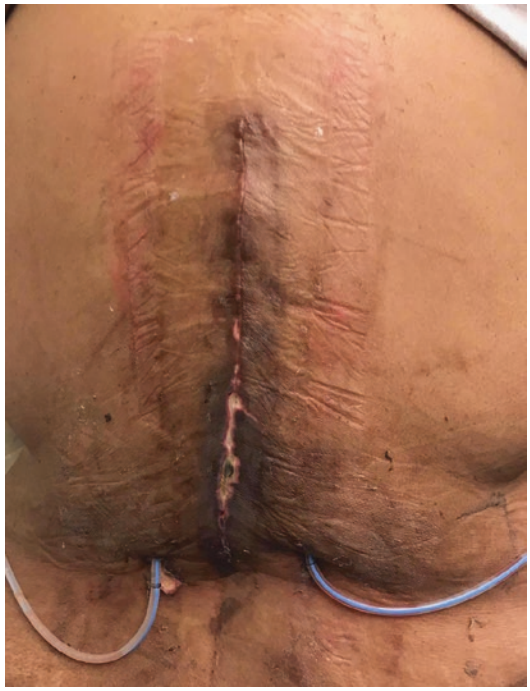

Fig. 48.1 Superficial dehiscence in the early postoperative period. Because muscle flaps deep to the superficial fascia remain intact, the instrumentation and graft are safely sequestered even from full-thickness skin breakdown

In order to optimize wound healing, even in the setting of muscle flaps, it is important to make sure all layers of closure are tension free with sufficient mobility to midline. Tension reduction can be achieved through advancement of the deep muscle layers of the spine, which allows for greater mobility of the more superficial layers. Relaxing incisions through the lateral muscle fascia can also be considered if greater tension reduction is still needed at the time of closure. Tension reduction is crucial as increased wound tension leads to excess force on sutures, causing ischemia of the wound edge, tissue necrosis, and potentially failure of the suture itself, thereby resulting in wound dehiscence.

It is important to note that preservation of the fascia surrounding the muscle flap increases the strength of the closure, as fascia is more able to bear tension from the sutures. Muscle alone often does not provide the necessary strength, and suturing muscle without its investing fascia may result in "cheese-wiring" of the sutures through the muscle, thereby resulting in flap dehiscence.

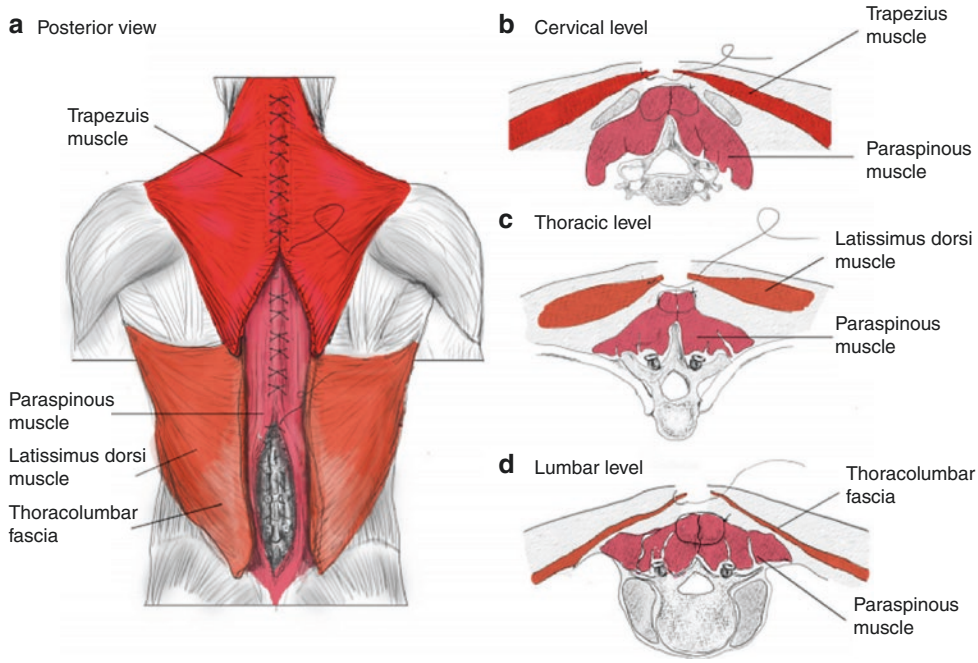

Fig. 48.2 (**a**) Posterior view of superficial and deep muscles of the back commonly used for flap reconstruction of the spine. Axial cuts of two-layer flap closures through the (**b**) cervical level, (**c**) thoracic level, and (**d**) lumbar level. (With permission from Franck et al. [22], Elsevier © 2018)

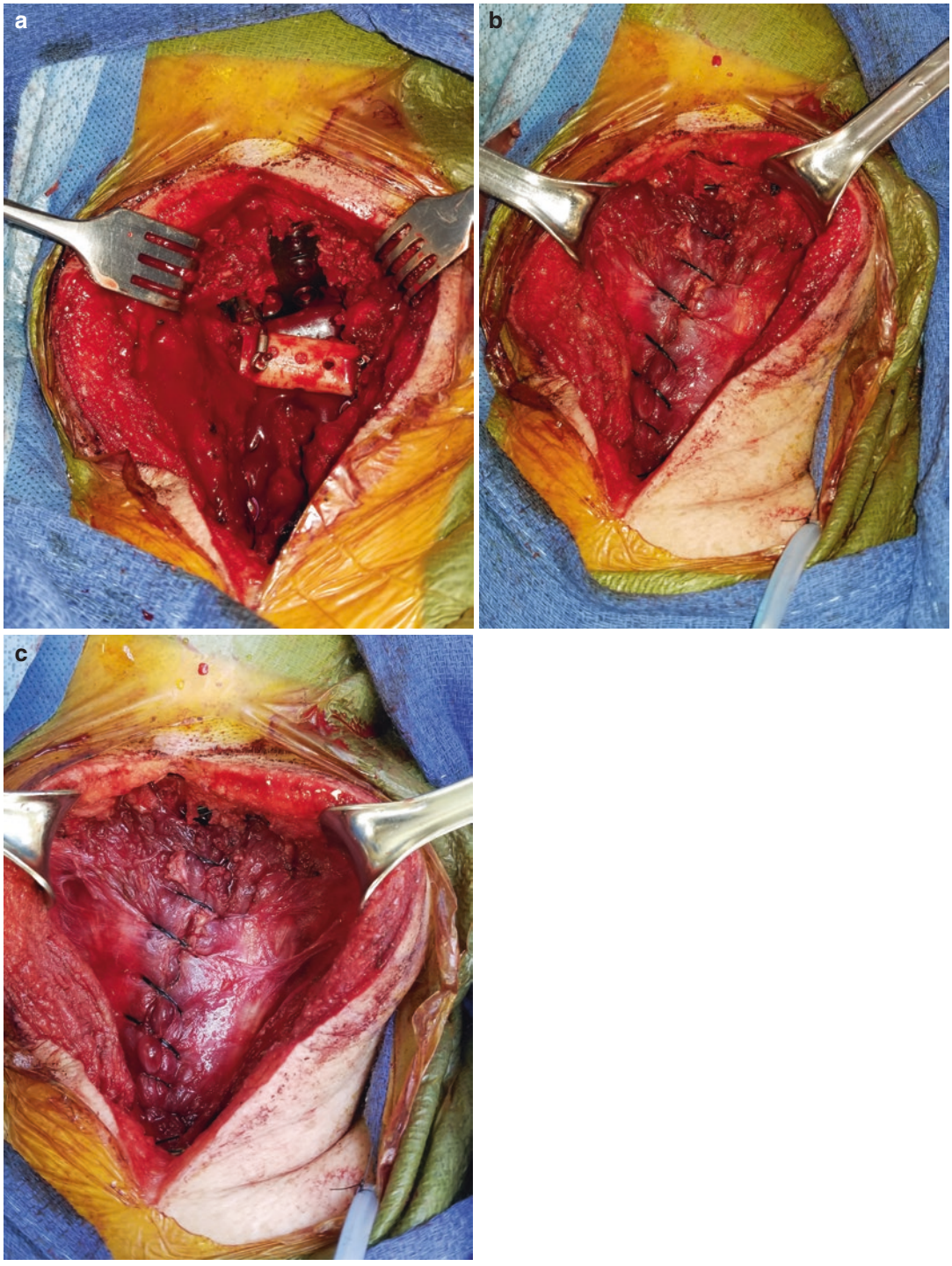

Fig. 48.3 (**a**) Open cervical wound with hardware and bone graft in place. After the deep and superficial muscle planes are dissected, (**b**) the deep paraspinous muscle flaps are approximated and imbricated to obliterate the underlying dead space. (**c**) Next, the superficial trapezius muscle flaps are approximated to provide a secondary layer of coverage over the previously exposed hardware

Revision Spine Surgery and Associated Challenges

Not surprisingly, patients who have undergone previous spine surgery are at higher risk for wound-healing complications. Reconstructive surgeons must consider the possibility that previous incisions may have interrupted blood flow to the soft tissue overlying the spine. Existing midline incisions do not usually pose an issue. In contrast, when paramedian incisions or scars deviating from midline are present, it is crucial to preoperatively plan the location of the new incision so as to maximally preserve blood supply. Previous spinal surgery is not a contraindication for closure with the previously discussed spinal muscle flaps, but it does mandate close preoperative communication between the spine and reconstructive surgeon.

Postoperative Optimization

As with any postoperative period, close and regular monitoring of both the surgical site and the patient's medical condition (i.e., vital signs, pain, and mental status) should be performed. In addition, prevention or elimination of any potential barriers to basic wound-healing physiology should be addressed.

The primary enemy of any healing wound is tissue hypoxia. Multiple sources may contribute to a hypoxic wound bed, including vasoconstriction (secondary to cold, pain, hypovolemia, cigarette smoking, vasopressors), atherosclerosis or microvascular disease, anemia, and decreased cardiac output (among other potential causes). Care must be given to maximizing oxygen delivery to the wound – the wound should be kept warm, pain should be well managed, and the blood count should be monitored for any drop in hematocrit and acted upon as necessary. Fluid status should be optimized to ensure adequate perfusion of the wound bed and muscle flaps to ensure sufficient oxygen delivery. Although smoking cessation is ideal in every patient, smokers should especially refrain from doing so during the immediate postoperative period. Although patients can be counseled ahead of time regarding methods of smoking cessation preoperatively, it is important that they are aware the postoperative period is also a critical time where smoking is detrimental to success of the surgery.

Even with preventive measures to mitigate hypoxia to the wound bend, the surgical site should be closely monitored for signs of hypoxia, especially during the early postoperative period. Skin color, temperature, turgor, and capillary refill should be regularly assessed, and any abnormality should be investigated as soon as possible. Beyond tissue hypoxia, there are numerous other postoperative parameters that should be monitored, which can have a direct effect on wound healing. Nutritional status should be monitored using a blood nutrition panel which tests parameters such as prealbumin, and deficiencies should be promptly corrected/optimized. Protein supplements should be also considered. And, similar to the preoperative period, immunosuppressive medications should be avoided if possible. If steroids must be given, then vitamin A should be given concurrently to counteract the detrimental effect of steroids on healing.

Pressure should be offloaded from the spine as much as possible. Using a pillow as a wedge to keep the patient propped to one side or the other and rotating every few hours is an effective way to ensure that there is no unnecessary pressure being placed on a fresh incision. Both the nurse and the patient should be educated about pressure offloading during the postoperative period. The wound should be kept clean, and any soiled dressings should be changed immediately.

More recently, many surgeons have opted for an incisional subatmospheric dressing, which not only ensures that the incision remains sterile but also encourages wound healing. Negative pressure wound therapy has been shown in the literature to facilitate wound healing as it relieves tension from the wound edges, decreases fluid accumulation, removes infectious material, and promotes the accumulation of granulation tissue. A newer use of subatmospheric pressure dressings has been over closed incisions. Known as an incisional subatmospheric dressing, these devices have been shown to decrease tension on the line of closure, lessen fluid accumulation/seroma formation, and provide

a sterile, airtight environment, all of which contribute to a decreased rate of dehiscence and infection [23–25].

Handling Wound Complications

Although spinal closures are subject to the potential complications of a standard surgical wound, including seroma, infection, and dehiscence, these patients must also be monitored for additional complications such as CSF leak and hardware exposure.

Seroma

Muscle flap closure reduces dead space and significantly decreases the risk of seroma formation, but the complication can still occur. Placement of appropriately sized drains (e.g., #15 Blake) beneath both the muscle and fasciocutaneous layers with application of suction will allow fluid to drain during the early postoperative period. A common goal prior to drain removal is for the 24-hour drain output to remain below 20–30 mL for two consecutive days. Our published experience demonstrates that drains may be left safely in place for 2–4 weeks as necessary and do not increase the risk of infection [4, 22]. Despite these interventions, seroma can still occur while the drain remains in place or after drain removal. Seromas are most frequently present as a painless fluctuant subcutaneous mass, but other less common signs and symptoms may include new or persistent pain, incisional drainage, or even new-onset neurologic deficits secondary to pressure [26].

Small and clinically stable seromas can be drained at bedside or in the clinic. If the seroma persists after multiple drainages, however, surgical intervention may be necessary as a mature cystic lining may prevent fluid resorption and healing of the opposing tissue interfaces. Drainage should be inspected closely, and anything other than a serosanguinous output (i.e., frank blood, pus, and CSF) should prompt further investigation. Large or rapidly progressing seromas in addition to those causing neurologic deficits should be considered for surgical or interventional radiologic drainage.

Cerebrospinal Fluid Leak

Potential signs and symptoms of a CSF leak include headache, photophobia, nausea/vomiting, and wound swelling. If concern for a CSF leak develops, all deep drains should be taken off suction and drained, instead, via gravity into a bile bag which will allow for excess fluid evacuation without exerting a suctioning force within the wound bed. If the drainage remains excessive and continues to result in symptoms, the drain should then be clamped. Other standard treatments such as horizontal positioning and decompressive drainage should be performed as necessary.

Dehiscence/Infection

As previously mentioned, in the event of a superficial dehiscence or even full-thickness skin loss, wounds have the potential to heal with nonoperative interventions if muscle flaps have been utilized. What would have likely been a deeper space infection that may have involved the hardware with a simple spinal closure remains a superficial one that may be treated only with dressing changes or subatmospheric dressings. Prevention of return to the operating room and salvage of the hardware is possible given the extra layers of protection from outside exposure and contamination, which also provide vascularization to the deeper spaces and act as a conduit to ensure adequate antibiotic delivery in the event of an infection.

In the event of a suspected or known infection, antimicrobial therapy should be initiated after sending cultures. The choice of antimicrobial should be guided by cultures and sensitivity results. Infectious disease physicians should be consulted as necessary. Operative intervention should be undertaken if there is clear evidence of involvement of the hardware or if local wound care is inadequate.

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49 Contemporary Radiation for Spinal Metastasis and Spinal Cord Compression

John Roberson, Bernard Newman, and Samuel Ryu

Introduction

Spine metastases are a common complication of many cancers. It is estimated that more than 40% of all cancer patients develop spine metastases during the course of their disease [1–3]. Spine metastases, like any other bone metastasis, commonly present with pain. However, as they progress, they can cause additional issues such as structural problems, due to vertebral compression fractures or bony retropulsion into the spinal canal or neural foramina with associated neurologic deficits. Traditionally, spine metastases have been considered a major sign of terminal stage disease, and, therefore, the goal of treatment has been palliative, relieving pain, and attempting to improve neurologic function and performance status.

With recent improvements in systemic therapy and the identification of an oligometastatic disease state, coupled with advancements in radiation delivery in the form of stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT), the treatment paradigm has been gradually changing toward more aggressive treatment to achieve local tumor control. Furthermore, as these advances have contributed to improve overall survival for select patients, the need for more definitive therapy resulting in durable palliation of symptoms and effective local control has arisen. Indeed, recent reports have demonstrated that patients with limited spine metastases treated with single-fraction radiosurgery to the involved spine have 49% 1-year and 35% 3-year survival rates, with varying median overall survivals based on the primary cancer site, from 1.8 months for lung primaries to 16 months for breast primaries [4]. An additional multi-institutional analysis demonstrated a median overall survival of 19.5 months in a similar group of patients [5].

Spine metastases commonly occur within the oligometastatic state, where SBRT has shown both improved local control and prolonged survival. Therefore, aggressive local treatment, with the goal of providing durable local control, may be strongly warranted in these patients. This chapter will focus on providing a review of the management of spinal metastases from the perspective of a contemporary radiotherapeutic approach.

Presentation and Diagnosis

Spine metastases frequently present with severe back pain that can limit a patient's ability to function, resulting in worsened performance status. This pain is highly complex as it can be due to direct tumor involvement of the vertebra, mechanical instability, or nerve impinge-

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ment including spinal cord compression, often making it difficult to accurately characterize and consistently assess. Pain from bone involvement is typically described as non-positional, constant, improved with movement, and steroid-responsive. Mechanical pain (reflecting spinal instability) is typically more positional and worsened with increased axial load or by bending or standing, though patients with kyphotic deformity may instead notice increased pain when lying flat. Radicular pain consists of a sharp, shooting pain in a dermatomal distribution, while central neurological pain may instead be constant and escalating with associated neurological dysfunction from epidural compression [6].

Neurologic compromise can also be the presenting symptom as approximately 10% of patients may ultimately develop spinal cord compression and/or cauda equine syndrome. These may manifest with weakness or paresthesia/anesthesia distal to the level of compression and/or inability to control bladder and bowel function, resulting in either incontinence or retention. To make an early diagnosis and provide treatment, patients with a known history of cancer who develop new-onset spine pain warrant prompt diagnostic workups with imaging studies including CT, MRI, and PET. For patients who are found to have a lesion without an oncologic diagnosis, biopsy or resection of the spine lesion should also be considered.

Vertebral Metastases

Spine metastases have long been regarded as an oncologic emergency often treated with at least one session of fractionated radiation. For patients without epidural disease, management can be made on a non-emergent basis with the urgency of management determined, at least in part, on the ability to control pain pharmacologically. Regardless, appropriate medical pain management is always required. With the use of aggressive local treatment to the involved spine, the first decision that must be made when assessing spine metastases is whether or not emergent treatment is warranted. Any patient who presents with the aforementioned neurologic signs or symptoms of spinal cord compression should undergo emergent evaluation of the spine with MRI to evaluate for the presence of spinal cord compression or canal compromise.

Spinal Canal Compromise Without Neurological Deficits

Epidural tumor causing canal compromise without neurologic abnormality can be incidentally found during staging workup or follow-up evaluation. If left untreated, this will almost inevitably progress to symptomatic spinal cord compression. In these cases, shared management decisions should be made on a relatively urgent basis through discussion between spine surgeons, radiation oncologists, medical oncologists, and patients. Epidural tumor control is imperative to prevent the development of neurologic dysfunction and progression to spinal cord compression and can be achieved by surgical resection and/or radiation. This represents an excellent clinical scenario in which contemporary spine SRS/SBRT can play a major role. To evaluate this, a reliable grading system (as described below) for canal compromise can be utilized.

Spinal Cord Compression

For patients with overt symptomatic spinal cord compression, glucocorticoids should be administered immediately. This management step has been shown to improve ambulation in such patients [7]. Trials have established the most commonly used regimen consisting of dexamethasone 10 mg IV bolus followed by 16 mg per day (4 mg every 6 hours), tapered over 2 weeks [8]. MRI should be obtained promptly to visualize the extent of spinal cord compression and to allow for treatment planning. For patients found to have spinal cord compression on a localized MRI, imaging of the complete spine to evaluate for multilevel cord compression is highly advised to allow for a more comprehensive treatment decision. Multimodality spine tumor board

discussion is highly recommended to coordinate available treatment options and formulate an optimal, individualized management strategy.

Incidentally Found Asymptomatic Lesions

Recently, MRIs have become more widely used for evaluation of spinal metastases, and due to their increased ability to detect lesions, they have resulted in finding incidental occult or small volume vertebral lesions without associated symptoms. In some instances, these lesions represent oligometastatic disease where SRS/SBRT can actually lead to prolonged survival, thereby opening a new realm for SBRT treatment of spine lesions [9]. Though decisions regarding treatment options in this particular clinical scenario are not well established, SRS/SBRT to the involved spine can be the treatment of choice. Even so, a multidisciplinary approach is necessary to facilitate treatment decision-making and coordinate this portion of the patient's total oncologic care.

Considerations of Management

Definitive treatment of spine metastases and/or spinal cord compression after initial imaging and initiation of glucocorticoids typically consists of either surgery with adjuvant radiation or radiation alone. Unlike other bone metastases, spine treatment evaluation should take into consideration the presence of spinal instability, degree of spinal cord compression, radiosensitivity of the tumor, and duration and rapidity of symptom development. Other factors, including control of systemic disease, number of levels involved by disease, and whether the patient has received prior local treatment to the area, also play a role in determining the management.

Oncologic Assessment

Assessment of the entire tumor burden including the primary site and all metastatic sites, along with their performance status, general condition, and comorbidities, is required to prognosticate patients' overall oncologic status. Radiosensitivity of the primary tumor is also an important factor in decision-making. Many patients who present with metastatic spinal cord compression will have known pathology, allowing for rapid estimation of radiosensitivity. When there is no previous diagnosis of cancer, initial surgical management may be both therapeutic and diagnostic. Radioresponsive or chemoresponsive tumors include lymphomas, seminomas, small cell lung cancers, and multiple myelomas and can be treated with either radiation or chemotherapy alone [10]. All other tumors will require radiation either postoperatively or as the sole treatment.

Conventional fractionation external beam radiation therapy (cEBRT) is delivered with the most common regimen of 30 Gy in 10 fractions. An early prospective trial of cEBRT alone for spinal cord compression conducted in the 1980s–1990s found that patients with myeloma or lymphoma remained ambulatory in 100% of cases (10/10) in which they were ambulatory prior to treatment and regained ambulation in 64% of cases (7/11) in which they were non-ambulatory prior to treatment [11]. As will be seen below, these numbers are comparative to more radioresistant tumors treated by either SRS/SBRT alone or surgery followed by cEBRT. For this reason, patients with radioresponsive tumors have been excluded from subsequent trials evaluating management options.

Prior Treatment

Accurate information regarding any previous spine treatment is also required when deciding management options, particularly whether patients have received any prior local therapy with surgery or radiation. cEBRT treatments typically include 30 Gy in 10 fractions delivered to the 1–2 spine segments above and below the involved segments. Any previous treatments have also delivered similar radiation doses to adjacent normal structures, including the spinal cord, lung,

esophagus, bowel, etc. Retreatment of the spine often is challenging in the setting of previous full-dose spine radiation. In many instances, these patients may be retreated with nearly full-dose radiation assuming that enough time has passed since the initial treatment. Yet, in some instances, patients will develop local progression or recurrence after only a relatively short period after the initial radiation treatment. Consideration of radiation dose, time interval, and target volume are important factors when considering retreatment, as well as patient's symptoms, oncologic status, general condition, and availability of other treatments. As will be discussed below, current evidence suggests a similar response to SRS/SBRT following initial cEBRT compared with de novo SRS/SBRT.

