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Updates in the management of brain metastases

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The clinical management/understanding of brain metastases (BM) has changed substantially in the last 5 years, with key advances and clinical trials highlighted in this review. Several of these changes stem from improvements in systemic therapy, which have led to better systemic control and longer overall patient survival, associated with increased time at risk for developing BM. Development of systemic therapies capable of preventing BM and controlling both intracranial and extracranial disease once BM are diagnosed is paramount. The increase in use of stereotactic radiosurgery alone for many patients with multiple BM is an outgrowth of the desire to employ treatments focused on local control while minimizing cognitive effects associated with whole brain radiotherapy. Complications from BM and their treatment must be considered in comprehensive patient management, especially with greater awareness that the majority of patients do not die from their BM. Being aware of significant heterogeneity in prognosis and therapeutic options for patients with BM is crucial for appropriate management, with greater attention to developing individual patient treatment plans based on predicted outcomes; in this context, recent prognostic models of survival have been extensively revised to incorporate molecular markers unique to different primary cancers.

Keywords: brain metastases, chemotherapy, stereotactic radiosurgery, surgery, whole brain radiation.

Brain metastases (BM) affect up to one-third of adults with cancer and are a significant cause of patient morbidity, anxiety, and mortality. With ~200 000 patients affected each year in the United States,[1,2] a number that is somewhat speculative since the incidence of metastatic disease is not a reportable event, and a presumption of increasing incidence, BM represent an important public health burden that is 10 times more common than malignant primary brain tumors. Despite this, the BM population has received less attention, with historical exclusion from many clinical drug trials, frequent misperceptions about prognosis by physicians and patients, and the variable involvement of different care providers who may not follow the patient longitudinally. Management of BM has changed substantially in the past 5–10 years, with more varied treatments which have a greater focus on survivorship and mitigating the effects of treatment. This review provides a summary of key updates and considerations in the current management of BM for practicing clinicians.

Incidence

The incidence of BM is believed to be rising in the setting of improved systemic therapies that control systemic disease and prolong survival but cross the blood–brain barrier (BBB) too poorly to prevent the brain from becoming a sanctuary site for metastatic disease. Accurate estimates of population-level

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incidence of BM are difficult to ascertain, as national registries such as Surveillance, Epidemiology, and End Results capture information related to initial diagnosis and management of cancer but not events that typically occur later in the disease course, such as the development of BM. Prior reports suggest that ~10%–35% of adult cancer patients develop BM.[1–4] In one metropolitan cancer registry from 1973 to 2001, the incidence proportion (IP) of BM across a variety of malignancies was 10%, defined as the percentage of patients who were diagnosed with BM at any point before death, with large differences according to primary tumor as well as age, gender, race, cancer stage, and age at cancer diagnosis.[4] In that study, the IP of BM for the 4 most common cancers that metastasize to the brain were lung (20%), melanoma (7%), renal (7%), and breast (5%), when combining all initial stages together for a given primary tumor. When examined according to stage, patients with lung cancer had the highest IP for developing BM among all patients with a stage I cancer, at nearly 10%, whereas among patients diagnosed with a stage IV cancer, melanoma had the highest IP for BM at ~37%. The notion that modern systemic therapies may alter the natural disease history and risk for BM in different cancers is perhaps most strikingly seen with human epidermal growth factor receptor 2 (HER2)–positive breast cancer,[5,6] melanoma,[7] and anaplastic lymphoma kinase gene (*ALK*) rearranged non-small-cell lung cancer (NSCLC).[8–11] In the trastuzumab era, the incidence of BM among patients with advanced HER2-positive breast cancer is 40%–50%, although survival following BM has improved substantially.[5,12] In melanoma, where the brain is a frequent site of metastases, new immune checkpoint inhibitors and molecularly targeted agents provide survival benefit in systemic disease and may offer CNS control.[7] In patients with *ALK*-rearranged NSCLC, the CNS is the first site of progression in 46% of patients treated with crizotinib.[11] Despite these remarkable subgroup findings, the only populations currently recommended by the National Comprehensive Cancer Network to undergo a screening brain MRI at diagnosis in the absence of neurologic symptoms are those with advanced melanoma, most patients with NSCLC, and all patients with small-cell lung cancer.[13]

Prognosis

While BM historically have been associated with a dismal prognosis and median survival of <6 months, a combination of earlier diagnosis in some cases, more effective treatments, and better understanding of which patients may survive for many months or years has led to improved prognostication tools. Estimating prognosis among patients with BM is clinically relevant, as it allows clinicians to recommend treatments that balance durability of intracranial tumor control with quality of life (QoL) and side effects of treatment. A landmark recursive partitioning analysis (RPA) of prognostic factors among 1200 pooled BM patients treated in 3 Radiation Therapy Oncology Group (RTOG) trials found that KPS, age, and extracranial disease status were key determinants of survival, with the longest-surviving group having a median survival of 7.1 months.[14] While this RPA was validated and widely used, at least 5 additional prognostication models were published in the subsequent 10 years, in an effort to further refine survival estimates in an era of improving systemic therapies.[15] The prognostic index that has now become the most prominent is the Graded Prognostic Assessment (GPA), which was originally developed from a database of nearly 2000 patients with newly diagnosed BM accrued to 4 RTOG protocols, and later serially refined to include patients treated across multiple institutions and to incorporate prognostic factors unique to different cancers, resulting in publication of the diagnosis-specific (DS) GPA in 2012.[16] In the DS-GPA, the significant prognostic factors vary substantially according to the type of cancer and include factors such as age, KPS, extracranial disease status, number of BM, and in the case of breast cancer, the molecular subtype (Fig. 1). Importantly, the stratification of patients by DS-GPA score within each cancer reveals marked heterogeneity in outcome, showing the important differences in prognostication for different subgroups. For example, patients with small-cell lung cancer with the lowest DS-GPA score were found to have median survival of <3 months, whereas breast cancer patients with the highest DS-GPA score had median survival of >2 years. The DS-GPA is increasingly being used as a stratification tool for clinical trials in BM and continues to be refined with incorporation of tumor molecular markers for some cancers.[17] The importance of molecular markers in estimating life expectancy was highlighted in a recent multi-institutional publication regarding prognostic factors among 90 patients with BM from *ALK*-rearranged NSCLC, which found that median overall survival (OS) after development of BM was over 4 years.[18]

In addition to prognostication tools, recent literature describing outcomes among BM patients has highlighted the importance of considering systemic disease status when counseling patients and selecting treatments. A large Japanese prospective observational study by Yamamoto et al among 1194 patients with 1–10 BM under 3 cm in diameter and KPS ≥ 70 who were treated with stereotactic radiosurgery (SRS) alone found that among the 850 patients who had died as of last follow-up, 92% died from systemic disease progression, and not from their BM.[19] This finding has been echoed in other recent studies[20,21] and runs counter to a common perception among physicians[22] that the development of BM necessarily indicates a grim prognosis, with rapid fatality consequential to the BM for all patients. In reality, among patients with cancer, the status of their systemic disease and its responsiveness to systemic therapy are much more likely to drive mortality outcomes than the presence of BM in the current era and together are a key competing risk.[23] For the majority of patients with BM, the lack of effective systemic therapies implies that most succumb within a few months of BM diagnosis, but an increasing subset of patients are experiencing longer survival, especially in the context of improving systemic disease control. In the DS-GPA model cited above, however, only the presence or absence of systemic disease was included in the multivariate analysis used to derive the model, without information regarding whether systemic disease was under control versus progressing. One retrospective study reported that if this information was added to the model for breast cancer patients with BM, dramatic changes in median survival were found compared with those predicted by the DS-GPA model alone,[24] and another group has developed a nomogram incorporating systemic disease status which demonstrates significant heterogeneity within each RPA class or DS-GPA score group, allowing for

Non–small-cell and small-cell lung cancer

Prognostic Factor	GPA Scoring Criteria 0	0.5	1.0	Patient Score
Age, years	> 60	50-60	< 50	____
KPS	< 70	70-80	90-100	____
ECM	Present	—	Absent	____
No. of BM	> 3	2-3	1	____
Sum total				____

Median survival (months) by GPA: 0-1.0 = 3.0; 1.5-2.0 = 5.5; 2.5-3.0 = 9.4; 3.5-4.0 = 14.8

Melanoma

Prognostic Factor	GPA Scoring Criteria 0	1.0	2.0	Patient Score
KPS	< 70	70-80	90-100	____
No. of BM	> 3	2-3	1	____
Sum total				____

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 4.7; 2.5-3.0 = 8.8; 3.5-4.0 = 13.2

Breast cancer

Prognostic Factor	GPA Scoring Criteria 0	0.5	1.0	1.5	2.0	Patient Score
KPS	≤ 50	60	70-80	90-100	n/a	____
Subtype	Basal	n/a	LumA	HER2	LumB	____
Age, years	≥ 60	< 60	n/a	n/a	n/a	____
Sum total						____

Median survival (months) 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

Prognostic Factor	GPA Scoring Criteria 0	1.0	2.0	Patient Score
KPS	< 70	70-80	90-100	____
No. of BM	> 3	2-3	1	____
Sum total				____

Median survival (months) 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

Prognostic Factor	GPA Scoring Criteria 0	1	2	3	4	Patient Score
KPS	< 70	70	80	90	100	____

Median survival (months) by GPA: 0-1.0 = 3.1; 2.0 = 4.4; 3.0 = 6.9; 4.0 = 13.5

Fig. 1. Diagnosis-specific graded prognostic assessment worksheet to estimate survival from newly diagnosed brain metastases.* Abbreviations: GPA, Graded Prognostic Assessment; KPS, Karnofsky performance status; ECM, extracranial metastases; LumA, luminal A; LumB, luminal B; GI, gastrointestinal. Breast cancer subtype definitions: Basal: triple negative. LumA: estrogen receptor (ER)/progesterone receptor (PR) positive, (HER2) negative. LumB: triple positive. HER2: ER/PR negative, HER2 positive. *Figure reprinted with permission. Sperduto PW et al: Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *Journal of Clinical Oncology*, 30(4):419–425.

more individualized survival estimation.[25] Therefore, prognostication tools continue to be refined and can increasingly help clinicians and patients best select treatments tailored to their situation.

Role of Whole Brain Radiotherapy

Whole brain radiotherapy (WBRT), including upfront surgery for a select minority of patients with bulky tumors, used to be the standard treatment for most patients with BM, given that WBRT could be initiated quickly, was widely available, treated both visible and occult BM, and provided symptom palliation.[26] During the past 2 decades, SRS has emerged as a common approach for patients with a limited number of BM, due to the conformal treatment targeting the metastasis alone, single-session delivery, minimal delay to continuing with systemic therapy, and importantly, less cognitive dysfunction. As recognition has grown that WBRT may cause prolonged fatigue and/or neurocognitive deficits among some patients with BM, there has been a desire to test whether WBRT can be safely omitted from the management of patients receiving SRS, and this has been the subject of 3 randomized trials from 2006 to 2011, highlighted below. A more recent, unpublished trial focusing on neurocognitive outcomes after SRS with or without WBRT, by the Alliance for Clinical Trials in Oncology (N0574), is described separately in the "Neurocognition and Quality of Life after WBRT" section below.[27] Collectively, these trials demonstrate consistent results for patients with a limited number (≤4) of BM: (i) there is no survival decrement by withholding WBRT; (ii) high rates of local disease control are achieved with SRS alone, but local control rates increase further with the addition of WBRT; (iii) higher rates of new, distant BM are observed

among patients receiving SRS alone, necessitating more frequent salvage treatment, though at least one-quarter of patients who receive upfront WBRT still develop new BM after WBRT; and (iv) the risk of cognitive dysfunction is lowered, but not eliminated, when WBRT is withheld.

The Japanese Radiation Oncology Study Group (JROSG) randomized 132 patients with 1–4 BM to SRS alone versus WBRT (30 Gy in 10 fractions) plus SRS, and found no differences in median OS between arms (8.0 vs 7.5 mo, respectively) but found that WBRT significantly decreased both local recurrence (LR) from 27% to 11% and distant brain recurrence (DBR) from 60% to 35%.[28] Similarly, the European Organisation for Research and Treatment of Cancer (EORTC) enrolled 359 patients with 1–3 BM treated with either SRS or surgery and randomized them to observation versus WBRT (30 Gy in 10 fractions), with a primary endpoint of the maintenance of functional independence at 6 months.[29] Similar to the JROSG trial, the EORTC study found that median OS was not different between arms (10.9 vs 10.7 mo) and that WBRT reduced LR at 2 years from 31% to 19% and DBR from 48% to 33%, with no difference in functional independence. Of note, WBRT added no OS advantage after either SRS or surgery, echoing the findings of the classic "Patchell" trial of surgery with or without WBRT.[30] Finally, a smaller trial at the MD Anderson Cancer Center randomized 58 patients with 1–3 BM to SRS with or without WBRT (30 Gy in 12 fractions), with the primary endpoint of neurocognitive deterioration at 4 months, defined as a 5-point drop on Hopkins Verbal Learning Test–Revised (HVLT-R) total recall.[31] Early stopping rules were met after results suggested higher neurocognitive decline in the SRS + WBRT arm (52% vs 24% for SRS alone). While the addition of WBRT was associated with lower LR (33% vs 0%) and DBR (73% vs 27%), similar to the JROSG and EORTC trials, surprisingly the SRS + WBRT arm was associated with shorter survival, with median and 1-year OS being 15.2 versus 5.7 months, and 63% versus 21% for SRS alone versus SRS + WBRT, respectively. This survival result has been scrutinized by some and attributed to imbalances between the treatment arms, particularly with regard to discordant systemic disease burden and rates of salvage therapy, despite randomization; for example, there were 16 deaths from systemic disease (64%) in the SRS + WBRT group compared with 10 deaths (50%) in the SRS alone group.

Taken together, these 3 trials established that the addition of WBRT to SRS for up to 4 BM categorically reduces LR in the original BM sites as well as providing prophylaxis against DBR, and all 3 trials found no OS advantage to WBRT. Based on these data, the American Society for Radiation Oncology (ASTRO) issued a recommendation in September 2014 discouraging the addition of WBRT to SRS for patients with limited BM.[32] In 2015, investigators from these 3 trials published additional analyses using the original trial data, focusing on particular patient subgroups. First, in a meta-analysis using individual patient data from 364 patients with 1–4 BM who received SRS with or without WBRT from all 3 trials, Sahgal et al[33] found no significant OS difference between patients receiving SRS versus SRS + WBRT in the overall cohort, but the authors reported that patients aged ≤50 years at the time of treatment had longer OS when treated with SRS alone. Hazard ratios (HRs) for survival with SRS alone ranged from 0.46 to 0.64 for age subgroups <50 years, and became statistically insignificant among older patients. This provocative finding is hypothesis generating and has raised questions regarding the modeling used given the small numbers of young patients in these trials (<35 patients per arm), the lack of restaging to establish the extent of systemic disease prior to protocol entry, and how the competing risk of systemic disease was handled.[34] In contrast to these data, a secondary analysis by Aoyama et al[35] of the original JROSG trial poststratified according to DS-GPA found that among the subgroup of 88 patients with NSCLC and 1–4 BM, those with higher DS-GPA scores (2.5–4.0) had significantly longer median OS when treated with SRS + WBRT compared with SRS alone (16.7 vs 10.7 mo, $P = .03$), whereas there was no OS difference among NSCLC patients with lower DS-GPA scores. This observation implies that improved brain control with WBRT, which has been demonstrated in every SRS ± WBRT trial, may translate into an OS advantage specifically among high DS-GPA patients because they do not die as rapidly from extracranial progression. However, because of the small patient cohort, lack of stratification according to DS-GPA in the original trial, and treatment era of 1999–2003, prior to several systemic therapy advances that likely impact extracranial and intracranial disease control, this retrospective study remains provocative but only hypothesis generating.

In summary, there may be patient subgroups that derive differential benefits from SRS versus SRS + WBRT, but for now the clinical trial data, while underpowered, largely suggest no OS difference between these 2 approaches, and prospective trials are required to test hypotheses from the secondary studies cited above. Clinical controversy remains regarding optimal patient selection for receipt of SRS alone, SRS + WBRT, and WBRT alone.[36,37] In addition, it should be emphasized that the majority of patients treated in the landmark SRS, WBRT, and surgery trials for BM cited above were unselected NSCLC patients, and therefore caution should be applied when generalizing outcomes about local therapies from these trials to various subgroups, such as HER2+ breast cancer or *ALK*-rearranged NSCLC patients. A summary of several key recent studies examining survival and functional outcomes after SRS, with or without WBRT, is provided in Table 1.

Stereotactic Radiosurgery Advances

Number or Volume of Metastases

While the landmark randomized trials from the last decade cited above enrolled patients with up to 4 BM, there has naturally been interest in the feasibility and outcomes of patients with >4 BM treated with SRS alone. There is nothing inherently limiting SRS only to patients with ≤4 BM, but the original randomized trials were conducted among patients with only limited intracranial disease, partly due to the belief that patients with many more lesions would be better served by WBRT or that SRS to so many lesions may be associated with excess toxicity or technical limitations. ASTRO published an evidence-based review on the role of SRS for BM in 2005 which recommended consideration of SRS for up to 4 BM that were ≤4 cm in size,[38] but this was prior to the publication of the seminal trials reviewed above, and the 2012 updated ASTRO guidelines[39] and 2011 American Association of Neurological Surgeons/Congress of Neurological Surgeons guidelines[40] do not make explicit recommendations

Table 1. Select studies of SRS ± WBRT for brain metastases

Study[a]	Year	Design	*N*	Primary Endpoint	OS (mo)	Functional Outcomes	Distant Brain Control
Alliance[27]	2015	Phase III RCT: SRS ± WBRT 1–3 BM	213	Any neurocognitive decline >1 SD at 3 mo.	SRS + WBRT: 7.5 SRS alone: 10.7 (P = NS)	*Neurocognitive decline at 3 mo* SRS + WBRT: 88% SRS alone: 62% (P = .002)	SRS + WBRT: 85% SRS alone: 51% (P < .001) [1 y]
EORTC[29,67]	2011	Phase III RCT: SRS or surgery ± WBRT 1–3 BM and stable systemic disease	359	PS ≤ 2 at 6 mo	SRS + WBRT: 10.9 SRS alone: 10.7 (P = NS)	*Time to PS > 2 mo* SRS + WBRT: 9.5 SRS alone: 10.0 (P = NS) *Quality of life* Inferior in WBRT arm at isolated timepoints, but transient	SRS + WBRT: 67% SRS alone: 52% (P = .023) [2 y]
MDACC[31]	2009	Phase III RCT: SRS ± WBRT 1–3 BM	58	5-point drop on HVLT-R total recall at 4 mo	SRS + WBRT: 5.7 SRS alone: 15.2 (P = .003)	*Neurocognitive decline at 4 mo* SRS + WBRT: 52% SRS alone: 24% (96% Bayesian posterior mean probability)	SRS + WBRT: 73% SRS alone: 45% (P = .02) [1 y]
JROSG[28]	2006	Phase III RCT: SRS ± WBRT 1–4 BM	132	OS	SRS + WBRT: 7.5 SRS alone: 8.0 (P = ns)	*Neurologic decline at 12 mo* SRS + WBRT: 28% SRS alone: 30% (P = .99)	SRS + WBRT: 53% SRS alone: 24% (P < .001) [1 y]
JLGK[19]	2014	Prospective observational: SRS alone 1–10 BM Stratified by 1 vs 2–4 vs 5–10 BM	1194	OS	1 BM: 13.9 2–4 BM: 10.8 5–10 BM: 10.8 (P = .78 for 2–4 vs 5 BM)	*Neurologic decline at 12 mo* 1 BM: 8% 2–4 BM: 9% 5–10 BM: 12% (P = .60)	1 BM: 63% 2–4 BM: 45% 5–10 BM: 36% (P < .0001 for 1 vs 2–4 BM; P = .067 for 2–4 vs 5–10 BM) [1 y]
EORTC/JROSG/MDACC[33]	2015	Pooled IPD meta-analysis of 3 RCTs: SRS ± WBRT for 1–4 BM analyzed according to patient age	364	OS	*Overall* SRS + WBRT: 8.2 SRS alone: 10.0 (P = NS) *HR for SRS alone vs SRS + WBRT* Age 35: 0.46 Age 40: 0.52 Age 45: 0.58 Age 50: 0.64 (all P < .05) Age >50 (P = ns)	NR	*HR for SRS alone vs SRS + WBRT* Age ≤ 50 (P = NS) Age 55: 1.67 Age 60: 1.95 Age 65: 2.27 Age 70: 2.65 Age 75: 3.09 Age 80: 3.60 (all P < .05)