Spinal Stability

An essential component in the assessment of spinal cord compression and vertebral column metastases is the structural stability of the spinal column. No amount of radiation or chemotherapy – no matter the histology – will stabilize an unstable spine. The Spinal Instability Neoplastic Score (SINS) has been developed to provide guidance in determining which patients have the greatest instability and uses the following criteria: vertebral body location, presence of pain, type of bone lesion, spinal alignment on imaging, presence of vertebral body collapse and extent of vertebral body involvement, and involvement of the posterior elements, with total scores ranging from 0 to 18. Lesions are then classified as "stable" (0–6), "potentially unstable" (7–12), and "unstable" (13–18) with recommendation for surgical consultation for all lesions that are unstable or potentially unstable (i.e., score > 6) [12]. Though the SINS may provide guidance in determining the necessity for stabilization of the spine, note that it is not a perfect classification system and lesions classified as "stable" may actually behave as if they were "unstable." Finally, even if a patient is determined to have an "unstable lesion," factors like extensive systemic disease or severe medical comorbidities signaling poor overall surgical outcome may also impact the advisability and necessity for spinal stabilization.

Duration and Severity of Neurologic Symptoms

The duration and severity of neurologic symptoms also play a significant role in determining the proper management of spinal metastases. As noted above, whether patients with spinal cord compression are ambulatory is an important hallmark of whether they will be ambulatory after treatment. This is seen in the literature regardless of histology or treatment method with cEBRT alone, SRS/SBRT alone, or surgery followed by cEBRT. Since these neurologic symptoms develop as a result of extrinsic compression on the spinal cord, it is believed that the longer a patient experiences such symptoms, the more likely they are to develop irreversible neurologic damage and the less likely they are to return to their previous level of functioning. Indeed, an analysis regarding the timing of surgery following onset of neurologic symptoms due to metastatic spinal cord compression demonstrated improved outcomes if patients underwent surgery within 48 hours of symptom onset, and it also established a negative correlation between delaying surgery and neurologic improvement [13]. Thus, both the severity and duration of symptoms and the rapidity of their development play a significant role in determining further management.

Extent of Spinal Involvement

Both surgical intervention and radiation therapy are directed to the involved spinal segment, meaning that an important aspect in determining treatment options is the extent of spinal involvement. Furthermore, since the goal of spine SRS/SBRT is to maximize local tumor control and preserve neurologic function while providing durable palliation, it is important to properly identify patients who may most ben-

efit from this treatment approach (as opposed to cEBRT). Much like in the setting of stereotactic radiosurgery for brain metastases, there is no clear-cut answer as to the number of spine levels that can be treated with spine radiosurgery. RTOG (NRG) 0631 includes different clinical scenarios: (1) solitary spine metastasis with or without epidural or paraspinal soft tissue extension; (2) two contiguous spine levels; (3) non-adjacent spine metastases (generally up to three sites); (4) diffuse metastases along the spinal column; and (5) multiple spinal level involvement with very small "occult" lesions visible only on MRI scan within the vertebral bodies (the size of these small lesions is defined as being less than 20% of the vertebral body). One future area of development includes defining how to best handle these occult metastases. Of note, caution must also be taken with larger targets (such as scenario 3 above) as the spinal cord dose tends to increase more with individual targets larger than 6 cm [4]. A paravertebral mass extending from an involved spine can also be treated with spine radiosurgery, though there is again no guideline as to the size of paravertebral involvement. In RTOG 0631, 5 cm was used as the size cut off for paraspinal masses, but it must be decided whether these paraspinal lesions can be safely included in the target volumes. Such factors also affect the decision-making to undergo surgery.

Spinal Cord Compression Grading Systems

With the routine use of MRI to evaluate epidural extension and spinal cord compromise and the more widespread availability of SRS/SBRT and sophisticated surgical methods to treat spine metastases, attempts have been made to develop grading of spinal cord compression. There are two main systems developed for evaluation of malignant spinal cord compression, one by Bilsky et al. based on MR images and another by Ryu et al. based on both MRI configuration and neurological status. Bilsky et al. developed a four-point grading system to assist with surgical decision-making, subdividing grade 1 into three separate grades, whereas Ryu et al. used grades 0–V based on the extent of the epidural lesion. The two available grading systems are essentially identical radiographically (Fig. 49.1). In both systems, involvement of the vertebral bone only is grade 0, with the other grades representing epidural impingement with no thecal sac deformation (Bilsky grade 1a = Ryu grade I), thecal sac deformation without spinal cord abutment (Bilsky grade 1b = Ryu grade II), spinal cord abutment (Bilsky grade 1c = Ryu grade III), partial spinal cord compression with visible CSF (Bilsky grade 2 = Ryu grade IV), and complete block with no visible CSF (Bilsky grade 3 = Ryu grade V) [14, 15]. In order to provide further assistance with making clinically oriented treatment decisions, Ryu et al. developed a dual grading system which takes into account both radiographic spinal cord compression and the neurological deficits [15]. In this system, patients receive a radiographic grade from 0 to V, which scales the degree of canal compromise and cord compression, and a neurologic grade from a to e, routinely used in clinic, corresponding to the Tomita functional motor grade [16]. Using this system, for example, grade IIIc indicates the spinal cord is impinged by tumor and the patient has mild muscle weakness with 4/5 power. This grading system is thus useful for treatment decision-making and monitoring epidural lesions and neurological status after treatment.

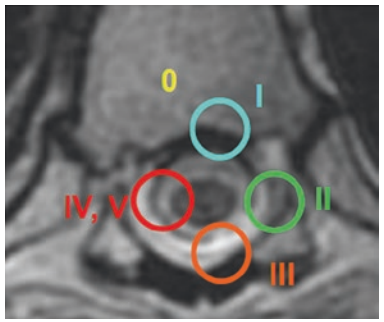
Treatment Options

The treatment paradigm for spine metastases and/or spinal cord compression with surgery and radiation has been changing over the last decade, with contemporary options including cEBRT, multiple fractionation schedules of radiosurgery, and various surgical or other interventional procedures, as well as combinations of these treatments in the form of multimodality therapy. It is thus important to understand how the various treatment modalities may be employed in the management of spine metastases.

a

Dual grading system (Ryu's)

Radiographic grade

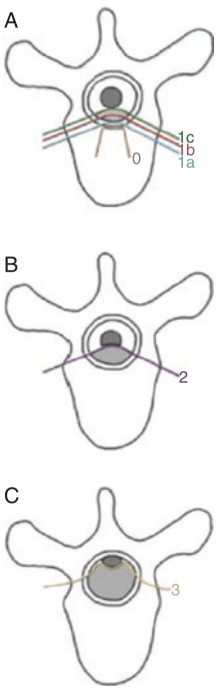


0	Spine bone metastasis No epidural lesion
I	Minimal canal compromise, Thecal can be impinged
II	Thecal sac compressed, but spinal cord is intact
III	Spinal cord impinged
IV	Spinal cord displaced/compressed, CSF visible, Partial block
V	CSF not visible, Complete block

Neurological grade

a	No abnormality
b	Minor symptoms (eg, pain, radiculopathy, sensory change)
c	Functional paresis Muscle power ≥ 4/5. -nerve root sign or spinal cord sign present -functional in the upper extremity muscles -ambulatory in the lower extremity muscles
d	Non-Functional paresis Muscle power ≤ 3/5. -non-functional in the upper extremity -non-ambulatory in the lower extremity
e	Paralysis, Incontinence

Surgical grading system (Bilsky's)



b

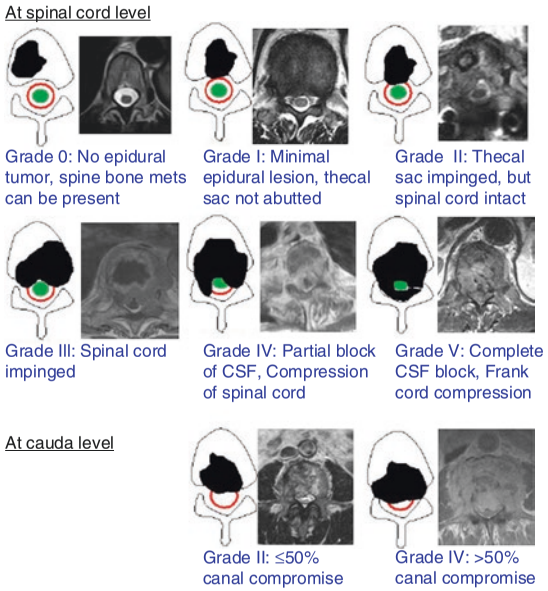


Fig. 49.1 Comparison of the proposed grading systems of spinal cord compression: Ryu's dual radiographic and neurological system (**a** and **b** with schematic drawing of radiographic grade), and Bilski's grading system

Surgical Management

Surgical treatment options include laminectomy, separation surgery, and direct decompressive surgery with corpectomy. Stabilization of the spine, often as a required component of surgery, may also be accomplished through different methods of instrumentation and reconstruction. Significant bony retropulsion due to a compression fracture should be managed surgically rather than with radiation. Likewise, structural spine instability should also be evaluated and managed surgically. Separation surgeries are intended to create a gap between the epidural tumor and the spinal cord, not necessarily removing the entire tumor, in order to allow for the full radiosurgery dose to be delivered to the gross epidural tumor. Regardless of the type of surgery employed, postoperative radiation is essential to prevent local recurrence and tumor progression. Further discussion of the surgical management of spine metastases is reserved for another chapter.

Conventional External Beam Radiation Therapy

Conventional external beam radiation therapy (cEBRT) has been used for palliation of pain and for spinal cord compression for decades. Studies have shown that multiple fractionation regimens are acceptable and provide equivalent response. The most common regimen has been 30 Gy in 10 fractions using simple radiation field arrangements. It appears that patients treated with a single fraction (e.g., 8 Gy in 1 fraction) as opposed to multifraction regimens (e.g., 3 Gy × 10 fractions) are more likely to require retreatment (21.5 vs. 7.4%) and develop pathologic fractures [17]. However, a more recent randomized trial comparing 8 Gy × 1 with 4 Gy × 5 showed no difference in outcomes for patients with spinal cord compression [18]. In general, the target volume includes the involved spine segments as well as 1–2 vertebral bodies above and below the intended target spine levels. The procedure for cEBRT includes assessing targeting accuracy, delineating tumor and normal tissues, and planning and delivering treatment. As in all radiation treatments, daily or less frequent image guidance is used, though in rare circumstances patient alignment can be done clinically. Since cEBRT uses greater margins around the involved level, it may be used to treat patients in extreme uncontrolled pain who are unable to comfortably lie still. Over the past two decades, the practice of radiation oncology has changed considerably with the use of radiosurgery for spine metastases and spinal cord compression showing promising results, leading to ongoing large randomized trials.

Surgery Followed by Radiation

Following a prospective randomized trial carried out in the 1990s, surgery with direct decompressive corpectomy followed by cEBRT to 30 Gy in 10 fractions became the standard of care for medically operable patients with at least 3 months to live and non-radiosensitive tumors [19]. The endpoint of this trial was the ability to ambulate, defined as four steps with use of an assistive device. The trial showed significant improvement in overall ambulatory rate with surgery plus cEBRT (84%) compared to cEBRT alone (57%) and an improved duration of ambulation of 123 days for surgery plus cEBRT versus 13 days by cEBRT alone. However, in the subset analysis, only 62% of non-ambulatory patients became ambulatory after surgery. This suggests that patients' initial ambulatory status is an important prognostic factor of functional outcome.

With the development of SRS/SBRT in the 2000s, the role of postoperative SBRT was also evaluated. The initial clinical experience was reported in 2006 and included 18 patients treated with SRS to 14–16 Gy in a single fraction delivered 1–2 weeks after open surgery. This demonstrated that postoperative SRS is well tolerated and associated with minimal morbidity [20]. However, one of the main difficulties with postoperative SRS involves delineation of the tumor and spinal cord in the setting of recently placed instrumentation hardware, resulting in poor CT and MR image quality. Because of this, CT myelograms have also been used to provide better

delineation of the spinal cord. In an effort to help define the postoperative target volume for SRS/SBRT, consensus guidelines were also developed by 10 experts from high-volume institutions [21]. The general consensus is to cover preoperative sites of osseous and epidural disease irrespective of the extent of surgical resection, including gross residual disease seen on postoperative imaging and the adjacent tissue at risk for microscopic disease extension, with PTV expansions varying from 0 to 2.5 mm. The spinal cord avoidance structure should also be subtracted from the final PTV for treatment planning. Surgical instrumentation and the incision do not need to be included unless believed to be specifically at risk for tumor involvement.

There is also concern raised about potential "underdosing" of portions of epidural tumor immediately adjacent to the spinal cord due to the inherent radiosurgical dose gradient in the spinal cord. To ensure that the full radiosurgical dose covers the epidural tumor while maintaining a safe spinal cord dose, separation surgery has been developed in which the strategy is both to decompress the spinal cord to allow full radiosurgical dosing and also to stabilize the spine. This strategy has been recommended for patients with high-grade epidural spinal cord compression or previously irradiated tumors [22]. An analysis of patients treated in this manner at Memorial Sloan Kettering demonstrated local tumor progression of 4–9% at 1 year following treatment with either 24 Gy in a single fraction or 24–30 Gy in three fractions [23, 24].

Stereotactic Radiosurgery

Stereotactic radiosurgery (SRS or SBRT) was initially developed as a primary treatment modality for spine metastases in the late 1990s. Multiple single institution experiences have reported durable and rapid pain control in the range of 90%. Median time to pain relief has been found to be just 2 weeks after treatment with select patients experiencing pain relief within 24 hours [25–27]. Median duration of pain control in the treated region of the spine has been shown to be 13.3 months [28]. Others have also demonstrated similar results regarding pain control in patients with spine metastases [27, 29–31]. Quality of life also was improved following pain control [27]. Local tumor control at the treated spine was achieved in 95% of patients with recurrence at the immediately adjacent vertebra in less than 5% [26]. Patients with oligometastatic disease had longer survival with more effective local treatment of the spine metastasis [4]. These clinical results support the idea that more intensive treatment may be appropriate for patients with localized spine metastases in order to improve their clinical outcome and overall quality of life.

The overall procedure for spine SRS/SBRT includes patient positioning and immobilization with imaging to provide targeting accuracy. Ensuring proper immobilization is the first step toward the clinical application of spine SRS/SBRT. Initial techniques included invasive procedures that anchored hardware to the cervical spine and skull or required a stereotactic frame to be attached under general anesthesia to the lumbar spinous processes [32]. Another early technique developed used a body frame with a contour mold fixation [33]. More recently, a frameless and noninvasive positioning method, used by most institutions, has been developed [25, 34]. There is no perfect method for immobilization. It is important to provide stability and support to patients in a treatment position that is comfortable. While breathing-related organ motion exists, it does not appear to affect treatment outcomes. Other voluntary and involuntary movements, such as swallowing, coughing, and pulsation, also occur, some of which may be controlled with premedication. Another important clinical scenario involves spine pain which may lead to random and unexpected patient movement. It is therefore important to properly manage spine pain with short-term pain medication prior to initiating the procedure.

The radiation doses used for spine SRS/SBRT also vary among investigators. An initial analysis of patients at Henry Ford Hospital treated between May 2001 and May 2003 found a strong trend toward improved pain control with higher doses, particularly of 14 Gy or more [28].

Based on this experience, RTOG 0631 adopted 16–18 Gy in one fraction as the standard dose to be evaluated [35]. Another analysis of patients treated with single-fraction SRS at Memorial Sloan Kettering suggested improved local control for patients treated with 23–24 Gy compared to lower doses [36]. It is important to note that the dose prescription methods are different between institutions, prescribing to either the tumor margin or the isocenter. There are other fractionated regimens for spine SRS/SBRT, such as 24–30 Gy in three fractions or 30–40 Gy in five fractions, while Canadian investigators are also testing 24 Gy in two fractions in a national clinical trial.

In terms of target delineation for SRS/SBRT, it is important to recognize that each vertebra consists of compact bone and marrow within a trabeculated network that extends from the vertebral body into the pedicles. Thus, while imaging may demonstrate gross disease within the vertebral body (i.e., GTV), this may not represent the full extent of tumor involvement. We, therefore, recommend using a clinical target volume (CTV) which consists of the involved elements of each vertebral body as the target. Examples of target volumes are illustrated in Fig. 49.2, adapted from Ryu et al. [4], showing the most common cases of vertebral body involvement. Guidelines for the delineation of such targets were adopted in the RTOG 0631 trial and have been further defined by consensus among experts at high-volume institutions [37].

The most critical normal structure for spine SBRT is the spinal cord. In order to delineate the spinal cord, T1-weighted contrast-enhanced and T2-weighted MR images are fused to the CT simulation images with 1–2 mm slice thickness. Due to the nature of radiosurgery with rapid dose fall-off, there is a degree of radiation dose gradient within the diameter of the spinal cord. The accumulated dose volume analysis of the spinal cord in 230 procedures by Ryu et al. demonstrated a partial-volume tolerance of the spinal cord of 10 Gy to the 10% cross-sectional area of the spinal cord (corresponding to 0.35 cc of the spinal cord volume), provided that the spinal cord is defined as 6 mm above and below the radiosurgery target volume. The reason for using this partial volume includes the rapid dose fall-off with SBRT from the 90% to 50% isodose lines of 5 mm when coplanar SBRT beams are used [4]. When non-coplanar beams are used, the absolute volume criteria are also used. Other investigators developed slightly different criteria to define the spinal cord dose, including a maximum dose of 12–14 Gy at the surface of an MRI-defined spinal cord or a maximum dose of 10 Gy to a myelogram-defined spinal cord [36, 38]. Taken together, these dose constraints appear to be in a similar range. It is also important to delineate other surrounding normal tissues, including the laryngopharynx, trachea, esophagus, bowel, and kidneys, with recommended dose constraints having also been published [39, 40].

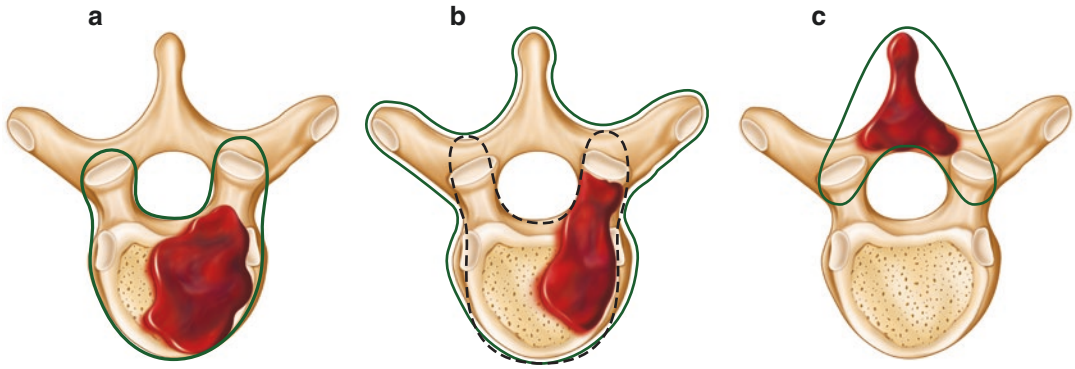


Fig. 49.2 Target delineation models for SRS/SBRT to spine metastases. (**a**) The most common form of spine metastasis involving the vertebral body. (**b**) Involvement of the vertebral body with extension into the pedicles; more extensive lesions can be treated either with generous margins (dotted line) or by including both anterior and posterior elements (solid line). (**c**) Involvement of the posterior elements only [4]

Decision-Making Algorithm

Historically, there was not sufficient need to develop radiation treatment algorithms since spine metastases were treated palliatively with cEBRT with or without surgery. However, with recent advances in systemic therapy, targeted therapy, immunotherapy, radiosurgery, and open surgery, treatment algorithms that aid decision-making will be essential, particularly in patients with oligometastatic disease. An interdisciplinary decision-making framework was developed which used components of neurologic, oncologic, mechanical instability, and systemic disease (NOMS) [22]. An update from the International Spine Oncology Consortium provided greater guidance based on the status of the systemic disease, including overall performance status, tumor systemic burden, and further treatment options [10]. When the results of ongoing large clinical trials assessing SRS/SBRT and the treatment of oligometastases become available, more detailed and practical guidelines should be developed.

Treatment Outcomes

Evaluation of treatment outcomes must take into consideration the patient's presenting symptoms as well as pretreatment imaging findings. For patients who present with back pain (a very common presenting symptom), the goal of treatment is primarily to relieve the back pain. For patients who present with neurologic symptoms and/or evidence of epidural tumor extension, treatment goals include decompression of the epidural tumor and thecal sac expansion as well as improving or maintaining neurologic function.

Control of Metastatic Spine Pain

Pain response after cEBRT, regardless of the radiation dose used, appears to be approximately 50–60% including 30–35% with a complete response [17]. Trials also indicate that the median duration of pain control after cEBRT is around 3–4 months regardless of treatment fractionation [41]. Meanwhile, initial results with radiosurgery suggest that pain control is seen in around 85–90%. A retrospective review of 500 lesions treated with spine SRS at the University of Pittsburgh to a median of 20 Gy in 1 fraction found long-term pain control of 86% [42]. A phase II dose escalation trial carried out at Henry Ford Hospital found increased pain control with doses above 14 Gy in 1 fraction with 1-year actuarial pain control of 84%. Duration of pain control after SBRT appears to be around 13 months [28]. It appears that higher doses seen with radiosurgery provide superior and more durable pain control than conventional palliative regimens. These observations served as the basis for the phase II/III RTOG 0631 trial, comparing 8 Gy in one-fraction cEBRT with 16 Gy or 18 Gy in one-fraction SRS. The result of this large randomized study showed equal rate of pain control between the two arms due to the unexpected low rate of pain control in the radiosurgery arm (presented at ASTRO 2019). Patients should be evaluated periodically to evaluate pain control after treatment. Providers must be diligent in distinguishing radiation site-specific pain from other pain complaints [6]. Patients with recalcitrant pain should be referred to a pain management specialist.

Epidural Tumor Control and Neurologic Compromise

The goals of treatment for spinal cord compression (or spinal canal compromise) are control of the epidural disease, decompression of the spinal cord, and preservation or improvement of neurological function. A prospective randomized trial carried out by Patchell et al. in the 1990s for patients with a single site of metastatic spinal cord compression with expected survival of at least 3 months and who were not paraplegic for more than 48 hours found that direct decompressive surgery followed by cEBRT(30 Gy in 10 fractions), compared to cEBRT alone, resulted in a better ambulatory rate for all patients (84% vs. 57%), for patients who were ambulatory prior to treatment (94 vs. 74%), and for patients who were not ambulatory prior to treatment (62 vs.

19%) [19]. While this trial defined ambulation as the ability to take four steps with the use of an assistive device, it is uncertain whether this relates practically to actual independent walking, though it is certainly important for activities such as transferring from bed to chair or commode and back. This trial established surgical decompression followed by cEBRT as the standard of care for this group of patients.

With advancements in radiation treatment, a phase II trial was carried out by Ryu et al. in the 2000s assessing SRS to a dose of 14–20 Gy in a single fraction in the management of epidural spinal cord compression. The results demonstrated that the mean reduction in epidural tumor volume was 65% at 2 months with an overall epidural tumor response rate of 80%, including 27% complete response, 30% partial response (> 50% tumor volume reduction), and 23% minimal response (25–50% reduction). This resulted in decreased epidural tumor area at the level of most severe decompression and improved thecal sac patency [15]. Importantly, the study also demonstrated that 94% (33 of 35) of patients who were intact before radiosurgery remained intact, and 63% (17 of 27) of patients who had neurologic deficits prior to radiosurgery demonstrated improvement. Excellent results for pain relief and improvement in neurologic deficits were obtained for multiple myeloma causing thecal sac compression, which commonly occurs in this disease [43]. An additional retrospective analysis with high-grade spinal cord compression (radiographic grades IV–V) treated with SRS to 18 Gy in one fraction was performed from the Henry Ford Hospital Database. Only 18% (6 of 33) deteriorated within 2 months of treatment and 67% retained their ambulatory status [44]. A more recent effort to relax the spinal cord dose in patients with spinal cord compression showed encouraging results for SRS with a spinal cord maximum dose up to 16 Gy in a phase I clinical trial [45].