Continued

Table 1. *Continued*

Study[a]	Year	Design	*N*	Primary Endpoint	OS (mo)	Functional Outcomes	Distant Brain Control
JROSG[35]	2015	Secondary analysis of NSCLC pts in RCT: SRS ± WBRT for 1–4 BM Stratified by DS-GPA[10] < vs ≥2.5	88	OS	*DS-GPA 2.5–4.0* SRS + WBRT:16.7 SRS alone: 10.6 (*P* = .04) *DS-GPA 0.5–2.0* SRS + WBRT: 4.8 SRS alone: 6.5 (*P* = NS)	*MMSE score at last follow-up* *DS-GPA 2.5–4.0* SRS + WBRT: 26.5 SRS alone: 28.0 (*P* = .NS) *DS-GPA 0.5–2.0* SRS + WBRT: 28.0 SRS alone: 27.5 (*P* = NS)	*DS-GPA 2.5–4.0* SRS + WBRT: 91% SRS alone: 71% (*P* = NR) *DS-GPA 0.5–2.0* SRS + WBRT: 88% SRS alone: 87% (*P* = NR) [timing NR]

Abbreviations: Alliance, Alliance for Clinical Trials in Oncology; MDACC, MD Anderson Cancer Center; JLGK, Japanese Leksell GammaKnife Society; RCT, randomized controlled trial; IPD, individual patient data; pts, patients; PS, performance status; ns, not significant; NR, not reported; MMSE, Mini-Mental State Examination.
[a]Arranged according to study design, with most recent Phase III trials listed first.

for patients with more than 4 BM. Many centers have offered SRS to patients with a larger number of BM over the past 10 years based on retrospective studies suggesting safety and efficacy. A comprehensive prospective observational study in Japan among nearly 1200 patients from 23 institutions with up to 10 newly diagnosed BM treated with SRS alone was published in 2014[19] and provided a helpful benchmark for understanding outcomes among this patient population. The largest single BM allowed per the inclusion criteria was <10 mL in volume and <3 cm in maximal diameter, and the total cumulative volume of all BM had to be ≤15 mL. The study included 208 patients with 5–10 BM, and this subgroup had a mean cumulative tumor volume of 3.54 mL (range, 0.02 to 13.90), 63% of whom had controlled systemic disease and 88% of whom had KPS ≥ 80. Baseline characteristics of the 5–10 BM group were not significantly different from the group with 2–4 BM, aside from slightly higher cumulative tumor volume (mean, 3.54 vs 3.07 mL), as expected. The principal finding of the paper was that median OS was similar between the 5–10 BM and the 2–4 BM groups (10.8 mo in both groups), which was statistically noninferior for the 5–10 BM group, based upon a noninferiority margin set at the upper 95% CI for an HR of 1.30. Secondary outcomes analysis demonstrated that patients with 2–4 BM as well as those with 5–10 BM had similar 2-year rates of neurologic death (5% vs 7%), new brain lesions (66% vs 72%), and salvage WBRT (10% vs 9%); the only parameter that was significantly higher among the 5–10 BM group was the risk of leptomeningeal dissemination (13% vs 22%). Toxicity was low and essentially identical between the 2–4 BM and 5–10 BM groups, with no significant differences in neurocognitive outcome at 4, 12, 24, or 36 months as assessed by the Mini-Mental State Examination. While not randomized, this large study provides some evidence of safety and efficacy of SRS alone for patients with up to 10 BM with a relatively low intracranial disease volume; of note, details regarding the frequency and costs of imaging and treatment were not reported. Additionally, investigators at the University of Pittsburgh have described their outcomes of SRS alone for ≥10 BM among a group of 61 patients who had a mean of 13 BM per patient, 62% of whom had received prior WBRT.[41] They found that survival was superior among patients with 10–13 BM compared with ≥14 BM, but importantly, median survival in the entire cohort was only 4 months. The role of SRS for patients with ≥4 BM is currently under further study in randomized trials at UC San Francisco/North American Gamma Knife Consortium,[42] and the MD Anderson Cancer Center.[43]

Technical Advances for Multiple Targets

While the increased use of SRS for patients with higher numbers of BM is predominantly driven by a desire to avoid side effects associated with WBRT, it also stems from improved technology in the past 5–10 years. Modern SRS can be delivered with increasing speed while maintaining precision and accuracy, which improves procedural tolerability. Standard SRS delivery has historically entailed placing an isocenter target within each BM and then setting up and treating each BM sequentially, which can take several hours to complete for patients with 5–10 BM for some SRS treatment platforms. In contrast, there has been increasing literature and clinical

experience over the past 5 years of using a single isocenter within the brain[44–47] and then using radiotherapy techniques such as helical tomotherapy and volumetric modulated arc therapy to deliver dose to multiple BM at the same time. While this technique relies on precise patient immobilization, it has the substantial advantage of being able to reduce treatment time for a patient with multiple BM down to minutes, without sacrificing accuracy or significantly increasing the integral radiation dose to the brain. For example, in one comparison of multitarget single-isocenter SRS versus standard sequential multiple-isocenter SRS using Gamma Knife (GK) among 28 patients with a mean of 3 BM, modeled median treatment time for standard GK was over 2 h compared with ~20 min with the single-isocenter technique.[46] This expedited treatment time for single isocenter has also been published by other groups[44] and makes SRS treatment of patients with 5, 10, 15, or more BM vastly more feasible and tolerable for the patient. Similarly, several centers are now using volumetric modulated arc therapy to combine both WBRT and simultaneous hypofractionated radiation boosts to individual BM within the same integrated treatment session. This allows for dose escalation to individual BM, without requiring separate treatment sessions from the WBRT fractions.[48] Ultimately, the decision regarding whether to employ SRS, WBRT, or both for patients with multiple BM depends on clinician discretion, patient values, and logistical considerations. The absolute BM number cutoffs are becoming less crucial in the modern era, as intracranial BM recurrence and QoL concerns need to be balanced for individual patients on a case-by-case basis, especially in the setting of substantial increases in life expectancy from better systemic control for some subgroups of patients with BM, with a longer timeframe at risk for treatment sequelae.

Hypofractionation and Resection Cavity Treatment

Given that SRS is typically reserved for BM that are 3 cm or less in diameter in order to reduce the risk of radiation necrosis (RN) in surrounding normal tissues, there has been increasing study of using hypofractionated SRS for larger BM that are not surgically resected, or BM near sensitive structures such as the optic nerves and brainstem. Hypofractionated SRS, also referred to as hypofractionated stereotactic radiotherapy (SRT), typically entails delivery of 3–5 fractions on consecutive or alternating days, with the rationale that fractionating the treatment allows increased recovery of nearby normal tissues and may reduce toxicity. In one survey of CNS radiation oncologists in the United States, the 2 most common hypofractionation regimens used were 25 Gy in 5 fractions, and 21 Gy in 3 fractions.[49] Retrospective studies of hypofractionated SRS for BM have demonstrated a favorable toxicity profile, with <5% of patients experiencing acute grade 3 toxicity and ~5% developing RN,[50,51] lower than might be anticipated if using single-fraction SRS for large lesions. However, the optimal dose/fractionation for hypofractionated SRS/SRT remains undefined, as the local control at 12 months ranged from 56% to 68% in 2 recent reports that predominantly utilized 25 Gy in 5 fractions,[50,51] suggesting that further dose intensification may be warranted when using hypofractionation, and prospective data are lacking.