Although it is not possible to compare two separate trials, the results of surgery versus radiosurgery are comparable in preserving or improving the neurological outcome. The subset results of Patchell's and Ryu's trials are summarized in Table 49.1. The rates of ambulatory or neurologically intact patients remaining ambulatory or intact were 94% after either surgery or SRS. The rates of non-ambulatory or neurological deficit patients improving to ambulatory or intact were 63% after either treatment. That said, treatment decisions must be individualized for each patient as discussed in this chapter and elsewhere in this book. The NOMS and SINS frameworks are useful, but providers must also integrate the patient's performance status, prognosis, and available systemic treatment options in the decision regarding optimal spinal metastasis management.

Table 49.1 Comparison of clinical trial results of surgery versus radiosurgery

	Patchell's phase III trial [19]			Ryu's phase II trial [15]
	Surgery + cEBRT	cEBRT alone		SRS alone
Overall ambulatory rate	84% (42/50)	57% (29/51)	Overall intact rate	81% (50/62)
Ambulatory pts remain ambulatory	94% (32/34)	74% (26/35)	Intact pts remain intact	94% (33/35)
Non-ambulatory pts improve to ambulatory	62% (10/16)	19% (3/16)	Deficit pts improve to intact	63% (17/27)

cEBRT conventional external beam radiation therapy, *SRS* stereotactic radiosurgery

Re-irradiation Outcomes

Approximately 50% of patients treated with cEBRT require re-irradiation following the initial treatment [46]. Re-irradiation with cEBRT is often done at lower doses than initial treatments and tends to be less effective, with overall response rates of 45–51% and complete response rates of only 11–14% [47]. By contrast, retreatment with SRS/SBRT provides local control rates >75% with a modest toxicity profile comparable to de novo SBRT [48]. For example, in an analysis of patients treated with salvage SBRT after in-field failure of initial SBRT (24 of whom had

already received prior cEBRT as well), the study demonstrated a 1-year local control rate of 81% with no radiation-induced vertebral compression fractures or myelopathy observed [49]. SBRT therefore is a good option for recurrent tumors.

Treatment Complications

Treatment Failure

Treatment failures after spine SBRT can be divided into three different categories: in-field failures (regrowth within the target volume), marginal failures (progression within the region of rapid dose fall-off surrounding the target volume), and distant failures. Each of these failures may have distinctive causes: for example, in-field failures due to the inherent radioresistance of tumors, marginal failures due to errors in patient setup or underestimation of the target volume, and distant failures due to continued progression of metastatic disease.

Previous studies have demonstrated low rates of in-field and marginal failures following SBRT of 5–6% [26, 38]. This low incidence of in-field and marginal failures helps justify the use of SRS/SBRT. It should also be noted that persistent or progressive pain may not be a good indicator for tumor progression, as there may be other causes including spinal instability and degenerative disorders that contribute to this pain.

Acute Complications

Acute exacerbation of pain occurs usually within 1–5 days after treatment, known as a pain flare. The incidence of pain flares after SBRT is reported to be 20–60% and can occur anywhere from the day after treatment until 20 days later [50]. Some have also found an increase in the incidence of pain flares after single-fraction SRS compared to multiple fractions [51]. Fortunately, pain flares are typically transient and very responsive to a short course of low-dose glucocorticoids (e.g., dexamethasone 4 mg daily for up to 5 days). Although some advocate using steroids prophylactically [52], we do not do so. In fact, we taper steroids immediately after the procedure for those who were already receiving steroids. The cause of the pain flare is unknown, but it is advised to limit the radiation dose to the spinal nerve root under 14 Gy.

Other side effects from radiation are related to incidental treatment of neighboring normal tissues, including the larynx, pharynx, esophagus, bowel, lung, kidneys, etc. and should thus be delineated. Symptoms may manifest as dysphagia, odynophagia, nausea, and bloating, depending in large part on what part of the spine is treated. Of note, we limit the esophagus to 10–12 Gy in a single dose [39]. These side effects are generally self-limiting and resolve within weeks after treatment, but long-term development of a tracheoesophageal fistula has been reported [53]. To avoid acute complications, efforts should be taken to minimize radiation doses to mucosal structures.

Long-Term Neurologic Complications

Radiation-induced damage to the spinal cord can severely adversely affect patients' quality of life. It is therefore imperative to make every effort to avoid unnecessary and/or excessive radiation to the spinal cord. As noted above, the spinal cord partial-volume tolerance dose has been defined as 10 Gy to the 10% partial volume of the spinal cord defined as including 6 mm above and below the target volume (calculated to be equivalent to 0.35 cc) [4]. The spinal cord tolerance dose can vary depending on the fractionation scheme. Other factors include host factors, comorbidities, oncologic status, and previous treatments. Regardless, it is always advised to minimize the radiation dose to any of the normal tissues.

Long-Term Non-neurologic Complications

Vertebral compression fracture has been reported to occur in about 10–15% of patients [54–56]. A similar rate of vertebral compression fractures

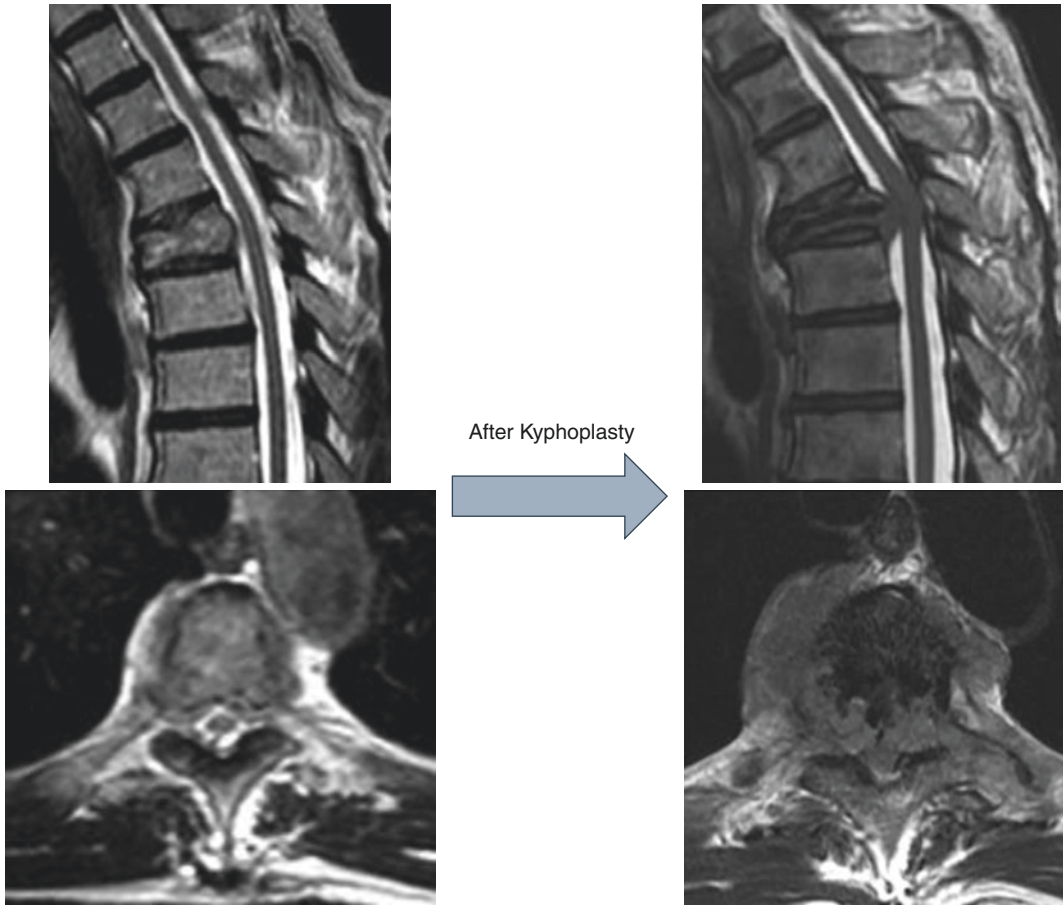


Fig. 49.3 An example of worsening of epidural compression after kyphoplasty

is also seen for SBRT delivered after cEBRT [48]. Analyses of predictive factors have found that patients with prior kyphotic/scoliotic deformity, lytic lesions, and receiving higher doses (≥ 20 Gy) are at a higher risk of developing vertebral compression fractures. In these instances, consideration must also be given to the extent of involvement of the vertebra, the presence of other degenerative changes, and whether the patient is symptomatic from the compression deformity. Some patients are candidates for kyphoplasty prior to SBRT when there is concern of developing a compression fracture particularly if they have pain and no evidence of epidural extension [57]. We have observed worsening of spinal cord compression by upfront kyphoplasty in patients with an existing spinal cord compression, making it more difficult to treat with SRS. An example of this case is shown in Fig. 49.3. We recommend initial SRS/SBRT for those who have any oncological issues unless management of the compression fracture or instability is more critical for total care of the patient after discussion at a multidisciplinary spine tumor board.

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50 Intraoperative Radiation for Spinal Metastatic Disease

Brandon S. Imber, Michael R. Folkert, and Yoshiya Yamada

Introduction and Rationale for Intraoperative Radiotherapy

Intraoperative radiotherapy (IORT) is a general term that describes the delivery of therapeutic doses of radiation during surgical resection of a tumor to the sites of greatest likelihood of recurrence (i.e., suspicion of microscopic positive margins). This can involve utilization of a small linear accelerator inside a shielded operating or treatment room, which delivers relatively superficial radiation dose to a surgical cavity, generally with electrons or low-energy photons. Alternatively, IORT may also be delivered using brachytherapy techniques, which are defined by the placement of radioactive sources directly into, or in close proximity to, a tumor or tumor bed.

The risk of radiation myelitis is one of the most feared complications of spinal radiotherapy. The classic spinal cord tolerance is typically felt to be around 45–50 Gy in conventional or standard fractions (e.g., 1.8–2 Gy per fraction) or 13–15 Gy in a single fraction [1], and this dose typically dictates the maximum possible dose of external beam radiotherapy (EBRT), which can be offered. However, prospective series with image-guided intensity modulated radiation therapy (IMRT) and proton therapy have explored raising this constraint to 54 Gy at the center of the cord and up to 63 Gy to the surface of the cord over a length of up to 5 cm using conventional fractionation [2]. The advantage of IORT compared to EBRT is that a highly ablative dose of radiation can be delivered to the area at risk with relative sparing of nearby radiosensitive structures (e.g., spinal cord and cauda equina). This can be achieved by using forms of radiation with high dose rate but low penetrative ability (e.g., electron beams or very low energy photons). For brachytherapy, nearby tissue sparing is possible due to the fact that dose rate falls off rapidly in accordance with the inverse square law, which states that the intensity of light is inversely proportional to the square of the distance. This results in rapid reductions in delivered dose within very short distances from the surface of the brachytherapy source.

IORT can also be used to supplement dose delivered with EBRT given pre- or postoperatively, where it can be an effective strategy for dose escalation since it enables greater focal dose delivery to tumors within the vertebral body or epidural space [3, 4]. Brachytherapy

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is particularly versatile for the following complex clinical situations:

(a) When there is a relatively radioresistant tumor histology (e.g., chordoma, renal cell carcinoma or sarcoma) where effective tumoricidal doses exceed the cord tolerance
(b) When circumferential disease involvement is present around the spinal dura
(c) In retreatment or salvage settings when the spinal cord has already received high radiation doses and additional external beam radiation could result in exceeding the tolerance of the cord

Historical Context

Brachytherapy is one of the oldest forms of therapeutic radiation and was first utilized for central nervous system tumors in 1912 by Hirsch with catheter injection of radium into the sella turcica [5]. The neurosurgeon Harvey Cushing implanted a "radium bomb" into an intracranial surgical cavity [6], but his disappointment with brachytherapy's modest results led him to quickly abandon the approach. Interest in central nervous system brachytherapy was strengthened by the development of stereotactic guidance in the 1950s, which enabled precise implantation of radioactive sources into inoperable brain tumors [7]. Over the ensuing decades, further advancement in stereotactic approaches and better image guidance enabled further refinement of brachytherapy techniques [8]. Today, numerous IORT strategies exist to address complex intracranial and spinal pathologies.

Physics of Accelerator-Based and Brachytherapy IORT

Since numerous IORT approaches have been employed for spinal disease, it is first important to understand potential treatment considerations. Accelerator-based approaches require a linear accelerator to generate either therapeutic X-rays or electrons [9]. A treatment cone or applicator is usually placed directly in a surgical cavity (at risk for microscopic residual disease after gross total resection) or potentially against areas of residual gross disease. The energy and type of radiation generated dictates how deeply the dose penetrates beyond the tumor bed.

Treatment of a spinal tumor using brachytherapy requires appropriate selection of a source, which is the radioactive material that delivers radiation dose. Table 50.1 highlights some of the common source isotopes utilized for spinal brachytherapy. There are several parameters that influence source selection:

- *Dose rate.* Spinal IORT can utilize either high dose rate (HDR) or low dose rate (LDR) radioisotopes. As the name suggests, LDR sources decay and deliver dose more slowly, typically between 0.4 and 2 Gy per hour, whereas HDR brachytherapy by definition

Table 50.1 Common spinal brachytherapy sources and their physical properties

Radioactive isotope	Decay emission	Mean energy of decay (MeV)	Dose rate (Gy/hour)	HVL (in water)	Half-life (days)
Iridium-192	Gamma	0.380		65 mm	73.83
Iodine-125	X-ray	0.028	Permanent: 0.07 Temporary: 0.5–0.6	17 mm	59.4
Cesium-131	X-ray	0.030	Permanent: 0.34	18 mm	9.7
Phosphorus-32	Beta	0.695 (Max = 1.7)	40–802	Range in water = 7 mm	14.28
Yttrium-90	Beta	0.934 (Max = 2.27)	40–80	Range in water = 12 mm	2.67
Samarium-53	Beta	0.225		Range in bone = 1 mm	1.93

delivers dose at 12 Gy per hour or more [10]. Selection of HDR versus LDR is often patient specific and is influenced by several factors including the size and topography of expected post-resection tumor, IORT dosing requirements, radiobiological assumptions of the tumor and adjacent normal tissues, prior radiation exposure, institutional and physician expertise, workflow requirements, and radiation safety concerns.

- *Source format*. Sources can be implanted permanently into a tumor or tumor cavity to slowly release radioactivity or can be placed temporarily to deliver a pre-specified amount of radiation. In general, permanently surgically implanted sources are usually LDR. For spinal IORT, sources take several forms such as small three-dimensional seeds or two-dimensional foil plaques that can be directly positioned on the dural surface.
- *Source physical properties*. In general, sources release radioactivity through decay and release of photons (X-rays), neutrons, gamma rays, or charged particles such as alpha or beta particles (helium nuclei or electrons). Source encapsulation will greatly reduce any component of dose from alpha or beta particles or neutrons for most clinically used sources—the greatest component of dose arises from gamma rays. The physical properties of the characteristic emissions of isotopes such as mean energy of the emission, half value-layer (HVL), and half-life are well characterized and determine the amount of time required for treatment and anatomic penetrance of the radioactivity. For example, a source with a very rapid dose fall off would likely be selected for a patient whose disease closely abuts the thecal sac. Figure 50.1 shows the dose profiles of commonly employed iso-

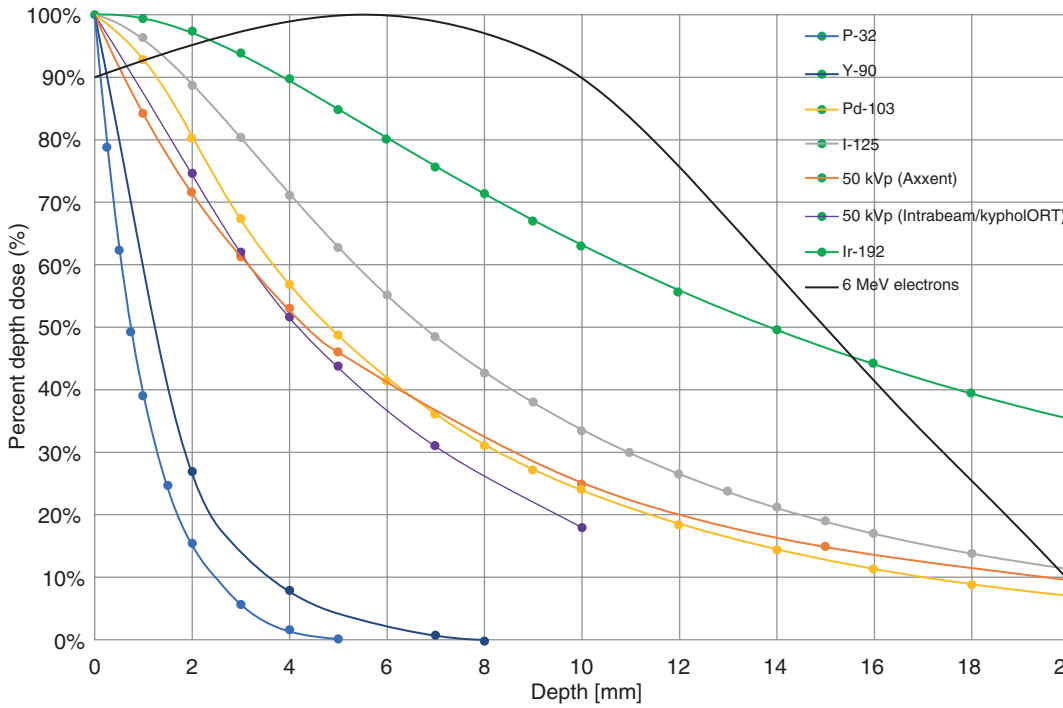

Fig. 50.1 Depth dose curves for various spinal IORT radiation sources are shown. Depth for all sources is specified in tissue with references as follows: P-32 – surface of the foil; Y-90 surface of the plastic applicator; 50 kVp Intrabeam – surface of 2 cm planar applicator; 50 kVp Axxent – surface assumed at 1.5 cm from center of source; 6 MeV electron – depth in tissue with 1 cm bolus applied; and I-125/Pd-103/Ir-192 – interstitial implant assumed with depth specified from the plane of the sources

topes. The dose profiles of high-energy X-ray emitting sources (e.g., Iridium-192) closely approximate the predicted inverse square fall off with small attenuation and scatter differences. Conversely, low-energy X-ray emitting sources (e.g., Iodine-125) penetrate less deeply due to photoelectric attenuation in tissue. Sources releasing charged particles (e.g., Phosphorus-32) have even steeper dose profiles and generally deliver the majority of their dose within millimeters of the source surface.

- *Dose specification*. For any IORT procedure (including accelerator-based techniques), the total dose of radiation to be delivered, as well as the reference point for the delivery of that dose, needs to be pre-specified. For example, a total dose of 8 Gy might be delivered at the surface of a plaque. The degree to which the surrounding tissue receives dose is dictated by the aforementioned physical properties.

Intraoperative Electron Beam Treatment

Technical Considerations

The Tokyo Metropolitan Komagome Hospital has reported one of the largest experiences using electron beam IORT [11–13]. Decompressive surgery with or without preoperative embolization was performed, though the authors specified that total resection of the tumor was often impossible. After hemostasis is achieved, the patients were transferred to the radiotherapy department where an electron cone (applicator) was placed directly in the surgical field. A custom 3–5 mm lead block was placed over the spinal cord to protect it from electron dose (Fig. 50.2). Each patient received 20 Gy in a single fraction. The electron energy was determined by measuring the anteroposterior thickness of the tumor by magnetic resonance imaging (MRI) so that the 80% isodose line falls at least 1–2 cm below the deepest aspect of the tumor. After treatment, the patient was returned to the operating room for wound closure.

Summary of the Literature

In the first series of 37 patients, of which 59% also received neoadjuvant or adjuvant EBRT, they reported that all patients had some degree of improvement in pain, neurologic function status, or both. No local failures were noted, and about one third of patients developed distant spinal metastatic disease. One case of radiation myelopathy was noted in a patient where the spinal cord was not shielded with lead. In an updated series of 79 lesions treated with posterior decompressive surgery followed by 20 Gy IORT, 86% clinical improvement in one domain of the Frankel classification scale with 2.5% local recurrence was reported [12]. Again, one case of myelopathy was noted in a heavily pretreated patient. In a retrospective review of 96 patients who were nonambulatory due to severe cord compression and who underwent posterior decompression with IORT, nearly 90% of patients had some degree of neurologic improvement and 80% regained ambulatory status after surgery [13] (Table 50.2).

LDR Brachytherapy for the Management of Spinal Lesions

Technical Considerations

Iodine-125 (I-125) has been the most widely reported source used for spinal LDR brachytherapy. Loose seeds can be implanted using a Mick applicator (Mick Radio-Nuclear Instruments, Mount Vernon, NY) or embedded on a suture and affixed using biologic adhesive [14, 15]. Stereotactic localization can be used to assemble the seeds into circular or linear arrays. Numerous methods of securing the placed seeds have been reported, including methyl methacrylate, staples, sutures, Gelfoam, or direct fixation to surgical hardware [16]. Correct placement of the seeds is critical, as the dose given by an I-125 seed near the spinal cord is very high, risking local myelitis. Reports from two groups describe wrapping the thecal sac with layers of either platinum [14] or gold [17] metal foil to shield the spinal cord from radiation from the implanted seeds.

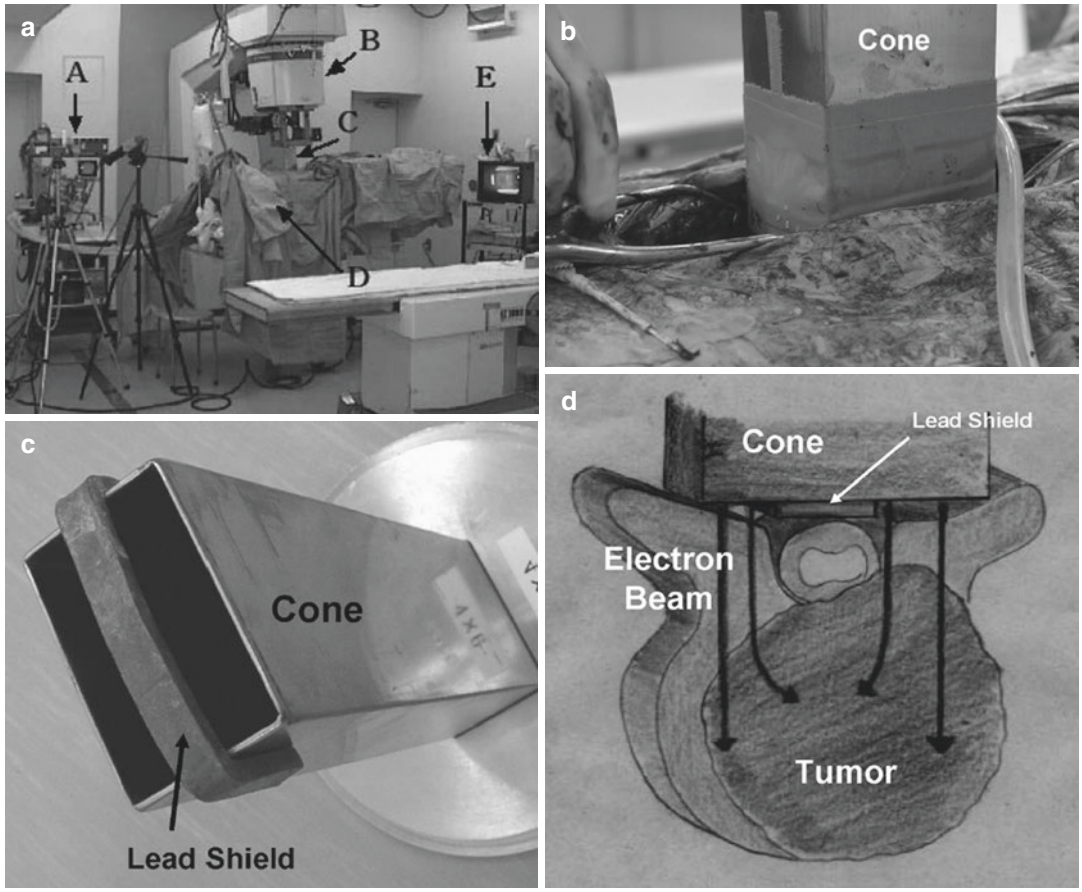

Fig. 50.2 Photographic and schematic representations of intraoperative radiotherapy. (**a**) View of the irradiation room. A: anesthesia machine; B: gantry, C: cone; D: operating table and patient; E: image from the camera located in the cone. (**b**) Cone set up in the surgical field. (**c**) View of the cone before attachment to the gantry with a midline lead shield for the spinal cord. (**d**) Schematic cartoon of intraoperative radiotherapy. (From Kondo et al. [13]. Reprinted with permission from Wolters Kluwer Health, Inc.)

Hamilton and colleagues delivered 120 Gy to an in-field thoracic spinal recurrence of chondrosarcoma in a 28-year-old patient who had previously received 45 Gy [17]. The tumor was resected, and the thecal sac was wrapped in two 0.025 mm thick layers of gold foil, after which point the I-125 seeds were sutured into the tumor bed. The prescription dose was 120 Gy at 5 mm depth, and the gold foil was predicted to reduce cord dose to less than 5% over the life span of the implant. Although the use of a foil is an excellent protection for the spinal cord, it has the disadvantage of potentially shielding the dural surface, which in many tumors with epidural extension is at risk for tumor contamination.

Summary of the Literature

Gutin et al. published one of the earliest reports, which analyzed 14 heavily pretreated patients who underwent re-resection and brachytherapy for recurrent paraspinal or skull base tumors [14]. Prescribed doses ranged from 70 to 150 Gy, and common histologies included chordoma (36%) and meningioma (21%). Outcomes were modest; two-thirds of evaluable patients at 6 months following IORT had local progression.

Kumar et al. have reported the use of I-125 in the management of previously irradiated clival and sacral chordomas [18]. The sacral lesion received 160 Gy and had excellent control until

Table 50.2 Summary of the literature using IORT for malignant spinal diseases

First author (year)	Dose rate	Isotope/source	*N*	Dose, Gy	Notes
Gutin (1987) [14]	LDR	I-125 (permanent)	13	70–150	Platinum foil cord shield 14% long-term remission
Kumar (1988) [18]	LDR	I-125 (permanent)	2	160, 400	1 patient with 3-year OS; 1 patient NED 19 months
Armstrong (1991) [15]	LDR	I-125 (permanent)	14	125	50% LC overall, 47% OS at 1 year, 12% at 2 years
	LDR	Ir-192 (temporary)	21	30	NSCLC and dural involvement negatively prognostic for LC
Hamilton (1995) [17]	LDR	I-125 (permanent)	1	120	Gold foil spinal cord shielding
Rogers (2002) [16]	LDR	I-125 (permanent)	30	50–160	2- and 3-year LC were 87% and 73%, but most patients did not receive post-brachytherapy imaging Majority received adjuvant EBRT and no myelopathy
Yao (2016) [21]	LDR	I-125 (permanent)	24	Median D_{90} of 99 (range 90–176)	Salvage reirradiation treatment using percutaneous seed implantation 6- and 12-month LC rates were 52% and 40%
Delaney (2003) [25]	HDR	Ir-192 YT-90	3 5	10 10	1/3 NED 1/5 NED
Folkert (2013) [30]	HDR	Ir-192	5	14 (12–18)	100% LC at 9 months 80% palliation reported 1–4 weeks post-procedure
Folkert (2015) [25]	HDR	P-32	68	10	LR 18.5% with plaque vs 34% without ($p = 0.04$) No IORT-associated myelopathy
Cardoso (2009) [32]	HDR	Sm-153	19	3 mCi of Sm-153 mixed with bone cement	Kyphoplasty performed with radionuclide impregnated bone cement No reported complications or hematologic toxicity 100% pain reduction, no discussion of LC
Saito (2006) [12]	IORT	11–20 MeV Electron beam	74	20	Posterior epidural decompression followed by single-fraction electron beam therapy 97.5% LC 86% improvements in pain, neurologic function, or both
Kondo (2008) [13]	IORT	Electron beam	96	20–30	All patients initially nonambulatory, and 89% regained neurologic status and 80% became ambulatory after treatment
Bludau (2018) [39]	IORT	50 kV X-rays	Phase I: 9 Phase II: 52	8 Gy at 8–13 mm depth	Phase I/II dose escalation study of kypho-IORT No dose-limiting toxicities Significant improvements in pain on VAS 3- and 12- month LC of 98% and 94%

Abbreviations: *OS* overall survival, *NED* no evidence of disease, *LC* local control, *EBRT* external beam radiotherapy, *VAS* visual analog scale

the patient ultimately succumbed to meningeal chondromatosis at 3 years. A transnasal approach was used to deliver 400 Gy to a small clival recurrence using two I-125 seeds. This patient was reported to be well 19 months after the procedure.

Larger LDR experiences were published by the Memorial Sloan Kettering Cancer Center (MSKCC) [15] and the Barrow Neurologic Institute (BNI) [16]. MSKCC reported the treatment of 35 patients who underwent brachytherapy following

incomplete resection of a paraspinal lesion. IORT utilized permanent I-125 seed placement (40%), or temporary single-plane implants using Iridum-192 (Ir-192) delivered 3–6 days after tumor resection via afterloading catheters (60%). Numerous metastatic and primary histologies were treated, including non-small-cell lung cancer (51%) and sarcoma (26%), and 60% of patients had received previous EBRT. Median doses were 30 Gy for patients delivered with Ir-192 and 125 Gy for patients delivered with I-125. Median estimated cord dose for Ir-192 treatments was 20 Gy. Local control (LC) was achieved for 51% of patients with median time to local failure of 1.3 years. However, overall survival (OS) of the cohort was poor; only two patients were alive with local control at the IORT site 3 years following the procedure. Surgeries requiring exposure of the dura and NSCLC histology were negatively prognostic for local control. The authors did not report any cases of radiation myelitis but acknowledge the poor OS.

Rogers and colleagues summarized the treatment of 30 patients at BNI who underwent paraspinal surgery for metastatic cord compression followed by IORT with permanent I-125 seeds in absorbable sutures [16]. The majority of the evaluable patients (56%) had received prior EBRT, and most (88%) of them also underwent adjuvant EBRT following IORT. They report 2-year and 3-year local control rates of 87% and 73%, respectively. Of note, most of the patients were surveilled clinically after IORT. Only 40% of evaluable patients had posttreatment imaging, but they report four radiographic local failures (16%) at a mean time of 20 months after IORT. Three of these failures occurred in patients who underwent IORT as salvage therapy after previous EBRT. OS was again poor, with 2-year OS rate of 24%. They report good functional improvement with 84% of patients having either normal or improved ambulation following surgery. No myelopathies or radiculopathies were noted.

A group from Peking University Third Hospital has described usage of CT-guided interstitial brachytherapy using percutaneously placed I-125 seeds for a variety of paraspinal lesions. Their retrospective experience has described the use of this technique for primary paraspinal lesions [19] or as salvage therapy for reirradiation of spinal metastases following prior EBRT [20, 21]. In the reirradiation setting, 26 lesions were contoured and pre-planned using simulation computed tomography (CT) in the prone position 3–5 days prior to brachytherapy [21]. Dose was prescribed as D_{90} (dose delivered to 90% of the clinical target volume), and seeds were implanted percutaneously, in a linear arrangement, under local anesthesia into the paraspinal lesions using a Mick applicator. Post-implant dosimetry revealed median actual D_{90} of 99 Gy (range 90–176) with median maximal dose to the spinal cord of 39 Gy (range 6–111). At a median follow-up of 9.5 months, they reported actuarial LC rates at 6 and 12 months of 52% and 40%, respectively. Nearly all patients reported some degree of pain relief following brachytherapy after 1–3 weeks, and the overall rate of neurologic functional recovery or retention using American Spine Injury Association (ASIA) grading was reported as nearly 80%. In general, the brachytherapy was well tolerated, with no myelopathy reported. Three patients (13%) suffered vertebral compression fractures 3–6 months after brachytherapy without concomitant tumor progression.

HDR Brachytherapy for the Management of Spinal Lesions

Background and Technical Considerations

Over the past decade, several changes have impacted the delivery of paraspinal radiation. First, improvements in image-guided radiotherapy have fostered the growth of ultrahypofractionated EBRT techniques. These strategies, also known as stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR), have enabled the safe delivery of very high doses of radiation in very close proximity to the spinal cord [22]. Second, the growth of conformal approaches such as proton therapy enables dose escalation to resistant spinal

histologies with relative sparing of the spinal cord [23, 24]. Despite these advancements, the treatment of contaminated dura or epidural surface remains a significant clinical challenge. Specifically, the risk of spinal cord myelitis sets an upper limit for the acceptable dose at the dural edge, which is often below the perceived tumoricidal threshold. To address this challenge, several groups have developed short-range HDR plaques that are directly affixed on the dural margin at risk.

Published reports of plaques have utilized beta-particle-emitting isotopes, including Yttrium-90 (Y-90) and Phosphorous-32 (P-32). The benefit of beta emitters is rapid dose fall off a short distance away from the source. Therefore, these sources enable high dose to be delivered directly to the dural surface; the nearby spinal cord typically receives a small fraction of the total dose. Short-range brachytherapy sources such as P-32 and I-125 can be used in any operating room with minimal risk to operative staff, while more penetrating radiation such as electrons or Ir-192 requires specially shielded operating rooms because of the radiation exposure. Furthermore, operative staff may need to leave the room when radiation is being delivered.

Review of the Literature

Delaney and colleagues at Massachusetts General Hospital designed a Y-90 foil in a semicylindrical polycarbonate plaque [25] (Fig. 50.3). The plaque was placed directly on the dural margin following gross total surgical resection of primary and metastatic paraspinal masses and removed after delivery of 7.5–15 Gy. Surface doses were reported as 29% and 9% at 2 and 4 mm from the surface of the foil, respectively. All patients had received pre- and/or postoperative EBRT using photon and/or proton beams. With the use of intensity modulated radiotherapy, a dose constraint on the dural surface can be applied at the time of postoperative radiation treatment planning to account for the radiation given intraoperatively with the plaque. The group reported a total spinal cord dose constraint to 63 and 54 Gy relative biologic effectiveness (RBE) to the cord surface and center, respectively. Of the eight treated patients, 75% had local control at median follow-up of 2 years post-procedure.

The group updated their experience in a more recent abstract [26], summarizing the treatment experience of 51 patients with primary (51%), recurrent (24%), or metastatic (12%) lesions. This experience included the use of multiple plaque-based brachytherapy sources, including Y-90, P-32, and Ir-192. With a median follow-up of 18 months post-brachytherapy, they report good local control rates across indications. No acute or late myelopathy could be attributed to dural plaque brachytherapy, and the authors conclude this is a safe and effective means of dose escalation for tumors with dural involvement. Due to the low-energy beta particles emitted by Y-90 and P-32, the source has an added advantage of limited radiation exposure to operating room staff; Ir-192 emits more penetrating radiation, requiring additional shielding or distance from the patient for staff safety.

The MSKCC group utilizes a P-32 plaque (previously RIC-100, R.I. Consultants, Hudson, NH, USA; now NucMedCor, San Francisco, CA, USA) where the isotope is bound chemically to a flexible and transparent polymer layer and coated with silicone; the overall thickness is approximately 0.5 mm [4, 27]. The thin plaque is then wrapped in iodinated surgical film (Ioban, 3M, St. Paul, MN, USA) to reduce the chances of microscopic isotope contamination of the surgical bed. This approach has several advantages. P-32 has a similar steep dose fall off as Y-90 but has a longer half-life, enabling longer shelf life. Dosimetric analysis suggests that the percent depth dose declines to 1% at 4 mm from the prescription depth [27]. The plaques can be cut to the appropriate shapes intraoperatively and do not require preoperative fabrication necessary for Y-90 products. The flat plaques are often easier to affix to a surgical contour compared to a curved semicylindrical construction. They also do not require special intraoperative shielding. P-32 plaques can also be used in conjunction with neoadjuvant or adjuvant EBRT, and the dose delivered to the dural surface enables better

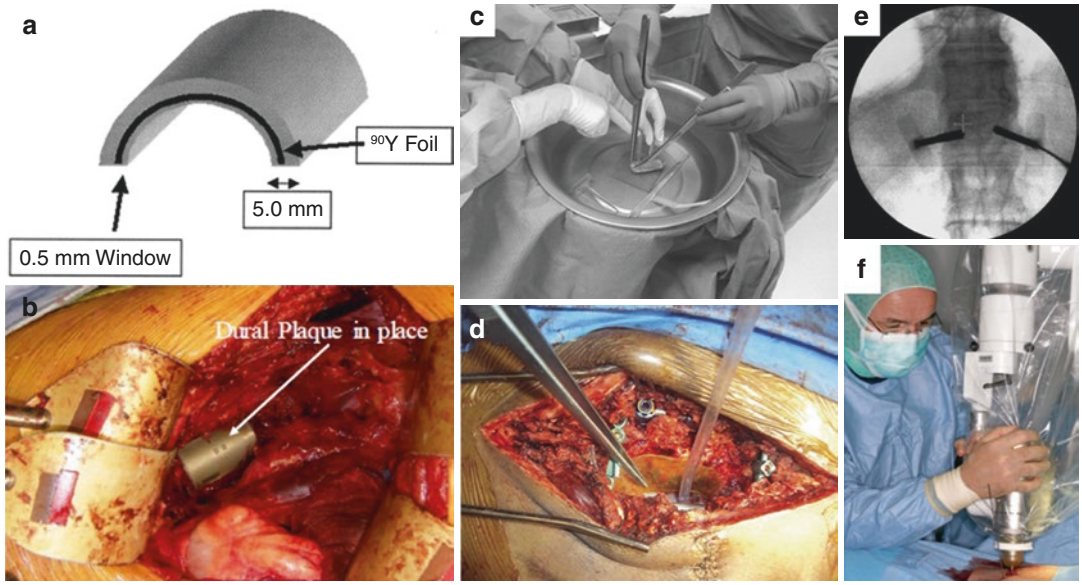

Fig. 50.3 (**a**) Diagram of the Y-90 foil-based semicylindrical polycarbonate plaque used for HDR brachytherapy. (From DeLaney et al. [25]. Reprinted with permission from Elsevier.) (**b**) In situ positioning of the Y-90 plaque against the dural surface after posterior decompressive surgery. (From Folkert [42]. Reprinted with permission from Oxford University Press.) (**c**) Assembly of the P-32 plaque under sterile conditions in the operating room. (From Folkert et al. [27]. Reprinted with permission from Oxford University Press.) (**d**) Positioning of the P-32 plaque against the dural edge by the neurosurgeon and radiation oncologist as part of separation surgery procedure with hardware stabilization. (From Folkert et al. [27]. Reprinted with permission from Oxford University Press.) (**e**) Radiographic confirmation of bipedicular placement of catheters as part of Kypho-IORT system. (From Wenz et al. [33]. Open Access, Creative Commons Attribution License.) (**f**) Treatment position of the Zeiss INTRABEAM system used to deliver X-ray-based IORT prior to kyphoplasty. (From Wenz et al. [33]. Open Access, Creative Commons Attribution License.)

homogeneity of the CTV coverage while satisfying cord constraints.

At MSKCC, patients often undergo separation surgery with a goal of partial resection to decompress the thecal sac to enable adjuvant SBRT [28]. For patients with extensive dural involvement, P-32 is placed intraoperatively on the surgical margin to deliver a dose of 10 Gy at a depth of 1 mm from the plaque edge.

Folkert et al. reported P-32 plaque outcomes for 68 patients with 69 treated lesions [25]. Most patients (86%) had previously received at least one prior course of EBRT and just over half had adjuvant EBRT following P-32 using single fraction (13%), high-dose hypofractionated (34%) or low-dose hypofractionated (53%) image-guided RT. At median follow-up of 10 months, local relapse of 26% was noted at 12 months. In the subgroup of patients who underwent adjuvant EBRT after surgery and P-32 IORT, rate of local failure was significantly lower at 19% compared with 34% for those who did not ($p = 0.04$). No acute or long-term complications were specifically attributed to the IORT.

The approach was also utilized for a pediatric patient with multiple recurrent thoracic spinal neuroblastoma, who had previously received 25 Gy in five fractions [29]. The patient was noted to have no evidence of local failure at 10 months post-P-32 but unfortunately had suffered out of field progression.

A catheter-directed interstitial HDR approach has also been described for patients with multiple relapsed spinal metastases [30]. Five patients who were felt to be ineligible for further EBRT due to prior cord exposure underwent intraoperative or percutaneous placement of vertebral catheters into gross disease. HDR was performed using Ir-192 to deliver 12–18 Gy in a single fraction. At a median follow-up of 9 months, 100% local

control was observed. The approach was effective for palliation as most patients (80%) had complete ($n = 2$) or partial ($n = 2$) pain reduction 1–4 weeks post-procedure. No brachytherapy-related complications were observed, even in patients with surgical hardware.

IORT for Painful or Unstable Spinal Metastases

The management of patients with malignant mechanical spinal instability typically requires multimodality treatment [31]. Typically, this requires a combination of a procedure to address the instability (e.g., kyphoplasty, vertebroplasty, invasive surgical stabilization, or less-invasive percutaneous screw placement) together with radiation for further palliation and local tumor control. Several strategies have been reported to combine the two interventions such that tumor control and skeletal stabilization are performed concurrently.

One approach has been direct injection of radionuclides into the bone at the time of kyphoplasty. Cardoso and colleagues have described kyphoplasty using Samarium 153 (Sm-153) mixed with polymethyl methacrylate (PMMA) bone cement [32]. Sm-153 was selected as it has bone-seeking properties and releases beta particles to irradiate adjacent tumors. The group reported no procedural complications or hematologic toxicities, and all patients had at least partial improvement in pain. Local control was not explicitly quantified; however, Sm-153 beta has a very short decay range and thus can only effectively treat a limited distance from the source (i.e., the bone cement), which will limit the amount of tumor that this approach can effectively treat to within a few millimeters of the PMMA.

Wenz and colleagues have described a hybrid brachytherapy and kyphoplasty approach, which they term kypho-IORT [33, 34]. A pilot case of a 60-year-old patient with breast cancer metastatic to the T12 vertebra was presented. A percutaneous, bipedicular approach into the vertebra was chosen with insertion of specially designed metallic sleeves to guide the electron drift tube of a miniature X-ray generator (INTRABEAM, Carl Zeiss Surgical, Oberkochen, Germany), with a maximum energy of 50 keV. At this point, IORT was performed to deliver 8 Gy at 5 mm distance from the source, which was completed in 90 seconds. The INTRABEAM device was then removed and kyphoplasty was performed per the usual approach.

Since then, several reports showed the feasibility, safety, and efficacy of the approach [35–38]. For example, Reis et al. reported short-term outcomes after treatment of 18 lesions, noting radiographically stable disease in 93% of patients with significant improvements in pain and no severe complications [35]. A Phase I/II dose escalation trial studied three IORT dose levels and found no dose-limiting toxicities [39]. Fifty-two patients were subsequently enrolled in a Phase II portion, and median pain score on the visual analog scale (VAS) significantly dropped from 5 preoperatively to 2 at the first postoperative day ($p < 0.001$). Of 43 patients who reported a pre-interventional pain level of 3 or more, 30 (70%) reported a reduction of ≥3 points on the first postoperative day, and most had persistent pain reduction. The 3-, 6-, and 12-month LC rates were excellent at 98%, 94%, and 94%, respectively. The 6- and 12-month OS were 64% and 48%, respectively. Given this promising early data, the Universitätsmedizin Mannheim is currently conducting a Phase III trial, randomizing kypho-IORT with a single fraction of 8 Gy versus conventional palliative EBRT to 30 Gy in ten fractions [40].

Summary

As systemic therapies continue to advance and OS improves, the prevalence of spinal metastatic disease will rise [41]. The management of primary spinal tumors also remains a significant therapeutic dilemma. While EBRT remains a mainstay of treatment, addressing recurrent disease remains a clinical challenge. IORT is a versatile strategy for focal treatment and retreatment of malignant spinal lesions especially when dural involvement is suspected. This approach is particularly attractive for patients with prior EBRT

exposure where significant additional dose risks spinal cord myelopathy. Spinal plaques allow for the delivery of focused treatment of the surface of the thecal sac and can augment conformal SBRT for the combined delivery of high-dose radiation to the full extent of paraspinal and epidural diseases.

In terms of outcomes, IORT has proven effective for palliation and can be combined with bone-stabilizing procedures such as kyphoplasty for patients with mechanical instability. Most series do describe high rates of at least partial neurologic improvement that can be durable. While the data exploring spinal IORT remains limited to a small number of institutions with particular expertise in the management of complex spinal disease, the approach seems to be safe and transferable, with relatively few examples of IORT-related myelopathy in the published literature. However, interpretation of these series does require caution since many of the treated patients suffered from metastatic cancer with a low-baseline anticipated survival; therefore, they may not live long enough to develop long-term sequelae of their treatment.

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Part VII

Pain

51 Approach to Pain in Patients with Central Nervous System Metastases

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Introduction

Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage…" and, therefore, involves more than the mere detection of a (potentially) harmful stimulus by the body (which describes *nociception*). Pain, rather, is a subjective, complex condition affected or modulated by many physiological and psychological factors. In this chapter, we describe briefly first the concept of "pain processing," followed by an overview of the various types of the pain, classified by tissue type. The remainder of this chapter describes select pharmacologic agents used to manage specifically the *neuropathic* component of pain in central nervous system metastases. Evidence to support each specific agent's use in this particular condition will be provided, where available.

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An Overview of Pain Processing

Within the body's somatic tissue (muscle, bone, joint, tendon, skin, organs, etc.), specific nerve fiber types of sensory neurons, known as A-Δ (or *A-delta*) and C fibers, have in their peripheral terminals specialized receptors that respond to nociceptive stimuli. These specialized receptors, called *nociceptors*, may be activated by chemical, thermal, and/or mechanical stimuli that reach the nociceptor's high threshold for response. These specific "pain" fibers, with their cell bodies located in dorsal root ganglia (or respective cranial nerve ganglia), travel in peripheral nerves (or cranial nerves V, VII, IX, and X) to synapse with second-order neurons located in the central nervous system (either dorsal horn neurons of the spinal cord or neurons within brainstem nuclei). Release of excitatory neurotransmitters, such as glutamate and aspartate, occurs at these nerve synapses, resulting in travel (and modulation) of the nociceptive signals to higher CNS centers, via ascending projections in various tracts (the spinothalamic tract being an important example). An important supraspinal structure in this ascending system is the thalamus, which receives the nociceptive input and sends projections further to other structures in the brain that influence both the discriminative and affective components of pain.