Finally, there is a rapidly expanding recent body of literature on outcomes of single-fraction SRS or hypofractionated SRS targeting the resection cavity after surgical resection of BM[52] as a means of avoiding adjuvant WBRT. An initial experience published by Stanford University in 2008 among 72 patients observed a 79% local control rate at 12 months, using a median dose at the margin of the target/cavity of 18.6 Gy.[53] Many retrospective studies have reported local control rates in the 85%–95% range,[54,55] and the addition of a 2-mm margin around the resection cavity has been shown to be associated with improved local control.[56] Some reports have suggested a higher risk of leptomeningeal dissemination among patients with breast cancer BM treated with cavity SRS,[57] though other studies have not observed this.[58] Hypofractionated SRS has also been used by many centers for larger surgical cavities measuring well over 3 cm, with local control found to be similar to single-fraction SRS.[59,60] However, a randomized trial has not yet been published examining how cavity SRS compares with adjuvant WBRT after surgical resection of BM, and 2 randomized trials are currently ongoing to answer this question with more statistical rigor. One is from the MD Anderson Cancer Center[61] and is evaluating local control after either observation versus cavity SRS following resection of BM. The second is being conducted through the Alliance for Clinical Trials in Oncology (N107C)[62] and examines OS and neurocognitive function 6 months following adjuvant WBRT versus cavity SRS for resected BM. In addition, there are emerging data on the use of preoperative SRS administered shortly before resection, as opposed to postoperative SRS, with the goals of improving local control due to improved targeting of an intact metastasis and reducing risks of leptomeningeal dissemination and RN. One multi-institutional retrospective study of 180 patients treated from 2005 to 2013 with SRS before or after resection, 37% of whom received preoperative SRS within 48 h before surgery, demonstrated similar rates of local control between those receiving pre- versus postoperative SRS but significantly higher rates of leptomeningeal disease (16.6% vs 3.2%, $P = .01$) and symptomatic RN (16.4% vs 4.9%, $P = .01$) at 2 years among those receiving postoperative SRS.[63] New trials are in development that will further compare pre- versus postoperative SRS.

Neurocognition and Quality of Life after WBRT

Over the past 5 years, there has been accumulating evidence on deleterious effects patients may experience after WBRT in particular, as well as new approaches to potentially mitigate those harms. Most distressing to patients are the risks of neurocognitive decline after WBRT, which was investigated in the MD Anderson trial[31] cited above, but was expanded in the much larger Alliance N0574 randomized trial[27] that was recently presented at the American Society for Clinical Oncology 2015 Annual Meeting. In the Alliance trial, 213 patients with up to 3 BM received SRS with or without WBRT, with primary endpoint being cognitive progression at 3 months, defined as a decline by >1 standard deviation in any of the 6 neurocognitive tests administered. At 3 months, cognitive decline was observed in 88.0% of patients in the combined arm versus 61.9% in the SRS-only arm ($P = .002$), including domains such as immediate recall, delayed recall, and verbal fluency. There were no statistically significant OS differences between arms, though

intracranial tumor control was higher in the WBRT-containing arm, as anticipated. Another large recent study that informs our understanding of the risks of irradiation of the entire brain was a pooled secondary analysis of 2 randomized trials evaluating the role of prophylactic cranial irradiation (PCI) in non-small-cell or small-cell lung cancers, which included 410 patients who received PCI and 173 patients who did not.[64] PCI was associated with an approximately 3.5 times higher risk of decline in self-reported cognitive functioning at both 6 and 12 months compared with patients not receiving PCI (both $P < .001$). Objective declines in neurocognitive testing, as ascertained by the HVLT, were also associated in PCI at those same time points (both $P = .002$), but intriguingly, correlation between objective decline and self-reported decline was not significant ($P = .86$ at 12 mo). The clinical findings of cognitive decline following WBRT are echoed in a retrospective study of 68 patients who survived at least 1 year after treatment: 97% of patients who received WBRT developed white matter changes on MRI compared with only 3% of those who received SRS.[65]

In addition to neurocognition specifically, QoL in general is an important consideration for patients and physicians in the selection of treatment for BM. A decline in neurocognition has been found to precede and predict a deterioration in QoL in this patient population,[66] and thus they are not completely distinct entities. The EORTC published health-related QoL results[67] in 2013 on the patients with 1–3 BM enrolled in the SRS or surgery ± WBRT trial[29] described above. Patient compliance with QoL recording had dropped to only 45% by 1 year of follow-up, and thus only the first year after treatment was analyzed. While QoL scores were generally lower among patients receiving WBRT in addition to SRS/surgery, the effects appeared to be relatively transient. QoL scores were statistically significantly lower for global QoL among patients who received WBRT only at 9 months, but not at 2, 3, 6, or 12 months, and similarly were lower for cognitive functioning at 12 months, fatigue at 2 months, and physical functioning at 2 months, as isolated timepoints. These data could be used to support the contention that QoL is lower among patients who have received WBRT, but more importantly show that most patients do not have chronically, consistently worse QoL globally or within specific domains after WBRT.

Approaches to Reduce Cognitive Side Effects from WBRT

In an effort to reduce the neurocognitive sequelae of WBRT, 3 recently reported trials have investigated different strategies to accompany WBRT. Firstly, RTOG 0614 was a Phase III trial investigating memantine, an *N*-methyl-D-aspartate receptor blocker shown to be effective in vascular dementia, and included 508 patients with BM who were randomized to either WBRT plus placebo versus WBRT plus daily memantine for 6 months.[68] The study narrowly missed meeting statistical significance on the primary endpoint of less decline in delayed recall at 6 months favoring the memantine arm ($P = .059$), likely a result of patient mortality with only 280 analyzable patients (55% of enrollees). The memantine arm did show significantly longer time to cognitive decline (HR 0.78, $P = .01$), with probability of cognitive decline at 6 months being 54% in the memantine arm and 65% in the placebo arm. Memantine is now being prescribed to patients receiving WBRT by many providers on the basis of these data, as both this trial and the Alliance trial of SRS with or without WBRT[27] again highlighted the cognitive side effects of standard WBRT. However, neurocognitive deterioration is still quite common among patients with BM, even among the superior-performing trial arms, with over half of the patients in the arm receiving memantine (RTOG 0614) and over half of the SRS-alone treated arm (Alliance) experiencing neurocognitive decline within 3–6 months.

A second strategy to ameliorate the neurocognitive effects of WBRT has been to use intensity-modulated radiotherapy (IMRT) treatment planning to develop conformal whole brain radiation plans that preferentially spare the bilateral hippocampi. This is based on the role of the hippocampus in developing and preserving memory. RTOG 0933 was a single-arm Phase II trial that enrolled 113 patients who received hippocampal-avoidance WBRT for BM and assessed neurocognitive function, including a primary endpoint of HVLT-R delayed recall at 4 months, compared with a historical control group.[21] Only 42 patients were analyzable at 4 months, again highlighting the challenges to conducting trials among BM patients due to high mortality. Patients receiving hippocampal-avoidance WBRT had no measurable decline in QoL and a mean relative decline in delayed recall score of 7%, which was lower than the 30% decline seen in the historical control ($P < .001$). This study has been considered hypothesis generating and has not been adopted as standard of care, as it was only a single-arm study. NRG Oncology has initiated 2 trials to further explore whether hippocampal avoidance during WBRT decreases the incidence of neurocognitive sequelae. The first is NRG-CC001, a randomized Phase III trial examining memantine and WBRT with or without hippocampal avoidance, with a primary endpoint of time to neurocognitive decline.[69] The second trial will be NRG-CC003, a randomized Phase II/III trial of PCI with or without hippocampal avoidance among patients with limited or extensive stage small-cell lung cancer who achieve at least a partial remission to chemotherapy.

Finally, a recent multi-institutional trial has investigated the efficacy of the dementia medication donepezil, to evaluate whether this neurotransmitter modulator may improve cognitive function among patients who had previously received partial brain RT or WBRT. In the Phase III trial, 198 patients with primary ($n = 130$) or metastatic ($n = 68$) brain tumors who were at least 6 months out from brain-directed radiation received donepezil or placebo for 6 months.[70] Cognitive composite scores, the primary outcome, did not differ significantly between the treatment arms, yet significant differences in 2 domains of memory, as well as motor speed and dexterity domains, were statistically improved in the donepezil arm. In all, the recent trials of memantine, hippocampal avoidance, and donepezil all showed some improvements in neurocognition in patients with BM.

Diagnosis and Management of Radiation Necrosis after SRS

With the growing role of SRS in the management of BM, alongside advances in systemic therapy leading to longer overall patient survival, an increasingly common late side effect that

physicians confront in clinic is the development of RN after SRS. After high-dose, conformal radiation to the brain such as with SRS, vascular endothelial cells may become damaged and lead to fibrinoid necrosis of small arteries, tissue hypoxia, and damage of neurons and glial cells, which is mediated by various cytokines as well as vascular endothelial growth factor (VEGF).[71,72] RN occurs in at least 10% of patients who receive SRS, typically between 6 and 18 months after treatment, and is often challenging to distinguish from recurrent/progressive BM based on conventional MRI given the often similar appearance of both contrast enhancement and edema.[73,74] In addition, radiographic evidence of SRS-induced breakdown of the BBB without development of an overt necrotic mass, as occurred in 10% of patients in the EORTC trial of SRS with or without WBRT,[29] is often referred to as "radiation treatment change" and may represent early stages of RN. Moderate doses of corticosteroids such as dexamethasone are often prescribed to control associated neurologic symptoms and/or potentially reduce local inflammation associated with RN. While the gold standard for diagnosis is surgical resection of the lesion, this is not always feasible or desirable, and may show a mix of RN and tumor. Several recent studies have investigated the role of various noninvasive neuroimaging approaches to help distinguish RN from tumor recurrence. These include MR perfusion[75] and dual-phase PET,[76] among others. While these tests can provide adjunctive information, no modality has yet shown adequate sensitivity and specificity to reliably differentiate these 2 phenomena noninvasively, as acknowledged in the recently published Response Assessment in Neuro-Oncology–Brain Metastases (RANO-BM) guidelines.[77] Most frequently, clinicians must rely on the pretest probability/clinical suspicion of RN, and serial MRI over time if the patient is asymptomatic, to guide management. While standard risk factors for RN include SRS dose, volume treated, prior irradiation, and chemotherapy,[73] there are growing reports that immunotherapies and targeted systemic therapies that cross the BBB may increase the risk of RN.[78–80]