This entire "nociceptive system" may be modulated at multiple points along the pathway.

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For example, chronic nociceptive input (with resultant release of inflammatory mediators) may sensitize peripheral nociceptors, leading to a lowered threshold for response or an increased responsiveness to normal suprathreshold input (a condition known as *peripheral sensitization*). Repetitive stimulation can also result in lowered thresholds for response or increased suprathreshold response of the second-order, dorsal horn neurons (*central sensitization*) or an increased output: input ratio (referred to as the *wind-up phenomenon*) of these neurons.

In contrast to pain facilitation as described above, modulation of nociceptive signals by certain *descending* supraspinal systems results in inhibitory modulation of pain. Some of the structures associated with this descending inhibitory system include the periaqueductal gray, the serotoninergic raphe nucleus, and the noradrenergic locus ceruleus. These systems influence the dorsal horn neurons of the spinal cord via projections within the dorsolateral funiculus. The endogenous opioid system (endorphins, enkephalins, and dynorphins) also exerts its pain inhibitory effects at both the peripheral and central nervous system levels.

The affective component of pain may significantly influence the patient's perception of the pain experience. Spinal pathways leading to both limbic structures and medial thalamic nuclei provide input to areas of the brain related to affect/emotion. For instance, the anterior cingulate cortex of the brain, and its association with limbic structures, appears to be intimately involved in conferring the emotional aspect to pain, having a role in the sensorimotor, cognitive processing, visceromotor, endocrine outflow, skeletomotor outflow, and other responses to nociceptive stimuli.

Types of Pain

There are various ways by which to classify pain, based on factors such as time (acute, chronic), mechanism (trauma, surgical, etc.), or by tissue type (Table 51.1), among other classification schemes. In this chapter, we describe pain by tissue type, using IASP terminology, as follows:

Table 51.1 Classification of pain type by tissue

Nociceptive pain	Examples
Somatic Visceral	Skin, bone, joints, connective tissue, muscle Lung, liver, esophagus, pancreas, intestines, colon, bladder.
Neuropathic pain	Examples
Central pain Peripheral pain	Brain, spinal cord Cranial nerves, spinal nerves and their branches, ganglia

Nociceptive Pain

There are two main types of nociceptive pain – somatic and visceral. Somatic nociceptive pain is associated with injury to somatic, nonneural tissues. Somatic nociceptors innervate somatic structures such as, but not limited to, the skin, subcutaneous tissue, joint capsules, muscles, ligaments, tendons, fascia, periosteum and endosteum of bone, parietal pleura, and parietal peritoneum. Somatic nociceptive pain is usually localizable by the patient.

Visceral nociceptors innervate thoracic, abdominal, and pelvic viscera, and its surrounding connective tissue/capsule, usually not the organ parenchyma proper. Visceral nociceptors are activated by organ distention, inflammation, and ischemia, rather than stimuli such as cutting, stabbing, or burning. Visceral pain is usually described as poorly localized and may be accompanied by autonomic symptoms. Pain from visceral structures may refer to, and be perceived in, a different area of the body – this is due to the convergence of visceral afferent nociceptive fibers with somatic afferent nociceptive fibers onto the same dorsal horn neurons within a similar segment of the gray matter of the spinal cord.

Neuropathic Pain

Neuropathic pain is "pain caused by a lesion or disease of the somatosensory nervous system," as defined by the IASP. There are two subtypes of neuropathic pain – (1) central and (2) peripheral neuropathic pain. Central neuropathic pain (or

simply "central pain") is a type of neuropathic pain "caused by a lesion or disease of the central somatosensory nervous system," whereas peripheral pain involves the peripheral somatosensory nervous system.

The quality of neuropathic pain is described as a burning, throbbing, electrical-shocking, or "pins and needles." Neuropathic pain can be associated with abnormal sensations, spontaneous or evoked, known as *paresthesias*, or with both unpleasant *and* abnormal sensations, called *dysesthesias*. *Allodynia* is a condition whereby pain is experienced from a normally innocuous stimulus, for instance, light touch.

Select Pharmacologic Agents for Neuropathic Cancer Pain

In this section, we describe the major classes of analgesics used for neuropathic cancer pain, including those caused by CNS metastatic disease. A survey of select agents from each class is described below.

Opioid Analgesics

Opioid analgesics (henceforth referred to simply as *opioids*) are drugs that bind to and assert agonist effects on the opioid receptors of the nervous system. Opioids are considered the gold standard in the management of cancer pain, of all types – neuropathic and nociceptive. Opioids produce analgesic effects but may also result in other potentially unwanted side effects (some of which are described in more detail in subsequent sections of this chapter). For instance, central effects from opioids can produce euphoria, dysphoria, sedation, nausea (through direct effects on the brainstem chemoreceptor trigger zone), cough suppression, and probably the most feared complication – respiratory depression (through direct effects on the brainstem respiratory centers). Peripheral effects of opioids can result in constipation (from slowing of gastrointestinal motility), biliary smooth muscle constriction, urinary retention, and pruritis, among many other effects. Below we discuss select opioid analgesics most commonly prescribed for cancer pain by the Pain Service at the authors' institutions. Evidence of efficacy specifically on neuropathic-type cancer pain in human subjects is provided in this section. Table 51.2 is a sample opioid equianalgesic dosing reference from the authors' institution.

Morphine Sulfate

Morphine is known as the prototypic opioid. It is a full agonist at the *mu*-opioid receptor, which is the predominant analgesic receptor within the nervous system. Morphine is absorbed well orally, but undergoes extensive hepatic first-pass metabolism, and therefore, oral dosages must be increased compared to parenteral doses. Morphine undergoes glucuronidation by the liver, with the resulting major metabolite known as morphine-3-glucuronide (M3G). To a much lesser extent, morphine-6-glucuronide (M6G) is produced, this metabolite being more potent than the parent compound. Excretion of morphine and its byproducts is through the renal route. There is concern, therefore, for using morphine in the

Table 51.2 Equianalgesic dosing table

Opioid	Oral dose (PO)	Parenteral dose (IV)	Conversion factor for changing parenteral opioid to oral opioid	Conversion factor for changing oral opioid to oral morphine
Morphine	15 mg	6 mg	2.5	1
Oxycodone	10 mg	N/A	N/A	1.5
Hydrocodone	15 mg	N/A	N/A	1
Oxymorphone	5 mg	0.5 mg	10	3
Hydromorphone	3 mg	1.5 mg	2	5
Fentanyl	N/A	60 mcg	N/A	Should be managed by clinicians experienced in pain management

Note: Methadone should be initiated and managed by clinicians experienced in pain management
Source: UT MD Anderson Cancer Pain – Adult Practice Algorithm

renal patient population, as active metabolite accumulation could lead to neurotoxic and other significant adverse effects. Morphine is often combined with other agents and adjuvants [1–3] for neuropathic cancer pain, and it is one of the few drugs approved by the United States Food and Drug Administration (FDA) for use in intrathecal drug delivery systems.

Tramadol

Tramadol is a synthetic opioid with dual properties – agonist effects on the *mu*-opioid receptor and norepinephrine/serotonin reuptake inhibition. Tramadol undergoes hepatic metabolism, with one of the active metabolites, desmetramadol, being notable for its much higher affinity for the *mu*-opioid receptor compared to its parent compound. Tramadol and its by-products are excreted renally and also must be used carefully in renally impaired patients. Tramadol was assessed [4] for efficacy, safety, and quality-of-life impact for patients with neuropathic pain in cancer. In this double-blind, placebo-controlled study, patients were randomized to receive either tramadol or placebo. Thirty-six patients were enrolled and equally divided into each study group. Tramadol was given in the treatment arm at 1 mg/kg every 6 hours and increased to 1.5 mg/kg every 6 hours if necessary. The group receiving tramadol showed major improvement in pain intensity, Karnofsky scores, sleep quality, and activities of daily living, compared to the placebo group. In this study, tramadol was concluded to be a therapeutic option to control neuropathic cancer pain and improve quality of life in the cancer patient.

Hydromorphone

Hydromorphone, like morphine, undergoes metabolism by conjugation to form metabolites hydromorphone-3-glucuronide (H3G), predominantly, and 6-glucuronide, which are excreted in the urine. Similarly to the morphine metabolites, these byproducts may also contribute to neurotoxic side effects, requiring caution when prescribing to the renal population. Hydromorphone is considered, mg to mg, about five times more potent than morphine.

Fentanyl

Fentanyl is a synthetic, highly lipophilic opioid, with a potency of roughly 100× that of morphine. Fentanyl has properties of rapid onset and short duration of action and is used commonly in perioperative and intensive care settings. There are various preparations of fentanyl for different routes of administration, including parenteral, transmucosal, transdermal, and spinal. Fentanyl's major metabolite is norfentanyl, which is inactive and thus considered less risky to use in the renally impaired patient population.

N-Methyl-D-Aspartate (NDMA) Antagonists: Methadone and Ketamine

Methadone

Methadone, a synthetic opioid, is an agonist at the *mu*-receptor, but also an antagonist of the N-methyl-D-aspartate (NMDA) receptor, which is implicated in central sensitization/hyperalgesia. Methadone has highly variable pharmacokinetic properties and a long half-life. In addition, methadone is biotransformed hepatically and may be affected by other drugs that inhibit its metabolism; therefore, expert prescribing and monitoring of methadone is necessary to minimize risks of respiratory depression. Methadone is regularly prescribed at the authors' institution for cancer-related neuropathic pain, as there is both anecdotal and scientific evidence [5–7] supporting its use in this condition, particularly when the neuropathic pain is refractory even to high-dose opioids. For example, Sugiyama et al. [8] performed a retrospective study on the effectiveness of changing patients' opioid regimens to methadone for cancer-related neuropathic pain. The Faces Pain Scale (FPS) was used to measure pain intensity and pain relief. Twenty-eight patients on other potent opioids were changed to methadone, and 78.6% of those patients, within 2 weeks, had a significant reduction in their mean FPS score, and 12 out of 17 patients either reduced or discontinued entirely adjuvant analgesics.

Ketamine

Ketamine is an anesthetic that has analgesic and dissociative properties. Its analgesic property is

thought to be related to its antagonism of the NMDA receptor. Although randomized clinical trials show little efficacy for ketamine in managing cancer pain, there are a number of case series and open-label studies that show benefit [9]. For instance, Mercadante et al. [10] published a case report on administration of ketamine as a subcutaneous infusion in a patient who experienced opioid-resistant neuropathic cancer pain, with dramatic reduction in opioid requirement and continued relief after 13 months with treatment, despite progression of disease.

Ketamine is utilized in the authors' pain clinic practice as an intravenous infusion at 0.5 mg/kg, over a one-hour duration; however, there is no consensus as to the optimal protocol, and, consequently, there exist many parenteral ketamine protocols for treating unremitting cancer pain [11–13].

Opioid Safety Considerations

In this section, we describe some of the most pressing or concerning side effect and safety issues associated with opioid prescribing. As the use of opioid medications for pain management has increased steadily over the past decades, the incidence of opioid-related deaths has tracked closely with this trend, as reported by the Center for Disease Control and Prevention (CDC). Initial public acceptance of opioid medications as generally safe agents has given way to an increased awareness of the risks associated with their use. Additionally, increased prescription of opioid medications has increased the incidence of diversion and misuse. Indeed, the Center for Medicare and Medicaid Services (CMS) has declared the opioid misuse epidemic a public health emergency, and many policies are in place to address this opioid crisis here in the United States. For instance, the CDC has published guidelines on opioid therapy for chronic pain. (Notably, the CDC states that their chronic opioid prescribing guidelines are not applicable for patients on active cancer treatment, palliative care, or end-of-life care.)

Opioid medications remain a major component of the treatment of cancer pain, due to the wide range of available agents and routes, availability of immediate- and extended-release formulations, and efficacy in many types of pain. These benefits must be carefully considered against the side effect profile common to most opioid agents, as well as the significant risk of disorders related to opioid use. Awareness of the side effects and safety considerations involved in opioid therapy, as well as a proactive approach to addressing them, are imperative in effective risk management for patients using opioid medications.

Cognitive Impairment

Concurrent use of opioids with sedating agents may increase the risk of cognitive impairment. Because cognitive impairment can present either in opioid overdose or in the course of regular opioid use, it is important to readily identify whether a patient may indeed be in overdose – a potentially fatal situation. For example, *rapidly* declining cognitive status after opioid administration is more concerning for overdose and warrants prompt evaluation. In cases where cognitive impairment seems to be linked to regular opioid use and has a more gradual onset, there are a few strategies available for the prescribing provider. The first is to consider dose reduction if analgesia is sufficient at the current dose; this is done with the knowledge that pain may worsen. If dose reduction is not a viable option, consider opioid rotation or dose reduction alongside the addition of an adjuvant analgesic (next section of this chapter).

Opioid Overdose

The 2017 data from the National Institutes of Health demonstrate a continued trend of increasing opioid overdose deaths, with opioid pain relievers accounting for approximately 40% of total opioid overdose deaths. Though the great majority of these events involve diversion, co-ingestion, or misuse, prescribers should be aware of the risk and available treatment.

Co-ingestion with sedating agents, including but not limited to benzodiazepines and alcohol, dramatically increases the risk of respiratory depression. Additionally, any condition (pulmonary disease/compromise, sleep apnea, stroke history, brain injury) or prescription medication that increases the patient's risk of respiratory depression must be weighed when initiating or escalating opioid therapy. For example, the FDA has in place a box warning as of 2016 regarding the combined use of opioids and benzodiazepines, due to evidence of the combined increased risk of respiratory depression and death when these agents are used in conjunction. Prescribers should counsel patients on this risk when initiating opioid therapy for a patient already on benzodiazepines or those with comorbid conditions. A low starting dose and slow drug titration can help minimize the risk of overdose and respiratory depression.

Opioid misuse can stem from the intentional therapeutic use of the opioid, but in an inappropriate way. Abuse occurs when patients use opioids for intentional nontherapeutic use to achieve a desirable effect. Patients on daily opioid medication must be counseled therefore to take their medication strictly as prescribed. Daily opioid use can lead to the development of physiologic tolerance, a condition of diminishing analgesic effect over time. Rapid development of tolerance is a phenomenon known as *tachyphylaxis*. Another concept, called the opioid-tolerant state, is defined as the state whereby a patient is taking at least 60 mg daily of oral morphine or its equivalent, for at least 1 week. This state is in contrast to the opioid-naive state, where the patient has no regular exposure to opioids, and to the opioid *non*-tolerant state, where the patient is using opioids regularly, but not to the amount sufficient to meet the criteria for the opioid-tolerant state. A period of abstinence can lead to the loss of the opioid-tolerant state, which can result in unintentional overdose when the patient attempts to resume their opioid therapy. Therefore, it is advisable for physicians to check with their patients at every appointment to ensure they understand the importance of taking their medication as directed. If a patient abruptly discontinues opioid therapy, he/she may experience a withdrawal syndrome, resulting in an "autonomic arousal" described as a limited period of irritability, agitation, lacrimation, yawning, abdominal cramping, and loose stools, among other unpleasant sensations.

Despite preventative measures, opioid overdoses continue to occur at increasing rates, year after year, in the United States. As part of a broader harm-reduction initiative, the FDA approved the opioid antagonist naloxone (trade name Narcan) in 1971 for treatment of opioid overdose. Initially available only as intravenous or intramuscular injections, naloxone is now available as a subcutaneous injectable, intramuscular auto-injector, and intranasal spray. The latter is seeing increased use as an effective rescue medication deployed by first responders and community bystanders to reverse opioid overdose, and its prescribing is encouraged under the "Surgeon General's Advisory on Naloxone and Opioid Overdose," by the current US Surgeon General, Dr. Jerome Adams, for patients who are at higher risk for opioid-use disorders. Increasingly, physicians are co-prescribing naloxone with opioids for patients on nominally high doses, patients with preexisting risk factors for respiratory depression, or patients where the risk of opioid overdose is felt to be significant [14, 15]. This measure was added to the CDC's 2016 prescribing guidelines for opioid therapy as a harm-reduction strategy worthy of consideration when initiating or escalating opioid therapy. Naloxone, available in easily administered intranasal or intramuscular forms without a prescription in 48 states, acts within minutes to displace opioid agents from central *mu*-receptors. Patients who are at higher risk for an overdose event should be educated on the use of naloxone, and more importantly so should any individual who will be with the patient on a regular basis. Like intramuscular epinephrine auto-injectors for patients with anaphylaxis, naloxone will often be administered to the patient by someone who is with them around the time of overdose.

Naloxone has proven to be extremely efficacious as a rescue agent, with a 2014 meta-analysis [16] demonstrating an Odds Ratio (OR) 8.58 of

increased recovery from opioid overdose when naloxone is administered. Its pharmacokinetic profile allows for rapid decoupling of opioid agents from the *mu*-receptor, but it also dissociates itself from the *mu*-receptor within minutes. Depending on the location and response time of emergency services, it may be necessary to administer multiple successive doses of naloxone to maintain respiratory function until first responders arrive.

Diversion

Diversion, either intentional or unintentional, is a major concern for physicians, patients, the healthcare system, and law enforcement agencies. A landmark 5-year national study of diversion revealed over 64,000 reported cases [17]. Due to acknowledged study shortcomings, and Substance Abuse and Mental Health Administration (SAMHSA) survey data showing abuse rates of hydrocodone and oxycodone measuring 17.7 million and 13.6 million individuals, respectively [18, 19], there is good reason to suspect the actual rate of diversion is far higher.

Several trends have emerged in diversion and prescription opioid abuse. The first is that, overall, immediate-release (IR) formulations are diverted and abused at higher rates than extended-release (ER) formulations. The second is that an initial preponderance of prescription opioid abuse in rural communities, thought to be secondary to higher availability of street drugs in urban communities, has begun to level off. Prescription drug abuse is seen now at high levels in urban, suburban, and rural settings across all socioeconomic strata. The third is the importance of cultural and employment differences between rural and non-rural settings; in communities where the majority of employed adults perform manual labor (e.g., coal mining, farming, logging, fishing), the incidence of occupation-related pain is higher. Thus, the prevalence of pain and the prevalence of pain medication prescribing are higher on a per capita basis. The widespread nature of prescription opioid utilization in these communities is thus more commonly accepted as a part of life, as are the dependence and abuse that follow. The fourth, and perhaps most important, is the lack of consensus on the actual mechanics of opioid diversion. SAMHSA data, which rely on self-reporting, show that 75% of opioid abusers obtained medications from a family member or friend. Increased activity at all levels of law enforcement to counter street and internet sales of prescription pain medication has not addressed, therefore, what may be the most common route of opioid diversion. While opioid medications continue to maintain a high street price, making them a lucrative option for patients in financial strain, the data suggest most diversion is not transactional. Diversion from friends and family, whether solicited or unsolicited, seemingly constitutes the major access route for individuals seeking unprescribed opioids. That said, hard data on diverting mechanisms are scarce due to a variety of social and political factors, as well as limits in effective data collection.

Regardless of routes to diversion, the fact agreed upon most commonly is that the major source for diverted opioids is patients who receive prescriptions for opioids. The prescribing physician, then, plays a role in reducing diversion. This fact is reflected in increased scrutiny by federal agencies of physicians' prescribing practices, as well as pharmacies that dispense opioids. Here is a selection of some tools physicians can utilize to reduce the risk of involvement in diversion:

- *Pain Contract:* In its most basic form, a pain contract will bind the patient to three rules. First, that their pain physician will be his/her only source of opioid prescriptions. Second, that he/she will only use one pharmacy to fill his/her prescriptions. Third, that he/she will be the only ones to use his/her prescribed opioid medications. Additional language may include a promise not to miss appointments or use other sedatives, consent to random drug screens at office visits, or restrictions on refills in the event of lost or stolen medication. This document, signed by the patient and countersigned by the prescribing physician, acts as a code of conduct for both parties and defines the terms under which the prescribing physi-

cian will continue to prescribe opioids to the patient. The contract is enforceable to the extent that the physician is willing to stop seeing a patient who violates its terms.

- *Drug Screen:* Used in conjunction with a contract, random drug screens, most commonly using hair, urine, or saliva, are a way to ensure a patient is taking prescribed medications and no other agents of concern [20, 21]. Older drug tests could only detect opioids generally, while newer tests can detect active drug and metabolites for a variety of commercially available and illicit agents. If a patient is diverting their prescribed medication, or if they are using any prescribed agents in conjunction, a drug screen will be able to reveal this.
- *Prescription Drug Monitoring Program (PDMP):* PDMP systems, which have been developed in North America, Australia, and some European countries, have allowed an increased degree of prescription monitoring. Patients are entered into a database by pharmacies, listing their prescribed controlled agents, dosing, prescriber information, and filling pharmacy. These programs were started in an effort to reduce "doctor shopping," whereby patients would go to multiple physicians to get opioid prescriptions, filling them at multiple pharmacies to avoid raising suspicion. Where available, PDMP data should be reviewed at every patient visit to ensure fidelity with single-prescriber and single-pharmacy rules. If any discrepancies are revealed, they should be discussed with the patient.

Opioid medications, owing to their effectiveness against multiple pain mechanisms, are widely used in the treatment of cancer pain. Effective pain management, in turn, improves quality of life for patients with cancer and also increases their ability to continue treatment. The safety considerations involved in opioid use are significant, and merit constant surveillance by prescribing physicians to ensure patients are using their medications appropriately with minimal adverse effects.

Adjuvant Analgesics

In this section, we describe some of the most commonly prescribed adjuvants for neuropathic pain. Adjuvant analgesics are drugs that with primary indications not related to pain but are found to be useful for their pain-relieving effects. The specific adjuvants detailed here are ones with historical benefit for a variety of neuropathic pain conditions, and many belong to the class of medications used to treat seizures and depression. In fact, anticonvulsants and antidepressants are considered first-line agents for neuropathic pain in cancer, often used in combination with opioids. Use of these adjuvants can reduce the patient need for opioids, an effect called *opioid-sparing*.

Anticonvulsants

Gabapentin and Pregabalin

The anticonvulsant drugs most commonly employed for neuropathic cancer pain are gabapentin and pregabalin. These two drugs have similar pharmacodynamic properties, in that they both inhibit voltage-gated calcium channels, through blockade of the α_{-2}/Δ_{-1} subunit of these channels, which are upregulated in pain states. Both gabapentin and pregabalin are structurally similar to gamma-amino-butyric acid (GABA); however, they are not ligands for the GABA receptor. These drugs are not metabolized, and drug clearance is through the renal route (urine); thus, dose adjustment is necessary in those with renal insufficiency. The most common side effects reported for these "gabapentinoids" include dizziness, drowsiness, weight change (gain), and edema of the hands and feet.

Several studies support the effectiveness of gabapentinoids for neuropathic cancer-related pain. For example, in a prospective, open-label study, Ross et al. [22] studied gabapentin effectiveness in two parallel groups – 25 patients in the first group had cancer-treatment-related neuropathic pain, while 37 patients, assigned to the other group, had tumor-related neuropathic pain. Gabapentin dosage was titrated to 1800 mg/day for patients in both groups. Pain scores per the

modified Brief Pain Inventory (BPI) were assessed as the primary outcome measure, and the results of the study showed a significant reduction in "worst," "average," and "current" BPI pain scores, but not the "least" score. Of the total patients, 45.2% achieved a minimum of one-third reduction in the pain score. The authors of this study concluded that gabapentin was indeed effective in the treatment of cancer-related neuropathic pain.