Emerging treatments for RN that have published in the past 5 years include bevacizumab and laser interstitial thermal therapy (LITT; otherwise known as laser induced thermotherapy). Bevacizumab is an antibody against VEGF factor A and was tested in a small randomized trial of 14 patients who experienced symptomatic brain RN after fractionated radiotherapy for primary brain or head/neck tumors and were randomized to either placebo or bevacizumab every 3 weeks for 4 cycles.[81] All patients who received bevacizumab had radiographic response with reduction in edema and contrast enhancement, and all had reduction in neurologic symptoms/signs, whereas no patients receiving placebo had an initial radiographic or symptomatic response, until the placebo group crossed over and received bevacizumab, and thereafter all experienced both radiographic and clinical response. Based on these data and additional institutional series, bevacizumab can be considered an option for BM patients without contraindications to its use, who have progressive symptoms from RN after SRS despite corticosteroids and are not felt to be good surgical candidates. However, to improve the evidence base for bevacizumab in the BM population, there is also an ongoing larger randomized Phase II study through the Alliance for Clinical Trials in Oncology evaluating the efficacy of corticosteroids with versus without bevacizumab for symptomatic RN specifically after SRS for BM, which will provide more robust data in an SRS-treated BM cohort.[82] In contrast to bevacizumab, LITT is an emerging technology that uses thermocoagulation to destroy inflammatory cellular infiltrate in the region of RN, and may potentially be used for RN, progressive BM after SRS, or a combination of RN and progressive BM, with an evidence base that is small but expanding. Neurosurgeons who perform LITT typically drill a burr hole or may perform a small open craniotomy and insert a flexible LITT probe until reaching the region of interest, at which point the probe is heated to the desired range. The lesion may be biopsied through the same probe, prior to performing thermocoagulation. Single-institution reports have found excellent outcomes after LITT, with low risks among appropriately selected cases.[83] LITT represents another option for clinicians to consider for RN depending on availability, if corticosteroids have failed and full surgical resection of BM that previously received SRS is not feasible, especially if biopsy of the lesion is desired for diagnosis as part of the same procedure.

WBRT and Concurrent Systemic Therapy

Randomized trials to date have not demonstrated an OS benefit from adding systemic therapy to WBRT (Table 2).[84,85] With regard to other endpoints such as radiographic response rate, progression-free survival, and time to neurologic deterioration, results are mixed. However, toxicity is generally increased when adding systemic therapy.[84] While a recent Phase II study of concurrent WBRT with erlotinib among NSCLC patients showed low toxicity rates,[86] a larger, randomized Phase III trial (RTOG 0320) reported grades 3–5 toxicity rates of 41%–49% in the arms receiving either temozolomide (TMZ) or erlotinib concurrently with WBRT, compared with 11% receiving WBRT alone.[87] It has been speculated that the shorter survival observed among the 2 concurrent chemotherapy arms of the RTOG trial may be attributable to higher rates of toxicity, but the trial was underpowered to prove this assertion. Most studies of WBRT with concurrent systemic therapy have enrolled lung cancer patients, and further studies are needed to examine the role of adding systemic therapy to WBRT across a variety of malignancies. While TMZ is sometimes administered concurrently with WBRT for patients with BM from malignant melanoma, the limited prospective data on this subject suggest minimal benefit.[88] In addition, a Phase II randomized trial of concurrent TMZ with WBRT for patients with BM from breast cancer showed no improvement in objective response rate, progression-free survival, or OS.[89] Ongoing randomized studies include a study of WBRT with or without lapatinib for patients with BM from HER2-positive breast cancer.[90,91]

Surgery

The role of surgery in the management of BM has evolved over time and remains a key treatment modality to consider especially for BM over 3 cm in size or otherwise bulky lesions causing neurologic symptoms, and when tissue is necessary to establish a diagnosis. While the increasing availability of SRS may lead to fewer resections among BM that are borderline in size, improvements in systemic therapy leading to longer patient

Table 2. Select trials of WBRT with concurrent systemic agents for brain metastases

Study[a]	Systemic Agent	Primary Cancer	Trial Design	*N*	WBRT Dose	Primary Endpoint	Overall Survival	CNS Response Rate (CR + PR) in Evaluable Patients	Other Outcomes
Guerrieri et al, 2004[161]	Carboplatin	NSCLC	Phase III randomized controlled trial (stopped prematurely due to poor accrual)	G1: WBRT ($N = 21$), G2: WBRT + carboplatin ($N = 21$)	20 Gy in 5 fractions	Overall survival	G1: 4.4 mo G2: 3.7 mo (P = NS)	G1: 10% G2: 29% (P = NS)	
Ushio et al, 1991[162]	Chloroethylnitrosureas tegafur	Lung	Phase III randomized controlled trial	G1: WBRT ($N = 25$) G2: WBRT + chloroethylnitrosureas ($N = 34$) G3: WBRT + chloroethylnitrosureas + tegafur ($N = 29$)	40 Gy in 1.5–2 Gy fractions	Tumor control	G1: 27 wk G2: 29 wk G3: 30.5 wk (P = NS)	G1: 36% G2: 69% G3: 74% G1 vs G2 (P = NS) G2 vs G3 (P = NS) G1 vs G3 ($P < .05$)	
Margolin et al, 2002[88]	Temozolomide	Melanoma	Phase II single arm trial	$N = 31$	30 Gy in 3 Gy fractions	Objective response	6 mo	10%	
Antonadou et al, 2002[163]	Temozolomide	Lung, breast, or unknown primary	Phase II randomized trial	G1: WBRT ($N = 23$) G2: WBRT + concurrent TMZ followed by 6 cycles of adjuvant TMZ ($N = 25$)	40 Gy in 2 Gy fractions	RR and neurologic symptom evaluation	G1: 7.0 mo G2: 8.6 mo (P = NS)	G1: OR 67% G2: OR 96% ($P = .017$)	Improvement in neurologic function in the TMZ group
Verger et al, 2005[164]	Temozolomide	Multiple (~50% lung, 15% breast)	Phase II randomized trial (stopped prematurely due to poor accrual)	G1: WBRT ($N = 41$) G2: WBRT + concurrent TMZ followed by 2 cycles of adjuvant TMZ ($N = 41$)	30 Gy in 3 Gy fractions	Neurologic toxicity	G1: 3.1 mo G2: 4.5 mo (P = NS)	Response at 30 d G1: OR 32% G2: OR 32% (P = NS)	Freedom from intracranial progression at 90 d was improved in the TMZ group

Continued

Table 2. *Continued*

Study[a]	Systemic Agent	Primary Cancer	Trial Design	*N*	WBRT Dose	Primary Endpoint	Overall Survival	CNS Response Rate (CR + PR) in Evaluable Patients	Other Outcomes
Sperduto et al, 2012[87]	Temozolomide or erlotinib	NSCLC	Phase III randomized trial	G1: WBRT + SRS ($N = 44$) G2: WBRT + SRS + TMZ ($N = 40$) G3: WBRT + SRS + erlotinib ($N = 41$)	WBRT: 37.5 Gy in 2.5 Gy fractions SRS dose was size dependent: lesions < 2 cm, 2.1 to 3.0 cm, and 3.1 to 4.0 cm received 24, 18, and 15 Gy, respectively	Overall survival	G1: 13.4 mo G2: 6.3 mo G3: 6.1 mo ($P = $ NS for G1 vs G2 and G1 vs G3)	Not reported	No difference between groups in time to CNS progression Grade 3–5 toxicity rates were 11% in G1, 41% in G2, and 49% in G3; high toxicity rates may have led to inferior survival in the combination arms
Welsh et al, 2013[86]	Erlotinib	NSCLC	Phase II single-arm trial	$N = 40$	35 Gy in 2.5 Gy fractions	Overall survival	11.8 mo	86%	No grade 4–5 toxicities Median survival was 19.1 vs 9.3 mo for patients with vs without an EGFR mutation
Knisely et al, 2008 (RTOG 0118)[165]	Thalidomide	Multiple (~60% lung)	Phase III randomized trial	G1: WBRT ($N = 93$) G2: WBRT + thalidomide ($N = 90$)	37.5 Gy in 2.5 Gy fractions	Overall survival	G1: 3.9 mo G2: 3.9 mo	Not reported	No difference between arms in time to progression or rate of death due to brain metastases. 48% patients discontinued thalidomide due to side effects
Neuhaus et al, 2009[166]	Topotecan	Lung	Phase III randomized trial (stopped prematurely due to poor accrual	G1: WBRT ($N = 49$) G2: WBRT + topotecan ($N = 47$)	20 Gy in 2 Gy fractions	Overall survival	G1: 95 d G2: 87 d ($P = $ NS)	Response 2 wk after treatment G1: 52% G2: 60%	No difference between groups in progression free survival

Abbreviations: CR, complete response; PR, partial response; OR, odds ratio. [a]Arranged according to systemic agent and study design.

survival may be increasing the number of patients with BM overall, including those requiring surgery. As discussed previously, results from the EORTC trial of SRS or surgery with or without WBRT[29] echoed those from the classic trial by Patchell et al[30] of surgery with or without WBRT, in that neither study demonstrated an OS advantage with the addition of WBRT after surgery. While most clinicians still appropriately recommend radiotherapy (WBRT or cavity SRS) after resection of BM for improved local tumor control, it is important to recall that this has not been shown in randomized trials to improve survival, and there may be patient-specific scenarios where surgery alone followed by surveillance is appropriate.

Other emerging updates with regard to the surgical management of BM have been cited above, including the increasing prevalence of postoperative SRS to the surgical cavity, which avoids WBRT, and investigation of preoperative SRS, which has been shown in at least one study to have similar local control as cavity SRS but with higher rates of both leptomeningeal disease and RN.[63] In addition, LITT is a new tool for neurosurgeons in the management of RN after SRS for BM as highlighted above, though its evidence base is thin and requires more study to better establish efficacy and optimal indications.