Caraceni et al. [23] performed a multicenter, randomized, double-blind, placebo-controlled, parallel-design trial to determine the analgesic effect of adding gabapentin to opioid therapy for managing neuropathic cancer pain. A total of 121 patients were enrolled in the study. Gabapentin was titrated to 1800 mg/day while patients remained on stable opioid therapy. Average daily pain was measured by Numerical Rating Scale (NRS) score, and the whole follow-up average pain score was used as the primary outcome measure. A total of 79 patients received gabapentin and 58 completed the study; 41 patients received placebo, of which 31 completed the study. Analysis showed a significant difference of average pain intensity between the gabapentin group and placebo group, supporting the effectiveness of gabapentin in improving analgesia in neuropathic pain cancer patients using opioids.

In a similar study [3], the efficacy and safety of pregabalin were evaluated in neuropathic cancer pain patients who were using morphine. Forty patients were randomized into two groups: the first group received pregabalin plus oral morphine in Phase I and then placebo plus oral morphine in Phase II, while the latter group received the opposite in each phase. There was a 1-week washout period between phases. The primary outcome measure was reduction in oral morphine dose. Results showed that there was a significant reduction in the mean minimal effective dose of morphine during treatment with pregabalin. The authors concluded that pregabalin enhanced the efficacy of oral morphine, while also reducing opioid dose-related side effects, in cancer patients with neuropathic pain.

In another study [24], low-dose gabapentin was studied in combination with imipramine for neuropathic cancer pain. Fifty-two patients were assigned into one of four groups. Those in group 1 were administered both gabapentin 200 mg and imipramine 10 mg every 12 hours; group 2, gabapentin 200 mg every 12 hours; group 3, gabapentin 400 mg every 12 hours; and group 4, imipramine 10 mg every 12 hours. Results showed that the low-dose gabapentin–imipramine combination significantly reduced total pain score, as well as daily paroxysmal pain episodes.

Pregabalin was compared to opioids for both safety and efficacy in treating neuropathic cancer pain in a prospective, head-to-head, randomized, open-label study [25]. A total of 120 patients were randomized into two groups, receiving increasing doses of either oral pregabalin or transdermal fentanyl. The main outcome measure was pain score by VAS. A significantly higher proportion of patients had at least 30% reduction in pain score, compared to the fentanyl group, and the percentage mean change (decrease) from pain baseline was significantly different for pregabalin versus fentanyl. Secondary measures of patient-reported satisfaction were also more frequent in the pregabalin-treated group, and adverse events and treatment discontinuation were higher in the fentanyl group. This study concluded that the use of adjuvants, like pregabalin, could lead to better neuropathic pain control and to opioid sparing effects.

A post hoc analysis [26] of pregabalin versus non-pregabalin-treated patients with neuropathic cancer pain in a 2-month multicenter, prospective, epidemiologic study showed a higher satisfaction rate, decreased benzodiazepine use, and decreased total pain intensity and interference in the Brief Pain Inventory for those patients treated with pregabalin polytherapy, compared to the non-pregabalin treatment group. The study authors concluded that the addition of more specific drugs that target neuropathic pain in affected patients provides more treatment satisfaction and better pain- and pain interference-related outcomes.

Carbamazepine and Oxcarbazepine

Carbamazepine and its structural derivative, oxcarbazepine, are sodium channel blockers that

appear to selectively inhibit active A-Δ and C nociceptive fibers, blocking both peripheral and central pathways for pain. Although the literature is sparse in describing their effects on cancer pain, these drugs are well established in managing other chronic pain conditions with a neuropathic component, such as trigeminal neuralgia [27] and various forms of peripheral neuropathy [28, 29]. Oxcarbazepine is considered to have a more favorable safety profile, with less risk for hepatic or hematologic adverse reactions, compared to carbamazepine.

Antidepressants

Duloxetine

Duloxetine is a serotonin- and norepinephrine-reuptake inhibitor (SNRI) antidepressant, approved by the US FDA to treat depression, generalized anxiety disorder, and pain associated with various conditions, such as painful diabetic peripheral neuropathy, fibromyalgia, and chronic, multisite musculoskeletal pains. In the cancer patient population, duloxetine has been used to manage chemotherapy-induced peripheral neuropathy pain [30, 31] and joint pains from aromatase inhibitor therapy [32, 33]. Although less well supported, duloxetine has been routinely used also to manage cancer pain with a neuropathic component. In a small retrospective pilot study, Matsuoka et al. [34] assessed the effectiveness of duloxetine in patients with cancer-related neuropathic pain refractory to opioids and gabapentinoids, finding it to be effective in reducing pain scores in 7 of 15 patients. The same authors have underway a prospective, randomized phase III study [35] to further establish evidence to support duloxetine use in this setting.

Amitriptyline

Amitriptyline is a tricyclic antidepressant, with evidence supporting its efficacy as an adjuvant for neuropathic pain in conditions such as central pain related to stroke and spinal cord injuries, as well as peripheral neuropathic pain related to diabetes, chemotherapy, and postherpetic neuralgia, among many other neuropathic pain conditions. There are few, small studies supporting its use for neuropathic cancer pain. For instance, a study by Banaerjee et al. [36] compared the efficacy and safety of amitriptyline versus gabapentin as a co-analgesic for patients receiving opioids to manage cancer-related neuropathic pain. Eighty-eight patients with neuropathic pain in malignancy were randomly assigned to two groups. The first group received gabapentin and tramadol, while the second group received amitriptyline and tramadol. At 6 months, there was a decline in Visual Analogue Scale (VAS) scores from baseline in both treatment groups, without any statistically significant difference between groups. The authors of the study concluded that amitriptyline could be an appropriate alternative to gabapentin for managing neuropathic pain from cancer.

In a prospective randomized study, Mishra et al. [37] compared the efficacy of amitriptyline, gabapentin, and pregabalin for neuropathic cancer pain. A total of 120 patients with neuropathic cancer pain were enrolled and divided into four different groups: amitriptyline group, gabapentin group, pregabalin group, and placebo group. A significant reduction in VAS scores were seen in all groups, with the authors concluding that all of the anti-neuropathic drugs studied demonstrated effect in relieving cancer-related neuropathic pain.

Topical Agents

Lidocaine

Lidocaine is a local anesthetic of the amide type. Lidocaine inhibits voltage-gated sodium channels within nerve cell membranes, preventing depolarization and, therefore, action potential generation. Lidocaine is available in topical form, and it can be helpful in relieving malignant neuropathic pain. Lopez Ramirez [38] conducted a study aimed to evaluate the efficacy of lidocaine 5% patch for focal neuropathic pain in patients with or without cancer. Fifteen patients were recruited. Six of the fifteen patients had cancer-related neuropathic pain. Eight out of the 15 patients treated reported a potent analgesic effect, and four patients reported partial analgesia.

Fleming and O'Connor [39] retrospectively audited the use of lidocaine patch 5% in a comprehensive cancer center. Among the 97 patients prescribed the patch, 26 were for persistent postsurgical neuropathic pain, 24 were for postherpetic neuralgia, and 18 were for cancer-related neuropathic pain. Allodynia was a feature in 60% of these patients, and analgesic efficacy in those with allodynia was "potent" in 35%, 38%, 39%, respectively.

Kern et al. [40] performed a retrospective analysis of 68 case reports regarding 5% lidocaine medicated plaster for cancer pain with a neuropathic component or for trigeminal neuropathic pain. The plaster was found most helpful for surgical- or chemotherapy-related neuropathic pain, with at least 50% of those using the plaster able to dose-reduce systemic analgesics. In trigeminal neuralgia, potential predictors of response to lidocaine plaster were found to be hyperalgesia, allodynia, continuous pain, among others.

Capsaicin

Capsaicin is the substance that gives chili peppers the characteristic burning sensation with tissue contact. Capsaicin, along with heat, acid, and other ligands, binds to transient receptor potential vanilloid subtype 1 (TrpV1), a cation receptor expressed on the peripheral and central terminals of nociceptive neurons. Prolonged capsaicin exposure is thought to result in a paradoxical desensitization of TrpV1, with subsequent analgesic effect. Although well studied for nonmalignant neuropathic pain conditions [41, 42], capsaicin has limited evidence in the cancer neuropathic pain patient. One study, however, of chronic postsurgical neuropathic pain in 99 cancer survivors [43] involved an 8-week application of 0.075% capsaicin cream four times daily to the affected painful area, followed by 8 weeks of placebo cream application, or vice versa. The capsaicin cream arm of treatment had a significant reduction in pain compared to placebo. The capsaicin treatment arm was associated, however, with significantly more skin burning and redness, but treatment arm discontinuation was similar in both groups. At the end of the study, participants were asked which treatment arm was most beneficial – 60% chose the capsaicin arm, 18% chose the placebo arm, and 22% chose neither. The authors of the study concluded that topical capsaicin cream significantly decreased postsurgical neuropathic pain in cancer patients and was preferred by patients over placebo by a 3:1 margin.

Conclusion

Cancer-related neuropathic pain, such as from CNS metastases, can be a challenging condition to manage. A multidisciplinary strategy, including potential interventional pain management strategies discussed elsewhere in this book, is essential to optimize patient outcomes. Providers should consider not only opioid drugs but also other adjuvants with analgesic properties such as antidepressants, anticonvulsants, and local anesthetic classes, among others.

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Interventions for Refractory Pain in Cancer Patients

52

Michael G. Kaplitt

Introduction

Pain is a serious complication of cancer that can severely limit quality of life as well as reduce longevity due to inability to perform activities essential to maintaining health, such as physical activity and proper nutrition. Medical therapy is generally the first treatment for patients with severe cancer pain, often consisting of opiates. When this is inadequate, however, alternatives for pain control are necessary. There are also increasing societal pressures regarding responsible administration and consumption of opiates for chronic diseases. In the cancer population, however, sensitivities around opiate abuse must be considered in the context of often recalcitrant pain and limited lifespan. Radiation and/or chemotherapy, to control the lesion(s) responsible for the pain as a palliative measure, are also often successful at reducing pain adequately to relieve distress and improve quality of life. When these treatments are unsuccessful or not feasible for a given situation, there are a variety of more interventional procedures which can be quite effective for patients with cancer-related pain. Here, we will review the causes of pain in cancer and current surgical procedures available for treating these complex patients.

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Mechanisms of Pain in Cancer Patients

Pain is a common problem in patients with cancer, particularly metastatic cancer. As with any pain, it can sometimes reflect a structural problem that needs to be addressed, such as spinal instability from a destructive lesion leading to mechanical back pain. This should be addressed if possible with resection and stabilization of the spine. However, for many cancer patients, chronic pain is a disease that needs to be addressed and does not necessarily reflect a more proximate problem that can be discretely fixed. The major cause of pain is generally activation of nociceptors by cancer cells or factors released by tumors, leading to typical aching, difficult to localize nociceptive pain [1]. This type of pain is generally treated with opiates, but resistance to opiates can develop, and in patients with longer life expectancies, concerns about opiate dependence and abuse are increasingly common even in the cancer pain population. There is also a paradoxical opiate-induced hyperalgesia that can occur from chronic opiate use [2]. In addition to releasing factors which activate nociceptors, tumor cells can also promote or induce inflammation, both locally within the cancer microenvironment and systemically, and this can cause or worsen pain as well. Cancerous lesions can also irritate local neurons which induce pain. Surgical therapies for nociceptive cancer pain described below

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are often tailored to patients based upon the type and location of the malignancy, the type of pain that they experience, and the nature of their responses and/or adverse effects to drug therapy for pain.

Cancer therapies can cause pain through different mechanisms than the cancers themselves [3]. These include neuropathies from radiation or chemotherapy, due to various known and unknown mechanisms that can permanently alter the function of sensory and pain neurons, leading to a more neuropathic type of pain, although inflammation from cancer therapy can also cause pain. Neuropathic pain is generally treated with antiepileptic medication or antidepressants, as with non-cancer neuropathic pain; however, it may be more difficult to obtain satisfactory responses to neuropathic pain in cancer patients as compared to non-oncologic neuropathic pain. Therefore, surgical therapies for patients with sufficiently severe and intractable treatment-related pain should focus upon those therapies, which are most appropriate for the mechanism causing the pain, which is generally neuropathic in nature.

Resective and Ablative Spinal Procedures for Cancer Pain

Spinal metastases are common in patients with cancer, occurring in up to 10% of patients with malignancies. Gross instability from destructive lesions can lead to severe mechanical back pain, which is characterized by pain with motion. This usually requires tumor resection and surgical fusion with hardware in order to promote healing and prevent spinal cord injury while also resolving the pain. For patients with vertebral body disease and pathological fractures, however, there are less invasive options. These patients usually do not have gross spinal instability but have pain either from biological factors released locally from the tumor or from microscopic instability. Vertebroplasty and kyphoplasty are percutaneous procedures that use fluoroscopic guidance to insert a needle into the affected vertebral body in order to inject bone cement (such as methyl methacrylate) [4]. This stabilizes the local bone while also potentially limiting effects of the tumor on local nerve endings. Vertebroplasty involves simply injecting cement into the affected vertebral body, while kyphoplasty uses balloon inflation to restore the lost height of a fractured vertebral body prior to injecting cement. While these are widely used for treatment of osteoporotic compression fractures, they were originally developed to treat hemangiomas and primary bone tumors and have been studied extensively in treatment of pain from vertebral metastases. Both procedures have been shown to substantially reduce pain from metastatic vertebral disease (60–70% or more) with substantial improvements in quality of life [5]. An ongoing randomized phase 3 study is exploring a combination of kyphoplasty and radiation to determine if there is superior short- and long-term pain control compared with patients receiving radiation alone, based upon phase 1/2 data showing substantial promise for this approach [6].

Ablation of specific tracts within the spinal cord has a long history in treating cancer pain patients [7]. Cordotomy has been the most widely studied, yet the availability of the technique has become increasingly limited due to lack of adequately trained practitioners, leading to an underutilization of this procedure [8]. Nonetheless, the vast majority of reports indicate that this is a very effective and safe procedure in appropriate patients with cancer pain treated by experienced practitioners [9]. The goal is to lesion the lateral spinothalamic tract, usually between the C1 and C2 spinal levels, in order to interrupt nociceptive fibers emanating from the contralateral body below the level of the lesion. This tract also subserves light touch and temperature, and so, these functions may be disturbed as a result of a successful procedure. Given this anatomy and physiology, the optimal candidate for the procedure is a cancer pain with nociceptive pain, usually visceral pain, below the level of the lesion and preferably in one hemibody in order to avoid the need for bilateral cordotomies which can be less effective and more morbid [10]. Initially, the procedure was performed with open surgery, but for at least the past 20 years, it has been largely a per-

cutaneous procedure performed with CT guidance [11, 12]. The patient undergoes a CT myelogram to identify the space for entry above C2. A needle enters the skin roughly just below the mastoid, then penetrates the CSF, and enters the spinal cord in an anterolateral location. The lesioning radiofrequency probe is then passed through the needle and into the spinal cord. Test stimulation at high frequency confirms the presence of paresthesias and/or temperature changes in the contralateral body, while low-frequency stimulation is performed to activate neurons in order to confirm that the nearby corticospinal tract is not being activated at a threshold that is too low. If this does happen and motor contractions occur at a low-voltage threshold, this suggests that the probe is too close to the corticospinal tract, risking hemiplegia if lesioning continues, so the needle and probe must be repositioned. A radiofrequency lesion is then performed at roughly 70–80 °C for 60 seconds, similar to other RF lesions such as those used to treat trigeminal neuralgia. Midline myelotomy is another spinal cord ablation technique, which is less technically challenging as this enters directly in the center of the dorsal spinal cord to create a punctate lesion that interrupts midline posterior column fibers as well as crossing fibers. This has been shown to be effective in a small series of patients with visceral pelvic and abdominal pain, but this has not been nearly as widely studied nor as clearly effective as cordotomy [13].

Lesioning of the dorsal root entry zone (DREZ) is another ablative procedure that has been used in neurosurgical treatment of pain for decades. This targets the neurons of the dorsal horn, as well as the lateral portion of the dorsal root fibers and a portion of the local projections between levels known as Lissauer's tract. A small hemilaminotomy is performed at the appropriate spinal level, followed by a durotomy to expose the spinal cord and existing dorsal roots. The dorsal rootlets are then elevated to expose the lateral entry zone. A lesion can then be created either by bipolar cautery or by insertion of a probe followed by radiofrequency lesioning; laser ablation has also been reported [14, 15]. It has most commonly been used for neuropathic pain from brachial plexus avulsion, which can lead to distorted anatomy at the DREZ region due to degenerative changes following the plexus injury. There have been many isolated reports and small series where DREZ has been explored in cancer pain [16]. Most of these studies have unsurprisingly explored DREZ lesions for either Pancoast tumors of the upper lung, which can impinge upon or infiltrate the brachial plexus, or for brachial plexitis and other neuropathic pain syndromes following radiation-induced injury. There have been some very promising outcomes in these reports, but to date, no definitive large or randomized study has been performed in cancer patients to clarify the best candidates for this treatment.

Intrathecal Delivery of Medication for Cancer Pain

Perhaps the most common procedure currently for treating intractable cancer pain is placement of an intrathecal pump. This is designed to deliver narcotics directly into the CSF, thereby limiting dose to the brain and essentially eliminating systemic toxicities from oral opiates [17]. For cancer patients with a very short life expectancy of only a few weeks, the treatment goals can frequently be achieved with placement of an externalized epidural catheter with constant epidural infusion. These are not generally effective for long-term treatment of months to years, however, due to the likelihood of catheter obstruction when not in a fluid compartment as well as the risk of infection from a long-term externalized device. While there is certainly a risk of both infection and catheter obstruction or malfunction with permanent intrathecal systems, these are very low risk even in medically complex late-stage cancer patients. Such permanent systems should be considered for those patients with evidence of response to systemic narcotics who either cannot obtain adequate pain relief or have unacceptable adverse effects to these medications.

Prior to surgery, patients often undergo a trial of epidural or intrathecal medication to determine the likelihood of response to a permanent

implant. While this is common for degenerative spine patients, we have published an algorithm for evaluation of cancer patients who may be optimal for this treatment without the need for an invasive trial [18]. Cancer patients can have blunted immune systems, coagulopathies, or other problems which make any intervention somewhat risky, and therefore, the ability to identify candidates for an intrathecal pump without the need for an invasive trial can be very helpful in this population. If a trial is done, we prefer to have externalized catheters removed the day before permanent implant to reduce the risk of infection. A longer period following removal would be desirable to further reduce any risk, but in our experience of implanting these devices for nearly 20 years at a major international cancer center, the risks of infection with this approach have been minimal, while the need for immediate implant in this particular population is usually very high.

The surgical procedure for implanting a system is fairly straightforward. Patients are placed in the lateral position, and fluoroscopy is used to identify the insertion point and to follow the catheter during implantation. The thecal sac is entered below the conus and usually at a less mobile level such as L3/4 to minimize risk of catheter migration. The needle tip should be in the middle of the spinal canal by fluoroscopy since CSF flow from the needle can still occur if the level is only partially in the subarachnoid space either posteriorly or anteriorly. The catheter should go in several levels to reduce the risk of migration and extrusion, and once in a good location, the anchor should be buried in the fascia, and the neck of the anchor should be sutured to reduce the risk of toggling that could also promote catheter extrusion. The level of the catheter tip is less important when pure opiate such as morphine are used since they will diffuse into the CSF. However, when mixtures of other agents are used, particularly when they include local anesthetics such as bupivacaine, then the tip should be placed at the level of the spinal cord with dermatomes in the most painful body area to be addressed. This is because the effects of such agents are mostly local on the spinal cord, and as the drug emanates from the catheter, it will dilute along a gradient of CSF. As such, if the catheter is not close to the target area, then it is difficult with these agents to achieve adequate effectiveness at the desired spinal cord target. Combining opiates with agents such as bupivacaine or clonidine can be particularly effective in patients with a mixed picture of nociceptive and neuropathic pain.

One long-term concern that is mostly relevant for patients with longer life expectancies is the development of inflammatory masses at the tip of the catheter [19]. These usually occur after many months and often years following the onset of treatment. They can lead not only to obstruction of the catheter tip but also to tethering of the spinal cord at the site and eventually to frank spinal cord compression with associated symptoms. If symptoms are mild or if the patient is asymptomatic, then reducing or eliminating the drug that is causing the problem can lead to resolution. However, if the mass is large and causing spinal cord compression, then open resection as if the mass were a tumor can be required to prevent permanent spinal cord injury [20]. Given the relatively shorter life expectancy of metastatic cancer patients compared with the larger population of degenerative spine patients with pumps, this is usually thought to be less of a concern. However, while any drug can lead to this problem, it is more common with agents that are off-label or made by compounding pharmacies [19]. Regardless of drug, though, any patient with a pump and new neurologic spinal symptoms should prompt consideration of an inflammatory catheter mass in the differential.

Spinal Stimulation for Cancer Pain

Neuromodulation devices such as spinal cord stimulation have become very popular for treatment of neuropathic pain, particularly pain in the extremities. The most common application of the technology is in patients with either degenerative spinal column disease who have failed to respond to either complex spine surgery or conservative management or in patients with injuries such as orthopedic trauma that have led to long-term neu-

ropathic pain from nerve injury. Cancer pain is rarely neuropathic in nature, and therefore, this has not been commonly used in such patients. However, as indicated earlier, treatment for cancer, such as chemotherapy or radiation, can result in neuropathies and severe neuropathic pain that is better treated with antiepileptics or antidepressants than with opiates [3]. When this is inadequate, spinal stimulation can be very effective [21]. Spinal stimulation is usually trialed with externalized leads placed percutaneously into the epidural space, unless there are structural problems such as scar or hardware that prevents passage of leads to the correct level. In those cases, a surgical paddle lead can be placed at the target spinal level through a small laminotomy. Generally, pain relief of greater than 50% during the 5–7-day trial period is considered necessary to justify proceeding with a permanent implant. This increases the likelihood of success following a permanent implant, since those with a more modest response are unlikely to do better with a longer period of stimulation.

Traditional spinal stimulation devices for neuropathic pain used relatively low-frequency stimulation (10–40 Hz) to induce paresthesias in the area of pain, based upon the Melzak and Wall gate theory [22]. However, many devices now offer higher-frequency stimulation (from 1000 Hz to greater than 50,000 Hz) which are paresthesia-free and work by theoretically different mechanisms based upon the frequency range [23]. These have only been available commercially for a limited number of years, and so, it is unclear whether these may have a greater potential in cancer patients to treat nociceptive pain from cancer in addition to treatment-induced neuropathies.