Systemic Therapy

Challenges in Treating Brain Metastases with Systemic Therapy

Because active BM often coexist with active systemic disease, antitumor agents that can control both intracranial and extracranial disease are needed. Unfortunately, few clinical trials of systemic agents have been conducted to date in patients with BM, and this population has frequently been excluded from clinical trials of emerging investigational drugs.[92] Comparison across BM trials has also been hampered by clinical trial design including enrollment of heterogeneous populations and varying definitions of criteria to assess response and progression. Response Evaluation Criteria in Solid Tumors (RECIST) for response assessment sums representative target lesions across all organ sites, including CNS and non-CNS sites. For therapies with differential responses in CNS and non-CNS locations, RECIST may not adequately describe CNS progression or response. Strong consideration should be given to assessing CNS and non-CNS for progression as separate compartments. Indeed, RANO-BM is an international collaboration attempting to address these issues in clinical trial design and radiographic assessment by developing uniform radiographic response criteria for use in BM trials.[77,93,94] RANO-BM recommends assessing the CNS and non-CNS sites according to RANO-BM criteria and RECIST, respectively. These radiographic response criteria proposed by RANO-BM are now being adopted in clinical trials of patients with BM where the CNS outcomes are important primary objectives. In addition, the Jumpstarting Brain Tumor Drug Development Coalition Imaging Standardization Steering Committee (an international collaboration which includes members of RANO-BM) recently published consensus recommendations for a standardized brain tumor imaging protocol in clinical trials.[95]

BM differ from metastases to other organs from a pathophysiologic and clinical perspective.[96] The brain has a unique microenvironment and an immune system distinct from other organs.[96] For example, Zhang et al[97] showed that tumor cells with normal expression of phosphatase and tensin homolog (PTEN) lose PTEN expression after dissemination to the brain (but not to other organs) and regain PTEN expression after leaving the brain microenvironment in a process that is epigenetically regulated by microRNAs from brain astrocytes. BM patients may also develop neurologic deficits and seizures, which could require the use of medications (ie, enzyme-inducing anticonvulsants, steroids) that can interfere with the metabolism of antitumor agents. These issues in part lead to the perception that BM patients are less than ideal candidates for early-phase clinical trials. However, in a review of Phase I clinical trials at MD Anderson Cancer Center comparing patients with treated, stable BM versus those without BM, the presence of BM was not an independent factor for survival, and the time to treatment failure was not different between groups.[92] In addition, the incidence of serious adverse events including neurologic toxicity was not increased in the BM population. These data suggest that patients with treated and stable BM should indeed be included in early-phase clinical trials.

Another way that BM differ from metastases to other organs is the presence of the BBB, which is a specialized cellular barrier that prevents macromolecules from entering the brain and can efficiently pump out unwanted compounds through efflux transporters such as P-glycoprotein and the breast cancer resistance protein (ATP-binding cassette subfamily G member 2).[98] This is best demonstrated by targeted agents associated with good systemic control but insufficient CNS control, such as trastuzumab in HER2-positive breast cancer[99] and crizotinib in NSCLC with *ALK*-gene rearrangement.[100,101] Intrathecal chemotherapy can deliver drug directly to the CSF but cannot reliably treat parenchymal disease or even bulky leptomeningeal disease, as diffusion of drug into tumor deposits thicker than 1 mm, along nerve root sleeves, and into the Virchow–Robin spaces is limited.[102,103]

The BBB in BM is somewhat disrupted, as demonstrated by leakage of gadolinium enhancement into the tumor on brain MRI. However, there is debate about how disrupted the BBB is and whether we can rely on this disruption (however minimal) to permit sufficient drug penetration. For example, mouse models of BM suggest that penetration of lapatinib, a HER2-directed tyrosine kinase inhibitor (TKI), is variable between and within metastases, with some lesions demonstrating very high levels of lapatinib (17% freely permeable) and others not statistically distinct from normal brain.[104] The degree of drug penetration was not well correlated with lesion size. Similar findings were obtained in a prospective clinical study of capecitabine and lapatinib uptake in surgically resected BM from 12 breast cancer patients.[105] Detectable levels of capecitabine or lapatinib were found in resected tumor tissue, but drug distribution was widely variable among patients. In another experimental model of breast cancer, BM uptake of ^{14}C-paclitaxel and ^{14}C-doxorubicin was generally greater than normal brain but $<$15% of that of other tissues or peripheral metastases and reached cytotoxic concentrations in only a small subset ($\sim$10%) of the most permeable metastases.[104]

Attempts to improve drug delivery across the BBB include inhibition of drug efflux transporters, pulsatile dosing regimens, and BBB disruption with ultrasound, although these strategies remain in clinical development.[106] ANG1005 combines paclitaxel with an amino acid peptide that targets the lipoprotein

receptor-related protein 1 receptor (which mediates transcytosis on endothelial cells of the BBB and mediates endocytosis on multiple tumor cells). A Phase II study of ANG1005 in breast cancer patients with BM demonstrated antitumor activity in the CNS with radiographic response rates of 22%–40%.[107] Escalating dosing of the epidermal growth factor receptor (EGFR) TKIs gefitinib and erlotinib may increase CNS penetration.[108] Pulsatile dosing of erlotinib at 1500 mg once weekly is associated with a CSF concentration of 130 nM, sufficient to inhibit 50% growth in cancer cell lines.[109] A retrospective analysis suggested that pulsatile dosing is well tolerated and effective in patients with EGFR-mutant lung cancers with CNS metastases (parenchymal and leptomeningeal) even after progression on standard dosing erlotinib.[110]

Some antitumor agents are not dependent on whether they can cross an intact or even variably disrupted BBB—for instance, immune checkpoint blockade therapies such as the cytotoxic T lymphocyte antigen (CTLA)–4 antibody ipilimumab, which relies on activated T cells in the periphery to migrate into the CNS, as well as angiogenesis inhibitors such as bevacizumab, which need reach only the luminal side of the vascular wall. Both of these agents have demonstrated activity in BM and, as detailed above in the case of bevacizumab, against RN resulting from prior SRS. Of note, both ipilimumab and bevacizumab are monoclonal antibodies and are generally considered too large to cross an intact BBB. Nonetheless, ipilimumab has activity in BM from melanoma.[7] In a Phase II trial of ipilimumab in metastatic melanoma patients who were either neurologically asymptomatic ($n = 51$) or symptomatic and on a stable dose of corticosteroids ($n = 21$), the median OS was 7 months and 3.4 months, respectively.[111] The FDA's expanded access program reported 1-year survival rates of 20% in melanoma patients with stable, asymptomatic BM treated with ipilimumab 10 mg/kg.[112] In Italy, an ongoing randomized Phase III trial is examining the benefit of adding fotemustine or the anti–programmed cell death protein 1 (PD1) agent nivolumab to ipilimumab in patients with BM from metastatic melanoma,[113] and 2 other trials, based in the US and Australia, are also testing combination nivolumab plus ipilimumab in melanoma metastatic to the brain.[113,114]

Due to concerns for CNS hemorrhage, BM patients were excluded from early trials of bevacizumab.[115] However, analysis of datasets from bevacizumab clinical trials demonstrated low rates of CNS hemorrhage in patients with CNS metastases.[115] In patients with occult CNS metastases enrolled in randomized controlled Phase II/III trials, 3 of 91 bevacizumab-treated patients (3.3%) developed grade 4 cerebral hemorrhage, while 1 of 96 control patients (1.0%) developed a grade 5 cerebral hemorrhage. The inclusion of bevacizumab with standard cytotoxic agents has since been associated with durable response rates in BM from breast cancer[116] and in asymptomatic, untreated BM from nonsquamous NSCLC.[117] In the latter patient population, bevacizumab plus carboplatin and paclitaxel demonstrated an intracranial response rate of 61.2% and an extracranial response rate of 64.2% with an acceptable safety profile with only one grade 1 intracranial hemorrhage.[117] There is an ongoing randomized Phase III trial examining the addition of bevacizumab to cisplatin and pemetrexed as first-line therapy for patients with asymptomatic BM from NSCLC.[118]

Finally, targeted treatments of BM are often based on the molecular profiles of the primary tumor, as opposed to the BM itself. However, recent studies comparing molecular profiles of matched BM and primary tumors demonstrate that somatic alterations in the BM are frequently discordant with those in the primary tumor.[119–121] Brastianos et al[120] performed whole-exome sequencing of 86 matched BM and primary tumors (mainly breast, lung, and renal cell cancers) and found that 53% of BM harbored a potentially clinically actionable somatic alteration not detected in the matched primary tumor. The brain microenvironment may play an important role in driving some of these alterations. These data suggest that for clinical trials of targeted agents in BM, biopsy or surgical resection of BM may be indicated for molecular profiling.

Chemoprevention of Brain Metastases

In cancer patients with a high risk for CNS relapse, interest in pharmacologic prevention of BM (using the same classes of agents with proven activity either systemically for that cancer or in primary brain tumors) is growing.[122] Such a strategy may prevent brain recurrence while preserving neurocognition and QoL.[123] In preclinical mouse models of brain-tropic breast cancer, TMZ administered 3 days after inoculation prevented the formation of experimental BM from cells negative for O^6-methylguanine-DNA methyltransferase.[124] In a retrospective study of patients with EGFR-mutant advanced NSCLC, the risk of CNS progression initially treated with gefitinib or erlotinib is lower compared with upfront chemotherapy.[125] These data suggest a role for chemoprevention of CNS metastases in specific patient populations.