Brain Procedures for Cancer Pain

Targeting brain regions which process pain has long been of interest for patients with refractory pain syndromes, yet they are still rarely used in most centers [9]. One brain region used for neuropathic pain is the lateral thalamus, including the major sensory thalamic nucleus VPl [24], but this has largely been supplanted by spinal stimulation since the results are largely similar without the perceived risk of a brain implant. A second more medial thalamic target, including the periaqueductal and periventricular gray areas, is more relevant to cancer pain, since stimulation of this area leads to natural opiate release, resulting in a feeling of warmth that often leads to pain relief [25]. As with the more lateral target, this has also been largely replaced by intrathecal pumps which can increase CSF opiates without the need for brain penetration. A third target that is still considered in some centers for refractory patients is the cingulate cortex. This is a critical center for processing affective components of pain such as distress. Lesioning this area (cingulotomy) can lead to pain relief, although it does not block either the peripheral pain signals or central perception of pain but rather reduces the consequences of pain [26]. Patients often report that they still feel pain, but it no longer causes them anxiety or distress, and overall, their quality of life is generally improved despite ongoing perception of pain. Therefore, this is generally reserved for patients with few alternatives to address either the underlying cause of the pain or initial processing of pain signals with more common procedures. Although neurostimulation can be performed in this region, lesioning of the cingulate is preferred for cancer patients as this does not require any device implant, and usually, this is used in patients who are in later stages of disease. Cingulotomy is usually performed with a minimally invasive burr hole followed by stereotactic insertion of a radiofrequency probe into the anterior cingulate; however, radiosurgery has also been used for a less invasive approach [27]. Although radiosurgery is attractive, the efficacy of radiosurgery for functional goals usually is not evident for 2–3 months after treatment, since the outcome depends upon the response of target neurons and supportive cells to radiation and the resulting radiation-induced cell death, which is generally not immediate. This has to be considered when deciding upon a method for performing a cingulotomy in a cancer pain patient, since the life expectancy of the patient may influence whether a more immediate response is necessary.

A new method for immediate lesioning deep brain targets without invasive surgery and without radiation may ultimately hold promise for treating cancer pain patients who are refractory to or not candidates for extracranial therapies. MR-guided focused ultrasound (MRgFUS) was recently approved in many countries, including the United States and Europe, to perform noninvasive thalamotomies for essential tremor. Ultrasound can traverse the skull and pass through the brain with relative safety, but it is generally low energy. With MRgFUS, a helmet with an array of 1000 ultrasound transducers is placed over the head of a patient after fixation in an external frame to prevent movement of the head during treatment [28]. The transducers are all focused upon a single point in the center of the imaginary sphere of the helmet, so that the ultrasound beams from each transducer converge at the same target point. As a result, a large amount of energy can be delivered to a deep brain target when it is matched to the focal point of the array, and the energy is sufficient to raise the temperature of the tissue to a lesional level of 55–60 °C. Using MR thermometry, a heat map can be generated showing the volume of tissue that was raised to a particular temperature. When the appropriate temperature is achieved, the tissue is ablated, and when the lesion is therapeutically effective, the benefits are generally observed immediately. For tremor patients, the target is the cerebellar receiving area of the thalamus (so-called Vim nucleus), and when the target is ablated with focused ultrasound, the tremor usually improves immediately on the table [29]. The procedure is performed entirely within the MRI machine, and patients can usually be sent home the same day.

While this technique has been most widely used for tremor, there is great interest in applications for pain. One of the first clinical reports of MRgFUS was in fact an application of thalamotomy for pain, targeting the lateral thalamic region described above [30, 31]. This is adjacent to the area of the thalamus targeted for essential tremor so the procedure is technically very similar. Lesion efficiency was good, and patients experienced roughly 40–60% improvement of pain at 1 year. These patients were mostly those with nonmalignant causes for their pain. However, the ability to provide a noninvasive option for lesioning various brain targets associated with pain, without the need for radiation (which might also be a concern in patients with prior radiation to the brain) and with immediate responses, may be of great utility to cancer pain patients in the future.

Conclusions

Cancer patients have unique pain needs that are sometimes not accommodated by traditional oral opiate medications. In patients with short life expectancy, externalized intrathecal catheters are a quick, effective way of alleviating pain. In patients with longer life expectancies, implanted intrathecal pumps are generally the mainstay of interventional pain techniques. Techniques like cordotomy, DREZ lesioning, spinal stimulation, and others have their role, and their consideration should be individualized to each patient. Newer technologies like MR-guided focused ultrasound hold promise for noninvasive treatment of cancer-related pain.

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53 Complementary and Integrative Therapies (CIM) in Patients with CNS Metastasis

Santhosshi Narayanan, Wenli Liu, and Gabriel Lopez

Introduction

Cancer patients with metastasis to the brain experience a spectrum of symptoms such as headache, nausea, vomiting, seizures, fatigue, cognitive deficits, drowsiness, etc. In general, the use of complementary health approaches is highest among individuals with cancer [1–3]. Patients with central nervous system metastasis may resort to complementary and integrative therapies (CIM) in addition to conventional therapies for symptom management or for hope of cure. In an attempt to meet the patient's needs and appropriate the use of CIM, integrative oncology programs have developed or are under development in several cancer centers [4, 5].

According to a published expert consensus, integrative oncology is defined as a "patient centered, evidence-informed field of cancer care that utilizes mind and body practices, natural products and/or lifestyle modifications from different traditions alongside conventional cancer treatments. Integrative oncology aims to optimize health, quality of life, and clinical outcomes across the cancer care continuum and to empower people to prevent cancer and become active participants before, during and beyond cancer treatment" [6]. Here we will discuss some of the integrative treatments that can help symptoms of patients with metastatic cancer to the brain.

Definitions

Complementary and alternative medicine (CAM) is defined by the National Center for Complementary and Alternative Medicine (NCCAM) as a group of diverse medical and health systems, practices, and products that are not normally considered to be part of conventional medicine. It is classified into four broad categories: natural products (e.g., vitamins, minerals, dietary supplements, herbs), mind and body medicine (e.g., meditation, yoga, acupuncture), manipulative and other body-based practices (e.g., massage, chiropractic), and other CAM practices (e.g., Ayurveda, traditional Chinese medicine, energy therapies). CAM includes certain modalities that may or may not have high-quality evidence. Alternative medicine is when a patient makes use of a CAM modality for which there is no evidence of efficacy in place of conventional medicine. Complementary medicine is when a patient makes use of CAM modality for which there may or may not be evidence for its efficacy in combination with conventional medicine.

Integrative medicine or complementary and integrative medicine (CIM) uses evidence-based approach to merge conventional and nonconven-

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tional therapies. The consortium of Academic Health Centers for integrative medicine defines integrative medicine as "the practice of medicine that reaffirms the importance of relationship between practitioner and patient, focuses on the whole person, is informed by evidence, and makes use of all appropriate therapeutic approaches, health professionals and disciplines to achieve optimal health and healing." Integrative oncology is the application of integrative medicine to the care of patients with cancer and their caregivers [6].

Clinical Consultation

The goal of the physician consultation is to provide patients with an integrative care plan tailored to the individual and his/her unique disease trajectory [5]. Initial consultation involves a thorough evaluation of the patient, which includes detailed history of their cancer, current treatment, medical conditions, presenting symptoms affecting physical health and emotional health, and review of the laboratory tests and/or imaging. After a comprehensive assessment, the integrative oncology physician is able to create a personalized integrative care plan which may involve a combination of physical, mind-body, and social aspects of the patient's health as illustrated in Fig. 53.1. There is a growing evidence supporting the use of CIM therapies such as acupuncture, massage, and mind-body practices as a part of the standard of care. Some of the integrative approaches used in management of symptoms in patients with central nervous system metastases are listed below [7]. Other areas such as healing touch, homeopathy, energy therapies, and special diets have insufficient evidence to support their use as part of the standard of care. Here, we discuss some of the commonly used integrative approaches in caring for patients with metastatic disease to the central nervous system.

Integrative Therapies for Symptom Management in Patients with Brain Metastasis

Nausea

- Acupuncture
- Mind-body (guided imagery, hypnosis, music therapy, meditation)

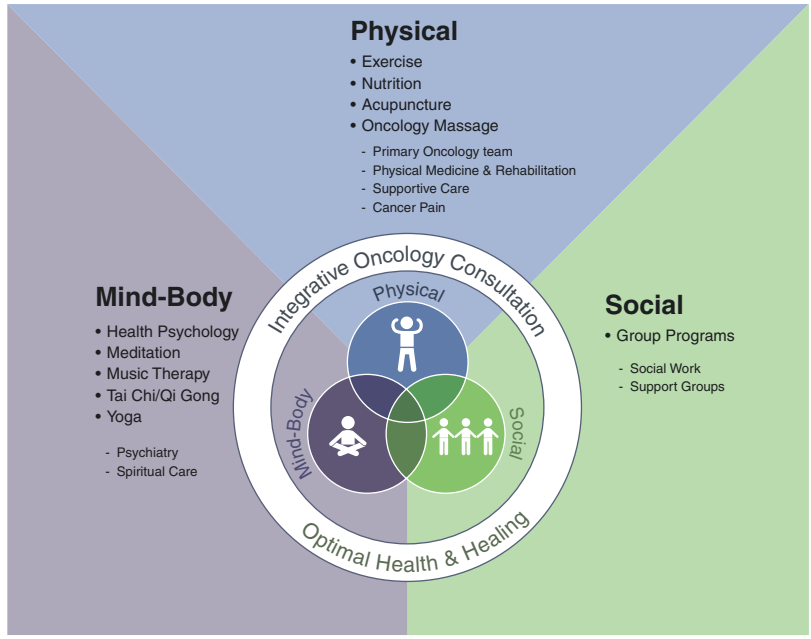

Fig. 53.1 Integrative medicine center model

Fatigue

- Discuss energy conservation/exercise counseling.
- Consider:
  - Physical health assessment/exercise counseling by physical therapy
  - Strategies to improve sleep if there is sleep disturbance
  - Yoga and oncology massage (Category 1, NCCN guidelines)
  - Acupuncture

Stress/Anxiety

- Expressive supportive counseling
- Consider:
  - Psychology
  - Psychiatry
  - Meditation or other mind-body practices such as yoga
  - Oncology massage
  - Social work and support groups

Insomnia

- Sleep hygiene counseling
- Consider:
  - Psychology and cognitive behavioral therapy
  - Exercise/physical therapy assessment
  - Meditation or other mind-body practices (tai chi, qigong, yoga) or music
  - Pulmonary/sleep evaluation
  - Medication

Headaches and Neck Pain

- Yoga/meditation
- Acupuncture
- Oncology massage

Neuropathy

- Acupuncture
- Massage

Dry Mouth

- Acupuncture

Alternative Therapies

- Education – discuss current evidence/risks versus benefits.
- Review motivations for use, and explore other opportunities to help meet patient objectives using evidence-informed approaches.
- Encourage/support ongoing communication with conventional oncology care team.

Acupuncture

Acupuncture, a therapy that has been used for more than 2500 years as part of traditional Chinese medicine (TCM), is now used worldwide. The practice of acupuncture involves diagnostic assessment of a patient's symptoms based on TCM principles, selection of acupoints, and insertion of fine needles into the selected acupoints. In modern practice of acupuncture, electric stimulation is often applied to the needles in addition to the traditional manual stimulation. Acupuncture has a well-established safety profile, with minor side effects of local pain (3.3%), bruising (3.2%), minor bleeding (1.4%), and orthostatic problems (0.5%) [8]. Its role in managing cancer- and treatment-related symptoms, such as pain, hot flashes, nausea/vomiting, fatigue, and xerostomia, is well-recognized [9]. Many comprehensive cancer centers incorporate acupuncture for cancer symptom management [4]. Our own published experience in an outpatient cancer care setting has demonstrated statistically and clinically significant effects of acupuncture on self-reported symptoms [10].

Headache, nausea/vomiting, fatigue, pain, and focal deficits are common symptoms of patients who have CNS metastasis. Acupuncture has shown promising treatment efficacy for managing headaches, nausea, and tumor-related pain and a low incidence of adverse effects [11–15]. Side effects, such as somnolence, change in mental status, and constipation, are commonly

seen with use of narcotics and antiemetic drugs. Acupuncture treatment, without the common side effects and adverse drug interactions of pharmacological agents, may be particularly a suitable adjunct modality for symptom management in this population.

Massage

Massage is shown to benefit symptoms such as anxiety and fatigue and leads to improved quality of life in cancer patients [16, 17]. Oncology massage involves modification of massage techniques in cancer patients. In patients with CNS metastasis, precautions need to be undertaken in the setting of recent surgery and/or history of seizures. Before the massage, the therapists review blood counts and other areas of metastasis and modify the massage techniques by avoiding certain sites, changing pressure, etc. If patients are neutropenic, massage is not recommended.

Patients with CNS metastasis may be treated with medications such as opioids for pain control and ondansetron for nausea which can contribute to constipation. Massage was shown to relieve constipation in several studies [18, 19]. There is anecdotal evidence suggesting massage can help provide relief for chemotherapy-induced peripheral neuropathy [20]. Massage may also be integrated into chemo-infusion suites to help with anxiety, nausea, and pain [21].

Mind-Body Practices

Mind-body practices are techniques that could help decrease distress and balance sympathetic and parasympathetic nervous system [22]. These include meditation, relaxation, tai chi, qigong, and yoga. The expressive arts such as music therapy, art therapy, dance therapy, and journaling are also considered mind and body practices. In addition to decreasing distress, mind-body practices have additional benefits on neurotransmitters (GABA, glutamate), balancing HPA axis, improving immune function, and other physiological benefits [23–25].

Yoga, tai chi, and qigong are movement-based mind and body practices which combine physical postures or movements, breathing techniques, and meditation with the goal to enhance health and well-being. Yoga has been shown to facilitate relief for a multitude of symptoms in cancer, improving quality of life, sleep, and fatigue [26–31]. Meditation, meditative movements such as yoga and qigong, and mindfulness-based stress reduction have been shown to improve cognitive functions in cancer patients and survivors [32–34]. Individuals affected by cancer may consider regular practice of a mind and body approach in support of overall health goals during cancer care, including cognitive benefits [35].

Physical Well-Being

Nutrition

Patients with CNS metastasis undergo radiation, surgery, or chemotherapy or a combination of these. During these treatments, nutritional protein requirements may increase, with goals set by expert consultation with a registered dietician (e.g., 1–1.2 g/kg body weight per day). Ketogenic diet (KD) is a high-fat, adequate-protein, low-carbohydrate diet. Energy-restricted ketogenic diet has been proposed as metabolic treatment in primary brain cancer patients, and patients often start ketogenic diet on their own without any supervision. It is based on the theory that tumor cells depend on glucose for energy metabolism whereas normal cells in the brain can use the ketones as a source of energy [36, 37]. However, there are no large trials which have shown the benefit of ketogenic diet in patients with CNS metastasis. Though anecdotal evidence suggests that side effects are minimal and keto diet is tolerated well in patients with primary brain cancers, we do not have information on the level of blood glucose or ketones and amount of calorie consumption per day that are associated with antitumor effect [38–40]. Per American Institute for Cancer Research (AICR) recommendations for cancer prevention, we advise patients to eat a variety of vegetables, fruits, whole grains, and

legumes such as beans, avoid sugary drinks, limit consumption of energy-dense foods, and limit alcoholic drinks [41].

Exercise

Fatigue can limit patients from exercising. Cancer itself or treatments such as radiation and chemotherapy can contribute fatigue. Encouraging patient participation in a program of regular, safe exercise, with supervision as appropriate, may be of benefit for supporting overall health during and after treatment. Aerobic exercise has neuroprotective benefits as it has been shown that 1 year of aerobic exercise increased hippocampal volume; this translates to higher BDNF which is a mediator of memory formation and therefore may lead to improved memory function [42]. Exercise helps to restore muscle mass and strength and also helps balance and mobility in addition to improving sleep quality [43]. Current American College of Sports Medicine recommendations include 150 minutes of aerobic exercise per week and 20 minutes of resistance exercises twice a week. However, we recommend individualizing exercise regimens. Referral to physical therapy for exercise counseling and review of energy conservation techniques in the setting of fatigue may help in the development of an individualized program of activity [44].

For patients who are sedentary or deconditioned, tai chi, Qi gong or yoga which are forms of meditative movements can be offered at a lower intensity. Tai chi or yoga may also enhance cognitive function [45, 46].

Psychosocial Well-Being

Stress and anxiety are commonly reported symptoms in patients with cancer. Stress-induced physiological changes in the body can adversely affect the patients in many ways. Studies in breast cancer patients show that patients who receive comprehensive education for stress management, maintain a healthy diet, and engage in regular physical activity had a survival advantage [47]. Stress leads to persistent increase in sympathetic nervous system activity and hypothalamic-pituitary axis which in turn causes changes such as increased blood pressure, heart rate, etc. Chronic psychological stress also impairs memory directly or through mediators of stress as shown in a study of caregivers of patients with dementia [48]. Patients and their spouses are vulnerable to experiencing distress as a result of the diagnosis and treatment of CNS metastases. Distress may exacerbate memory issues in these patients/caregivers and may also contribute to the development of headaches. Expressive supportive counseling is recommended in these patients. We recommend assessing patients for positive coping strategies such as hobbies and listening to music and negative coping strategies such as alcohol. Expressive supportive counseling may help in addition to referral to psychology or psychiatry based on their symptoms. In addition, mind-body practices may modulate pain/headache by other neural and cognitive mechanisms or may indirectly influence pain by lowering stress and anxiety [49]. It is important to note that caregivers may also be afflicted by significant stress and its associated maladies; providers should assess for caregiver stress and counsel appropriately. Meditative movement such as yoga can also help relieve distress experienced by caregivers [50].

Another commonly reported symptom in cancer patients with CNS tumors includes sleep disturbance. The root cause is often multifactorial and can be related to depression, stress, anxiety, poor exercise routine, treatment side effects, etc. Sleep impairment can cause worsening of memory issues [51] and can also contribute to fatigue and daytime drowsiness. Cognitive behavioral therapy is the gold standard for management of insomnia. Medications also have a role and should be prescribed as appropriate .Yoga or tai chi can be used as adjunct modality [52].

Herbs and Supplements

Patients often use herbs and supplements as part of their cancer care, typically when their cancer progresses despite conventional therapy. These

supplements are also used to help decrease side effects from conventional therapy or to augment the anticancer effect of their prescribed therapies. Some patients decline conventional therapies and instead look for alternative treatment options. Patients often have a list of natural products that they currently take or are interested in taking. Herbs and supplements should be treated similarly to prescription medications and entered into a patient's chart. The first step in the discussion is to assess motivation for use of herbs and supplements. The second step is to educate patients on the effects of supplements on their health and the potential interactions of supplements with their current treatments based on the best available evidence. Some products may cause negative clinical outcomes due to metabolic interactions, treatment interactions, organ toxicity, cancer promotion, or lack of quality control during the manufacturing process. For example, St. John's wort (*Hypericum perforatum*) may decrease the clinical efficacy of irinotecan or imatinib by induction of cytochrome p450 enzymes [53, 54].

Certain herbs and supplements are also antioxidants such as green tea extract (GTE) and vitamins A, C, and E. These antioxidant supplements may interfere with radiation and chemotherapeutic agents that depend on oxidative damage to exert their cytotoxic effect [55]. In a population of patients with head and neck cancer, use of beta-carotene and vitamin E during radiation treatment was associated with increased local recurrence and incidence of second primary cancer [56]. We recommend that patients obtain their antioxidants through whole food sources until more evidence is available regarding the safety of antioxidant supplements during treatment.

Certain concentrated natural products may also lead to organ damage such as hepatotoxicity or nephrotoxicity. For example, some green tea extracts (GTE) have been associated with drug-induced liver injury [57]. Other biosimilar compounds like amygdalin, laetrile (purified form of amygdalin), and vitamin B17 (extracted from apricot kernels) have noted antiproliferative activity in vitro but have been associated with cyanide toxicity in some patients [58, 59]. Life-threatening toxicities such as seizures, severe lactic acidosis, and coma have been reported [60]. Increased bleeding risk is associated with some supplements such as ginkgo biloba, fish oil, and garlic, and patients should be educated regarding this risk, with supplements discontinued before surgical procedure [61].

There are also concerns regarding harmful contamination of raw Chinese herbal medicines with heavy metals, which may lead to patient complications, as there is no standardized quality control for the herbs and supplements [62]. Even though some of the herbs have been shown to inhibit cancer cells in preclinical or laboratory studies, further research is needed for safe human use [63].

Conclusion

Patients are increasingly relying on recommendations from different sources such as media, the Internet, family members, other patients, and healthcare professionals. It is important for healthcare providers to be open and nonjudgmental about CIM options being used or considered. This will enable patients to have open conversations and not fear disclosure of current CIM use. Integrated oncology providers are an essential part of modern cancer care as they can guide patients in their use of natural products and other CIM treatments in order to optimize safety and synergy with their current conventional cancer treatments.

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54 The Palliative Care of Patients with Brain Metastases

Rebecca A. Harrison and Eduardo Bruera

Introduction

Central nervous system (CNS) metastasis is a significant and devastating complication of cancer. Dissemination of disease to the brain and spinal cord heralds an aggressive disease trajectory and often imparts a unique and disabling symptom burden. Within the cancer population, CNS metastases present in 10–30% of patients [1, 2]. Brain metastases remain the most common malignant brain tumor in adults [3], with an incidence that continues to rise [4, 5]. Intramedullary spine metastases, while present in only 0.9–5% of cancer patients, portend a similarly poor prognosis [6–8]. As such, a fundamental fluency in the care of these patients among oncologists is essential.

The Contribution of Palliative Care

Palliative care is a comprehensive medical and interdisciplinary care directed at improving patient quality of life. Central to its mandate is the concept that providing care for cancer patients should be broader than extending survival.

Palliative care was initially delivered to inpatients admitted to acute care hospital beds and palliative care units [9]. In recent years, multiple randomized controlled trials have demonstrated the value of early outpatient palliative care in improving multiple physical and psychosocial symptoms and end-of-life quality through reducing emergency room visits, intensive care unit admissions, and chemotherapy administration in the last days of life [10]. A number of studies have found that using the name "supportive care" for their outpatient program increases the likelihood of early referral by oncologists [11, 12] and results in earlier and higher numbers of patient referrals [13, 14].

Patient-centered outcomes, such as quality of life and cognitive performance, are increasingly incorporated as endpoints in therapeutic clinical trials, acknowledging the impact these factors should have on therapeutic decision-making [15, 16]. In the treatment of brain metastases specifically, treatment adaptations and interventions are being evaluated to try to minimize treatment toxicity and improve patient function [17, 18], and metrics evaluating cognitive outcomes and quality of life are routinely incorporated as clinical trial endpoints [19, 20].

Patients with CNS metastases are a distinct population (Fig. 54.1). Because of the substrate affected, the disease can cause changes in cog-

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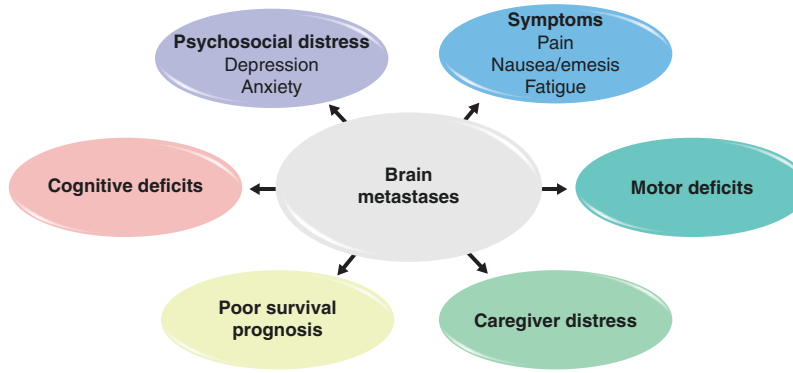

Fig. 54.1 The spectrum of complications in patients with brain metastases

nition, mobility, language, and independence. Furthermore, CNS-directed treatments used to prolong survival in these patients have the potential to augment these neurologic deficits. The fallout of these changes may include changes in social relationships, decision-making capacity, and autonomy.