Chemoprevention strategies have been preliminarily tested in clinical trials. While these studies have not met their primary endpoints of preventing BM, they are informative for future study design. The CEREBEL study was a Phase III, randomized trial of lapatinib + capecitabine versus trastuzumab + capecitabine for prevention of CNS metastases.[126] Unfortunately, the study was closed early and was inconclusive for its primary endpoint. Twenty percent of patients failed screening due to asymptomatic BM on brain MRI at study entry. The 3% and 5% rates of CNS as first site of relapse with lapatinib + capecitabine and trastuzumab + capecitabine, respectively, were far lower than the expected rates of 12% and 20%, respectively; these expected rates were based on historical trials in which baseline CNS imaging was not required (and hence likely included a substantial number of patients with occult BM who then had a higher likelihood of progression in the brain during the course of the trial). Therefore, the study was underpowered for its primary endpoint. A Phase II randomized study of maintenance TMZ versus observation for prevention of BM in high-risk NSCLC was also closed early with 53 patients enrolled.[123] There was no difference in the incidence of BM at one year (18% in the TMZ arm and 13% in the observation arm, $P = .6995$). Again, the incidence of BM was lower than expected (13% in the observation arm vs the 40% predicted based on historical data). Furthermore, TMZ prophylaxis is unlikely to be effective in view of its overall very low antitumor activity against NSCLC in general. Future chemoprevention efforts will need to be redesigned based on improved agents, a better understanding of the populations at risk for CNS relapse, pharmacokinetics

and pharmacodynamics, the emergence of improved imaging methods, and a better understanding of the safety of combining systemic therapy with radiotherapy. For the present and the foreseeable future, the best form of prophylaxis against BM will continue to be the discovery of agents and strategies with increasing overall activity against each type and subset of cancer.

Tumor-Specific Systemic Therapies for Brain Metastases

Guidelines from the National Comprehensive Cancer Network for management of BM recommend local radiation or surgery as upfront treatment.[127] Indeed, no chemotherapy is approved by the US FDA for management of BM from breast cancer, lung cancer, melanoma, or other solid tumors, and none of the available systemic therapies are generally considered first-line treatment for BM.[128] Nonetheless, in a few select patients with asymptomatic or minimally symptomatic BM, treatments with established efficacy in BM may be reasonable to consider as initial therapy.

In breast cancer patients, the risk of developing BM and survival after BM diagnosis vary according to tumor subtype.[99,129] In patients with triple negative breast cancer, the risk of CNS relapse may be as high as 46%, and CNS involvement often occurs in the setting of active systemic disease.[99] This high rate of CNS involvement is unlikely to be due to a sanctuary effect, but rather to the lack of effective therapies in general for this aggressive subtype of breast cancer.[23] In breast cancer patients with HER2-positive disease, up to 40%–50% will develop BM,[5] often despite controlled systemic disease.[99] Some studies suggest that up to half of HER2-positive patients die of BM-related causes,[130] emphasizing the importance of CNS control in this patient population. For the HER2-positive patient population, the American Society of Clinical Oncology offers recommendations on the management of BM.[6] Clinical trials of lapatinib in combination with capecitabine have demonstrated activity with a CNS objective response rate of 20% in patients with previously treated BM[131] and 66% (using a volumetric response criteria) in patients with previously untreated BM[132] (Table 3). More recent trials in the HER2-positive population with BM have examined the potential benefit of other HER2-directed TKIs. Afatinib (alone or in combination with vinorelbine)[133] did not demonstrate efficacy over investigator's choice for management of BM in HER2-positive patients and was not as well tolerated. Single-agent neratinib had low efficacy in previously treated BM with a CNS objective response rate of only 8%,[134] but neratinib in combination with chemotherapy may prove more efficacious. In the NEfERT-T trial for untreated metastatic HER2-positive breast cancer (including women with asymptomatic CNS metastases), the neratinib + paclitaxel arm had a lower incidence of CNS recurrences and delayed time to CNS metastases compared with trastuzumab + paclitaxel.[135] However, these results require validation in a larger study. Other promising agents in clinical trials for breast cancer patients with BM include trastuzumab + emtansine (for HER2+ disease),[136] pathway inhibitors of phosphatidylinositol 3-kinase–mammalian target of rapamycin, CDK4 inhibitors, and poly(ADP-ribose) polymerase inhibitors.[137]

For melanoma patients, up to 60% will develop BM during the course of their illness.[7] Ipilimumab[111] (as previously discussed) or BRAF inhibitors such as dabrafenib[138] (for patients with $BRAF^{V600}$ mutations) can be considered for management of progressive BM (Table 3). A Phase II study of dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma and previously untreated BM ($n = 89$) or treated BM ($n = 83$) demonstrated remarkable median OS of 33 weeks and 31 weeks, respectively.[138] In a Phase III randomized study of 704 patients with BRAF-mutant metastatic melanoma that allowed patients with stable, treated BM, the combination of a BRAF inhibitor and an inhibitor of mitogen/extracellular signal-regulated kinase (MEK) demonstrated superior progression-free survival and OS compared with a BRAF inhibitor alone.[139] The efficacy of combination therapy with a BRAF inhibitor and a MEK inhibitor for treatment of BRAF-mutant melanoma BM is now being evaluated in 2 Phase II studies.[140,141] Anti-PD1 checkpoint inhibitors such as nivolumab and pembrolizumab are also under investigation for BM from metastatic melanoma. Preliminary evidence from a small prospective series suggests that pembrolizumab may be active against melanoma metastatic to the brain and may be less toxic than ipilimumab.[142,143] The combination of ipilimumab and nivolumab has shown enhanced activity in systemic metastases of melanoma, albeit at the cost of increased immune-related toxicity.[144,145] Nonetheless, this strategy of combining anti–CTLA-4 and anti-PD1 agents is also undergoing evaluation in several prospective studies for melanoma patients with BM.[113,114]

The options for NSCLC patients with BM may include pemetrexed[146] or an EGFR TKI such as gefitinib[147] or erlotinib[148] (for patients with activating EGFR mutations) (Table 3). Response rates of BM to EGFR TKIs at conventional doses in patients with EGFR-mutant NSCLC may be as high as 60%–80%.[149] As previously mentioned, pulsatile dosing of erlotinib administered once weekly can be an effective strategy for management of BM even in patients who have progressed on daily erlotinib.[110] For the 2%–7% of NSCLC patients who harbor *ALK*-gene rearrangements, CNS metastases are a relatively common complication and represent a major barrier to achieving long-lasting disease control.[149,150] In a Phase III randomized trial of the ALK inhibitor crizotinib, ~35% of patients with *ALK*-rearranged NSCLC had BM at the time of study entry.[151] Based on pooled analysis of 2 large clinical trials of crizotinib in patients with *ALK*-rearranged advanced NSCLC, 20% of patients without BM at baseline and 70% of patients with known BM developed CNS progression while on crizotinib.[8] Second-generation ALK inhibitors with increased potency such as alectinib and ceritinib may have better CNS penetration. Preclinical pharmacokinetic studies of alectinib demonstrate improved CNS penetration over crizotinib, with CNS concentrations 63%–94% of serum concentrations.[152] In Phase I studies of alectinib or ceritinib that allowed patients with CNS metastases and no prior brain radiotherapy at study entry, 3 of 4 patients with measurable CNS disease in the alectinib study and 6 of 11 patients with measurable CNS disease in the ceritinib study achieved a complete or partial CNS response.[153,154] In a separate study of alectinib for crizotinib-resistant *ALK*-rearranged NSCLC that allowed stable, treated, or asymptomatic untreated BM at baseline, the CNS response rate in the 35 patients with measurable CNS disease was 57%.[155] At 12 months, the cumulative CNS progression rate (24.8%) was lower than the cumulative non-CNS progression rate (33.2%) for all patients. Ongoing trials of second-generation ALK inhibitors for BM in *ALK*-rearranged

Table 3. Select trials of systemic agents for brain metastases according to primary cancer

Study	Systemic Agent	Mechanism of Action	Population	Prior Treatment for BM?	Trial Design	*N*	Primary endpoint	CNS Response Rate (CR + PR)	Overall Survival
Melanoma									
Margolin et al, Lancet Oncol 2012[111]	Ipilimumab	CTCL-4 inhibitor	Melanoma metastatic to brain	41%–48% had received prior brain irradiation (WBRT or SRS)	Phase II	72 total: 51 in cohort A: neurologically asymptomatic ($N = 51$) Cohort B: symptomatic ($N = 21$)	Disease control (CR, PR, SD) at 12 wk = 18% in A and 5% in B	16% cohort A, 5% cohort B	7.0 mo in cohort A and 3.7 mo in cohort B
Long et al, Lancet Oncol 2012[138]	Dabrafenib	BRAF inhibitor	Val600Glu or Val600Lys BRAF mutant melanoma metastatic to brain	Cohort A previously untreated BM. Cohort B prior local therapy (surgery, WBRT, SRS)	Phase II	172 total: 89 in cohort A and 83 in cohort B	Intracranial response (CR + PR) Val600Glu 39.2% cohort A, 30.8% cohort B. Val600 Lys 6.7% cohort A, 22.2% cohort B	Val600Glu 39.2% cohort A, 30.8% cohort B. Val600 Lys 6.7% cohort A, 22.2% cohort B	Val600Glu 33.1 mo cohort A, 31.4 mo Cohort B Val600Lys 16.3 mo cohort A, 21.9 mo cohort B
Breast Cancer									
Lin et al, CCR 2009[131]	Lapatinib	HER2 inhibitor	HER2+ breast cancer metastatic to brain	All previously treated with brain irradiation (WBRT or SRS)	Phase II	242: 95 in cohort A (ECOG 0–1 and 1–2 prior trastuzumab regimens) and 147 in cohort B (ECOG 2 and/or >2 prior trastuzumab regimens)	CNS objective response (50% or greater volumetric reduction)	6% in cohort A and cohort B	6.4 mo (cohort A 9.6 mo, cohort B 5.5 mo)
	Lapatinib + capecitabine	HER2 inhibitor (lapatinib) and prodrug that converts to 5-fluorouracil (capecitabine)	HER2+ breast cancer metastatic to brain	Extension phase for patients on study who progressed on lapatinib	Phase II	Subset of 50 patients in above study	CNS objective response (50% or greater volumetric reduction)	20%	Not reported
Bachelot Lancet Oncol 2013 LANDSCAPE[132]	Lapatinib + capecitabine	HER2 inhibitor (lapatinib) and prodrug that converts to 5-fluorouracil (capecitabine)	HER2+ breast cancer metastatic to brain	Untreated (no prior WBRT, SRS, capecitabine, or lapatinib)	Phase II	45	CNS objective response rate (CR + PR)	49%	17 mo