While possible at any time in the course of illness, CNS metastases most commonly occur in the setting of advanced cancer. The vast majority of patients with brain metastases have a previously identified primary cancer, and most have either primary or secondary lung involvement before dissemination to the brain [21]. Similarly, most spine metastases are diagnosed just after 3 years after the initial cancer diagnosis [22] and often have disseminated cancer including brain metastases at diagnosis [23]. This renders these patients distinct from patients with primary CNS tumors, as they have often already accrued end-organ toxicities, fatigue, and psychological and social stressors with their cancer prior to their diagnosis of CNS disease. The nature of their symptoms and the poor life expectancy associated with CNS metastases highlight the value of integrative palliative and antitumor care in the management of patients with CNS metastases.

Prognostic Significance of CNS Metastases

Involvement of the nervous system in cancer is associated with poor survival. Not only are CNS metastases a mark of an aggressive systemic cancer, but also they are a therapeutic challenge. Protected by the blood-brain barrier, they are recalcitrant to many systemic chemotherapies, and CNS-directed therapies such as surgery and radiation may be limited by the associated neurologic toxicity. It is often the case that diagnosis of brain metastases signals likely poor survival, but this is not necessarily the case particularly in the era of immunotherapy and radiosurgery [24].

Intramedullary spinal cord metastases have a more precipitous symptom onset than primary spinal cord tumors [25, 26]. Surgery is rarely indicated for intramedullary spinal cord metastases, given the collateral neurological damage that can result [7]. As such, radiation as stand-alone therapy is more typically provided in this population. This is contradistinction to patients with vertebral column metastases who are often palliated with surgical resection and deformity correction followed by radiation. The mean survival after surgery for intramedullary spine tumors has been found to range from 5 to 11.6 months [22, 27]. The majority (80%) of patients with spinal metastases die within 3 months of diagnosis of spine involvement [28]. Most often, it is not the spinal metastasis but the widespread cancer that is the ultimate cause of mortality in this population.

Symptom Burden

Focal Neurologic Deficits

Focal neurologic deficits, including motor, sensory, language, and bulbar dysfunction, may

result dependent on anatomic location of the metastases. These classically obey the structure-function relationships of the nervous system. Motor deficits may arise from involvement of the primary motor cortex, spinal cord, supplementary motor areas, cerebellum, thalamic nuclei, and/or deep gray nuclei. Sensory deficits can similarly occur from involvement of the sensory cortex, thalamic nuclei, brainstem, and spinal cord. While neuropathic pain is rare in brain metastases, thalamic lesions have been reported to cause Dejerine-Roussy syndrome, a severe hemibody pain contralateral to the site of the thalamic lesion [29]. The brainstem carries the neural substrates for fundamental processes such as respiratory drive, autonomic control, alertness, and oropharyngeal function. Due to the frequent multifocal nature of CNS metastases, a comprehensive review of neurologic symptoms is essential in this population.

The nature of neurologic symptoms influences patient well-being. In patients with primary brain tumors, motor deficit, particularly gait impairment, is associated with worsened perceived symptom burden and contributes significantly to disability at end of life [30]. Motor impairment has also been identified as the most common reason for initiating hospice care [30]. In comparing patients with brain tumors to other systemic cancer patients, motor symptoms were a unique contributor to decline in quality of life among those with brain cancer [31]. These findings are extrapolated from the primary brain tumor literature; further study is warranted to understand the precise influence of these symptoms on patient quality of life and disease trajectory in those with CNS metastases. That said, regardless of pathology, substantial motor deficits significantly affect patient's quality of life and perception of disease burden.

The majority of patients with spinal cord metastases are symptomatic (92%) [32]. Among patients with intramedullary spinal cord metastases, the leading presenting symptoms are dysesthesia (77%) followed by paresis (68%) and urinary retention in a minority (23%) [22]. In most patients, neurologic deterioration occurred in days to weeks from presentation [28].

Headache

Headaches in patients with brain metastases can arise from mass effect; distortion of pain-sensitive intracerebral structures, such as proximal vessels, meninges, or venous sinuses; or the development of hydrocephalus. Integral to treating the headache is to understand its pathophysiologic contributors. Intracranial pain-sensitive structures generate visceral pain, which is referred to more superficial anatomic structures. As such, it may not be experienced as originating from the region of the mass: supratentorial lesions commonly generate frontal pain and posterior fossa lesions occipital pain. Patients with brain metastases, however, are unlikely to have early morning headache classically associated with elevated intracranial pressure [33]. The headaches can take on various semiologies of primary headaches, such as tension-type headaches (77%) or, less commonly, migraine headaches or other headache types. A pre-existing headache history is a risk factor for headache with intracranial tumor [34].

Fatigue

Cancer-related fatigue is a pervasive issue in patients with brain metastases, as it is in the cancer population as a whole [35]. Over 95% of patients receiving chemotherapy or radiotherapy have fatigue, emphasizing its prevalence [36]. This fatigue is disproportionate to exertion level and is not relieved by rest or sleep [37]. Many of the proposed mechanisms of cancer-related fatigue are central, including alterations in serotonin transmission and metabolism [38, 39], hypothalamic-pituitary axis dysfunction [40–42], and circadian rhythm dysregulation [43]. As such, it is logical that fatigue would be a prominent issue in patient's CNS metastases.

Similar to other symptoms in this population, baseline fatigue can increase with anticancer therapies. In evaluating fatigue scores in patients prospectively as they go through whole brain radiation therapy (WBRT) treatment using several different assessments [35], there was a noted increase in

fatigue scores from baseline to the first month after radiation therapy. In addition, sleep-wake disturbance occurs at increased frequency in patients undergoing brain radiation [44], with reduction in melatonin secretion and resultant hypothalamic dysfunction being proposed mechanisms [45].

Cognitive Dysfunction

Findings of cognitive impairment have been identified in one-third of patients with non-CNS cancer even prior to the initiation of anticancer therapy, a testament to the neuroactive impact of cancer [46]. This incidence is higher in patients with CNS metastases, with up to 90% of patients having cognitive impairment at time of diagnosis with brain metastases [47]. In addition to the metastases themselves, the systemic cancer, cytotoxic and hormonal therapies, as well as CNS-directed therapies such as radiation and radiosurgery may all contribute to this change. This cognitive change can have a breadth of implications for the patient, from navigating treatment decisions, social roles, and vocational commitments.

The nature of neurologic deficits in patients with brain metastases can be loosely predicted by the neuroanatomy affected, though this population also has more generalized cognitive changes than patients with other structural brain diseases. As a group, patients with brain metastases most commonly have memory impairment, with deficits in attention, executive function, and language also being present in comparison to healthy controls [48]. The severity of cognitive impairment in this population has been found to correlate with total tumor volume [49]. Notably, cognitive deficits have been identified in brain metastases patients that have no reported functional impairment [48], indicating the importance of awareness of this complication among providers and caregivers.

Seizures

The vast majority of brain metastases occur in the cerebral hemispheres (85%) and thus have the potential to be epileptogenic. Seizures are less common in patients with metastases than in those with primary brain tumors, with less than a quarter (24%) of patients with brain metastases being affected [50]. They are most common in those with melanoma brain metastases (67%) [50], with hemosiderin irritation of surrounding brain parenchyma being thought to further lower the seizure threshold. In addition to the structural lesions themselves, vasogenic edema, medications, and intercurrent illness may further lower the seizure threshold in this population. Aside from the medical implications of seizures, this comorbidity can have significant implications for the patient's psychological and social well-being. They can also contribute markedly to caregiver stress [51]. As such, they warrant dedicated medical attention, and there should be open discourse regarding any breakthrough seizures and recommended management.

Palliative and Supportive Care Interventions

Supportive/Palliative Interventions for Brain Metastases

- Surgery
- Radiation therapy
- Chemotherapy
- Steroids
- Seizure medications
- Analgesics
- Rehabilitation
- Cognitive exercises and treatment
- Caregiver support

Surgery

In addition to cytoreduction, surgery can provide symptomatic relief for patients with CNS metastases. In retrospective analysis, surgical resection of brain metastases was found to improve functional outcome, reduce neurologic impairment, and improve quality of life [52]. After surgery,

half of patients regained normal function for a period of time. Similarly, average performance status was found to improve with surgery in patients with spinal metastases [22], associated with improvements in motor and sensory function. After surgery, they may be treated with radiation, systemic therapy, or a combination of these [53]. In appropriately selected patients, surgery and adjuvant therapies can lead to significant symptom palliation. Patients with poor anticipated survival or rapidly progressing systemic disease may not benefit from surgical intervention as the neurologic symptom-free period may be rapidly eclipsed by symptoms from progressive systemic cancer [53].

Radiation Therapy

Along with surgery, radiation is a frontline treatment for brain metastases [54, 55]. Whether it be stereotactic radiosurgery (SRS) or whole brain radiation therapy (WBRT), most brain metastases are treated with radiation therapy of some form, regardless of histology. While little study has focused on the capacity of these adjuvant treatments to lead to symptomatic improvement, one study found the period free of neurologic progression after radiation was on the order of weeks, and steroids are often reintroduced to manage progressive symptoms [53]. In addition to prolonging patient survival, radiation can contribute to control of neurologic symptoms [56, 57]. However, toxicities of therapy may also contribute significantly to patient symptom burden.

Fatigue is a common early effect of radiation therapy. It often develops during or within a few weeks of WBRT completion for brain metastases, persisting for weeks after its completion [58]. More specific neurologic toxicities may also result from brain radiation. The neurotoxicity it imparts is influenced by the radiation modality used, the dose and fractionation schedule, the area of the CNS targeted, and the time elapsed since treatment. A temporally based classification scheme is frequently used to classify the neurologic effects of radiation; these include early acute (during radiation), early delayed (<6 months from radiation completion), and late delayed (>6 months from treatment completion) effects [59]. Risk factors for increased toxicity of radiation include age, with very young or old populations being more vulnerable, the size of the tumor, and the radiation dose delivered [58].

The resultant symptoms of brain irradiation result from its impact on cerebral vasculature, neuroglial cells, and neural progenitor cell populations. While whole brain radiation was previously associated with an acute encephalopathy syndrome [59], this has become less common given modern fractionation and dosing. Short-term memory deficits and verbal fluency deficits, however, have been identified from 3 months to 1 year following WBRT, with more generalized cognitive effects occurring and persisting subsequent to this [60–62]. Increased permeability of the blood-brain barrier during radiation can lead to focal vasogenic edema, leading to increased focal neurologic symptoms or seizures. This increased edema is self-limited, with resolution in the weeks or months following treatment. In the months and years following radiation, particularly SRS, radiation necrosis may result; this needs to be distinguished from tumor progression. Whole brain radiation has been found to be associated with greater cognitive impairment than SRS and has also been found to impact patient-reported quality of life [63, 64]. Attempts have been made to narrow the cognitive toxicities of radiation including hippocampal sparing techniques. In particular, the indications for WBRT have been narrowed in preference of less toxic strategies [60, 65]. Despite these efforts, current studies continue to report a sustained decline in cognitive function in patients treated with brain radiation.

Steroids

Corticosteroids are recommended to provide symptomatic relief from symptoms on intracerebral edema from brain metastases [66], as well as reduced tumor-associated pain, nausea, vomiting, and anorexia [67]. The significance of steroid response has also been evaluated, with

response to steroids being identified as a positive prognostic factor for patient survival [68]. While early symptomatic improvement has been noted with their administration during radiation [69], controversy persists over the precise dosing and indications for their use [70]. Individualized treatment tailored to patient symptoms and condition is recommended over standardized dosing regimens [71].

Despite the relative increased tolerability of dexamethasone as corticosteroid, there remain significant adverse effects with this agent. On evaluating 138 patients retrospectively during radiation for primary and metastatic brain cancer, the most common adverse effects were elevated serum glucose, anxiety, peripheral edema, and Cushing syndrome [71]. A proximal myopathy may also result from steroid use, contributing to functional disability. These adverse events increase with prolonged duration of use. Steroid side effects are dose-dependent: in randomizing brain tumor patients to either 4 or 8 mg per day versus 16 mg per day of dexamethasone, significantly more adverse effects were noted in the 16 mg per day group [72]. While recognizing the role of steroids in the symptomatic treatment of brain metastases patients, minimizing the dose and duration of steroid treatment is integral to minimizing their associated toxicity.

Anti-seizure Medicines

While obtaining control of seizures can contribute greatly to patient quality of life, a breadth of potential toxicities from anti-seizure medicines can occur, and agents are frequently chosen for the least offensive side effect profile for a given patient. In patients with cancer, levetiracetam and lacosamide are frequently used, as they bypass CYP450 metabolism and do not interact with other anticancer medicines, and have a lower incidence of adverse effects than many other anti-seizure medicines. In particular, anti-seizure medicines may impact cognitive function. In a prospective crossover study comparing levetiracetam and carbamazepine's neuropsychological effects [73], all subjects had worse performance while taking a medicine, and a significantly larger number felt their performance was worse with the carbamazepine than the levetiracetam.

These agents may also increase fatigue. In particular, those impacting the GABAergic neurotransmitter system are thought to augment this effect, with sodium channel antagonists having less of an impact [74]. The mechanisms of their influence are not clear, however, as are the relative contributions of medication dose or concurrent medicines on fatigue levels. While generally thought to have a more benign side effect profile than other anti-seizure medications, levetiracetam was found to have a more prominent impact on fatigue in one epidemiologic study [75], independent of its impact on mood. The side effect profiles of anti-seizure agents are varied, and attention to patient comorbidities and concerns is essential in selecting the most appropriate agent for the individual.

Rehabilitation

Rehabilitation in cancer patients possesses unique challenges. Concerns in regard to frailty and concurrent medical therapies may prevent full access and use of rehabilitative services [76]. Despite these challenges, rehabilitation is of demonstrated benefit in patients with CNS cancer. It leads to tangible functional improvement in patients with brain [77] and spinal cord tumors [78]. Functional improvement with rehabilitation has been found to be an independent predictor of overall survival in patients with primary and metastatic brain tumors [77], and interventions targeting motor impairment have been found to improve both independence and quality of life in brain tumor patients [79].

The impact of rehabilitation has been more extensively studied in patients with compressive disorders of the spinal cord. In this population, patients had sustained improvements in various functional measures, mobility, and self-care that were maintained 3 months after discharge [80]. Rehabilitation has also been associated with improvement in measures of pain, self-care, and

quality of life, as well as reduced depression scores [81]. In a population of patients with metastatic epidural spinal cord compression, rehabilitation had a positive impact on bladder control, with nearly one quarter regaining some control of bladder function with rehabilitation intervention [82]. The goal of rehabilitation should be to improve function, and the role of physical medicine and rehabilitation in these patients should be advocated.

Pain Management

While rare in patients with metastatic brain tumors, neuropathic pain may result from spinothalamic tract involvement of intramedullary spine metastases. While there are no evidence-based recommendations for treatment, pregabalin has been found to improve central neuropathic pain from spinal cord injury [83–85], with concurrent positive impacts on sleep and anxiety [83]. Amitriptyline has had variable efficacy in managing pain from spinal cord injury [86–88], as has lithium [89]. While opioid medications are not used first line for neuropathic-type pain, they have been found to be of benefit in central neuropathic pain [90], including neuropathic pain pretreated with anti-seizure medicine [91]. This may be of particular use in patients with concurrent somatic pain.

Management of Fatigue

In the patient with fatigue, a cursory screen of reversible or treatable contributors is advised. Medications should be optimized, with nonessential medications eliminated and minimum therapeutic doses used. A screen for depression should occur, with treatment initiated where appropriate. Evaluation for nutritional deficiencies and metabolic derangements is also warranted, particularly in the context of advanced cancer where end-organ dysfunction is more common. A review of sleep patterns is also indicated, as management of sleep disorders can improve cancer-related fatigue [92].

While there is a lack of studies evaluating interventions for fatigue in patients with brain metastases specifically, pharmacologic and non-pharmacologic therapies have been studied in other cancer populations. Psychoeducational interventions have demonstrated efficacy in patients with systemic cancer. Cognitive behavioral therapy intervention, consisting of eight weekly structured sessions with a psycho-oncologic support group, was found to improve fatigue in breast cancer patients at its completion [93]. Energy conservation programs have also demonstrated benefit in reducing fatigue in patients with systemic cancer [94, 95]. Exercise holds the strongest evidence of all non-pharmacologic interventions for fatigue, reproducibly demonstrating benefit in patients with brain tumors and the general cancer population. Systematic review of studies involving cancer patients (n = 4881) during or after anticancer treatments found that exercise significantly reduced cancer-related fatigue [96]. It appears to have a palliative effect as patients are undergoing cancer treatment and help with restoration of energy levels after treatment completion.

Stimulants are the primary pharmacologic intervention evaluated for fatigue in cancer patients. Methylphenidate, which increases dopaminergic and noradrenergic transmission, has been evaluated with mixed results. While methylphenidate has been shown to improve patient-reported fatigue [97, 98], several randomized controlled studies have failed to show significant improvement above placebo [99–101]. In a systematic review of cancer patients with fatigue (n = 426), the use of stimulants for cancer-related fatigue was supported with preliminary evidence [102], and stimulants are commonly used clinically when pharmacologic treatment is pursued. Similarly, the evaluation of stimulants in patients with brain tumor has yielded mixed results [103–105], and no single agent has been deemed reliably effective. Corticosteroids, frequently used to manage vasogenic edema in patients with brain metastases, improve fatigue in cancer patients in the short term [106]; however, the effectiveness and sequelae for long-term use are not known.

Cognitive Interventions

Identification of cognitive impairment should prompt screening for comorbid conditions, such as depression and fatigue [107, 108], as they may be contributing to cognitive deficits. There is a paucity of data evaluating treatments for cognitive impairment in patients with brain metastases specifically. Phase 2 pilot data has supported the use of donepezil in patients with primary brain tumors [109, 110], finding multi-domain improvement in neurocognitive function and quality of life measures. A phase 3 study in patients with primary brain tumors or brain metastases that had received brain radiation found improvements in both social and emotional well-being as well as overall quality of life in those with more cognitive impairment treated with donepezil; however, there was a negative impact on fatigue and functional well-being in those with less impairment [111]. Another phase 3 trial in primary brain tumors showed that there was no impact on composite cognitive scores, the primary outcome, but did show improvement in memory and dominant hand function [111]. Once again, patients with greater pre-treatment impairment were found to derive the greatest benefit, suggesting cholinergic therapy may be of some benefit to select, very symptomatic patients. Definitive evidence supporting a pharmacologic intervention in patients with brain metastases does not yet exist.

Endeavors to prophylax against treatment-associated cognitive impairment during WBRT have been evaluated. A placebo-controlled trial of memantine during WBRT found beneficial effects on memory function at 4 months, the primary outcome, but this result did not reach statistical significance [18]. Time to neurocognitive decline, however, was lower in patients that received memantine compared to placebo. While the primary outcomes of these studies were negative, it is important to note the small patient numbers and high attrition rates in these studies. As such, incorporating use of these agents, particularly memantine, into clinical practice has been variable. Please see the other chapters in this book related to neurocognition and radiation therapy for more details.

At this time, we do not have evidence supporting non-pharmacologic interventions for cognitive impairment in patients with brain metastases. Cognitive rehabilitation with computer-based attention retraining and compensatory skills training has been shown to benefit patients with lower-grade glioma [112], with immediate improvement in cognitive performance and sustained improvement after 6 months. Improvements in cognitive performance have also been noted in patients with systemic cancer with compensatory and computer-based cognitive training [113, 114]. Memory and adaptation training (MAAT), a form of cognitive behavioral therapy developed for cancer patients that builds adaptive skills to manage cognitive demands, has shown benefit in breast cancer patients without brain metastases in three clinical trials [115–117]. It is not clear whether these results can be applied to the patients with brain metastases, however, and as such, this population warrants independent study.

End-of-Life Care

Patients with CNS metastases may die from the progression of the systemic and/or the CNS disease [118]. Impaired quality of end of life has been found in cancer patients receiving more aggressive anticancer and medical treatments in the final weeks of life [119]. Despite the poor prognosis of patients with CNS metastases, evidence suggests this population is receiving anticancer therapy in very late disease stages. In a study of patients with non-small cell lung cancer with brain metastases, nearly a quarter of the over 5000 patients evaluated died within 30 days of CNS-directed treatments [120]. Death within 30 days of treatment could be reliably predicted using the graded prognostic assessment (GPA) system, incorporating patient- and disease-related information to prognosticate [121] suggesting timing of radiation referral could be better timed prior to the more imminent end-of-life period. Similarly, in patients evaluated from time of whole brain radiation therapy to death, the median overall survival after radiation was

80 days [122]. Of this cohort, nearly one-third of patients presented to the emergency room two or more times within the last 6 months of life, and only 68% were referred to palliative care, with 57% of these referrals being during inpatient hospitalizations. Given the heightened awareness of the value of symptom management in patients with brain metastases [17], and the positive value early palliative care can have in this regard [123], attention to the prognosis and the utility of medical interventions as patients approach end of life is of central importance.

Caregiver Needs

Caregivers often play a central role in the well-being of patients with advanced cancer. The unique symptom burdens in patients with CNS metastases imply a distinct role for their caregivers. At this time, there is a paucity of evidence characterizing the needs and challenges of caregivers of patients with CNS metastases, and as such, information can only be derived from the study of patients with primary brain tumors and other neurologic disease. From the study of caregivers of patients with brain tumors, we know that they frequently feel untrained, uncompensated, and unprepared for their role [124]. They find it difficult to adjust to their role at illness onset, as well as its increasing demands over the illness trajectory [124]. This difficulty is likely compounded by the rapid onset and progression of CNS metastases. Distinct from patients with primary brain tumors, most caregivers of those with CNS metastases have already been caring for the patient at time of diagnosis of CNS disease and, as such, may already have fatigue and frustration at onset.

Cognitive dysfunction may have a specific influence on caregiver resilience and coping. In a descriptive cross-sectional study evaluating common coping strategies of caregivers for patients with cancer, common and effective strategies included acceptance, planning, positive interpretation, and growth [125]. In patients with cognitive impairment, however, caregivers were more likely to use less healthy or effective methods of coping. In the dementia population, it is the neuropsychiatric symptoms of these patients that are most relevant to caregiver burnout and depression [126], suggesting particular attention to the needs of caregivers of patients that harbor these manifestations is warranted. A study of caregivers of persons with Parkinson's disease, who often harbor cognitive and motor dysfunction in late disease, shows they have unmet palliative care needs, and processes to improve caregiver ability to manage the neurologic disability have been suggested [127]. While we lack understanding of caregiver needs in patients with brain metastases, the study of caregivers of other CNS disorders supports this group facing unique challenges and suggests they may have distinct needs from caregivers of other cancer patients.

Conclusions

Cancer patients with metastases to the brain and spine have distinct symptom burdens and disease trajectories. Concurrent with the poor prognosis imparted by CNS involvement, these patients often suffer from disabling symptom burdens that can influence fundamental motor, sensory, and cognitive abilities. Clinicians and family members must be aware of the potential influence these changes may have on patient autonomy and decision-making. The importance of these issues is emphasized by the incorporation of patient-reported and cognitive outcomes as endpoints in clinical trials for brain metastases. Persistent clinical and academic attention to the palliative care needs of patients with CNS metastases will be central to alleviating the suffering imparted by the devastating complication of cancer.

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Index

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