Continued

Table 3. *Continued*

Study	Systemic Agent	Mechanism of Action	Population	Prior Treatment for BM?	Trial Design	*N*	Primary endpoint	CNS Response Rate (CR + PR)	Overall Survival
Pivot et al, J Clin Onc 2015 CEREBEL[126]	Lapatinib + capecitabine (lap + cap) vs trastuzumab + capecitabine (tras + cap)	HER2 inhibitors (lap, tras), prodrug that converts to 5-fluorouracil (cap)	HER2+ metastatic breast cancer without CNS metastases at baseline	No brain metastases at baseline	Phase III, randomized study, preventative trial. Study terminated early	540 (271 lap + cap and 269 tras + cap)	Incidence of CNS mets as first site of relapse: 3% in the lap + cap and 5% in tras + cap, difference not statistically significant	n/a	22.7 mo for lap + cap and 27.3 mo for tras + cap
NSCLC									
Bearz et al, Lung Cancer 2010[146]	Pemetrexed	Folate anti-metabolite	NSCLC metastatic to brain	71.8% received prior brain irradiation	Retrospective review	39	Not specified	38.4%	10 mo
Ceresoli et al, Ann Oncol 2004[147]	Gefitinib	EGFR inhibitor	Unselected patients with NSCLC metastatic to brain	2 groups: prior WBRT (44%) and no prior WBRT (56%)	Phase II	41	Disease control rate (CR + PR + SD)	10%	5 mo
Wu et al, Ann Oncol 2013 (CTONG-0803)[148]	Erlotinib	EGFR inhibitor	East Asian patients with adenocarcinoma or EGFR mutant NSCLC, asymptomatic brain metastases (total 16.7% mutation positive)	35.4% received prior WBRT	Phase II	48	PFS	58.3% systemic +intracranial RR (intracranial RR alone not reported)	18.9 mo [patients with EGFR mutant disease 37.5 mo vs EGFR wild-type 18.4 mo vs unknown EGFR status 19.4 mo, *P*-value .14]
Besse et al, Clin Ca Res 2015[117]	Bevacziumab + carboplatin and paclitaxel	VEGF inhibitor (bevacziumab), alkylating agent (carboplatin), taxane (paclitaxel)	Unselected NSCLC patients with asymptomatic, prevously untreated brain metastases	No prior treatment	Phase II (noncomparative study with 2 arms atlhough only the bevacizuamb + carboplatin and paclitaxel arm results reported)	67 in the B + CP arm	Investigator-assessed 6-month PFS rate	61.2%	16 mo

Continued

Table 3. *Continued*

Study	Systemic Agent	Mechanism of Action	Population	Prior Treatment for BM?	Trial Design	*N*	Primary endpoint	CNS Response Rate (CR + PR)	Overall Survival
Ou et al, J Clin Oncol 2016[155]	Alectinib	ALK inhibitor	ALk-rearranged NSCLC resistant to crizotinib, patients with stable treated or asymptomatic untreated brain and leptomeningeal metastases allowed	61 (73%) of 84 patients with CNS metastases at study entry had prior brain irradiation	Phase II	84 (61%) of the 138 patients enrolled on study had CNS metastases at baseline	Objective response rate (CNS objective response rate was a secondary objective)	57% in 35 patients with measurable CNS lesions	Not reported
Boggs et al, Lung Ca 2014[123]	Temozolomide (TMZ)	Alkylating agent	NSCLC stage IIIA, IIIB, or IV (only pleural or pericardia effusion), no brain metastases at baseline	No brain metastases at baseline	Phase II randomized trial – preventative trial Study terminated early	53 (26 TMZ, 27 observation)	Incidence of brain metastases at 12 mo: 18% in TMZ, 13% in observation	n/a	27.1 mo in TMZ vs 22.5 mo in observation ($P = .7$)

Abbreviations: CR, complete response; PR, partial response; PFS, progression-free survival; RR, response rate; mets, metastases.

NSCLC include a Phase II study of ceritinib for *ALK*-rearranged BM and leptomeningeal disease.[156] The randomized Phase III ALEX trial comparing alectinib versus crizotinib in treatment-naive patients with *ALK*-rearranged NSCLC allows enrollment of patients with asymptomatic BM and leptomeningeal disease and will measure time to CNS progression.[157] Given the recent approval of anti-PD1 antibodies as second-line therapy of both squamous and nonsquamous NSCLC, further study of these checkpoint inhibitors—alone[158,159] or in combinations with other agents[160]—in BM of NSCLC will also be pursued.

Conclusions and Future Directions

The clinical management and understanding of BM has changed substantially in the last 5 years. Several of these changes stem from improvements in systemic therapy, which have led to better systemic control and longer patient OS, associated with increased time at risk for developing BM. Being aware of significant heterogeneity in prognosis and therapeutic options for patients with BM is crucial for appropriate management, with greater attention to developing individual patient treatment plans based on predicted outcomes. The increase in use of SRS alone for many patients with multiple BM is an outgrowth of the desire to employ treatments focused on local control while minimizing cognitive effects associated with WBRT. Complications from BM and their treatment must be considered in comprehensive patient management, especially with greater awareness that the majority of patients do not die from their BM. Development of systemic therapies capable of preventing BM and controlling both intracranial and extracranial disease once BM are diagnosed is paramount. Many clinical trials are under way to establish the efficacy of systemic agents in BM, particularly for breast cancer, lung cancer, and melanoma. Standardization of radiographic response criteria and clinical trial design by the brain metastases working group of RANO will hopefully provide more uniformity in assessment of brain metastases and improve cross-trial comparison. Future directions and challenges also include development of drugs with better CNS penetration, earlier inclusion of BM patients in drug development, as well as increased understanding of the molecular basis of BM and the role of chemoprevention for BM.

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References

1. Gavrilovic IT, Posner JB. Brain metastases: epidemiology and pathophysiology. *J Neurooncol*. 2005;75(1):5–14.
2. Sawaya R, Bindal R, Lang F, et al. Metastatic brain tumors. In: Kaye A, Laws E, eds. *Brain tumors: an encyclopedic approach*. 2nd ed. London: Churchill Livingstone; 2001:999–1026.
3. Fox BD, Cheung VJ, Patel AJ, et al. Epidemiology of metastatic brain tumors. *Neurosurg Clin N Am*. 2011;22(1):1–6.
4. Barnholtz-Sloan JS, Sloan AE, Davis FG, et al. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. *J Clin Oncol*. 2004;22(14):2865–2872.
5. Lin NU, Winer EP. Brain metastases: the HER2 paradigm. *Clin Cancer Res*. 2007;13(6):1648–1655.
6. Ramakrishna N, Temin S, Chandarlapaty S, et al. Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2–positive breast cancer and brain metastases: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2014;32(19):2100–2108.
7. Ajithkumar T, Parkinson C, Fife K, et al. Evolving treatment options for melanoma brain metastases. *Lancet Oncol*. 2015;16(13):e486–e497.
8. Costa DB, Shaw AT, Ou SH, et al. Clinical experience with crizotinib in patients with advanced ALK-rearranged non-small-cell lung cancer and brain metastases. *J Clin Oncol*. 2015;33(17):1881–1888.
9. Chun SG, Choe KS, Iyengar P, et al. Isolated central nervous system progression on Crizotinib: an Achilles heel of non-small cell lung cancer with EML4-ALK translocation? *Cancer Biol Ther*. 2012;13(14):1376–1383.
10. Takeda M, Okamoto I, Nakagawa K. Clinical impact of continued crizotinib administration after isolated central nervous system progression in patients with lung cancer positive for ALK rearrangement. *J Thorac Oncol*. 2013;8(5):654–657.
11. Weickhardt AJ, Scheier B, Burke JM, et al. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. *J Thorac Oncol*. 2012;7(12):1807–1814.
12. Pestalozzi BC, Holmes E, de Azambuja E, et al. CNS relapses in patients with HER2-positive early breast cancer who have and have not received adjuvant trastuzumab: a retrospective substudy of the HERA trial (BIG 1-01). *Lancet Oncol*. 2013;14(3):244–248.
13. National Comprehensive Cancer Network. NCCN Guidelines for Treatment of Cancer by Site. Available at: www.nccn.org. Accessed May 3, 2016.
14. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys*. 1997;37(4):745–751.
15. Nieder C, Mehta MP. Prognostic indices for brain metastases—usefulness and challenges. *Radiat Oncol*. 2009;4:10.
16. Sperduto PW, Kased N, Roberge D, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J Clin Oncol*. 2012;30(4):419–425.
17. Sperduto PW, Yang TJ, Beal K, et al. The effect of gene mutations on survival in patients with adenocarcinoma of the lung following the development of brain metastases. *Int J Radiat Oncol Biol Phys*. 2015;93(3):S37–S39.
18. Johung KL, Yeh N, Desai NB, et al. Extended survival and prognostic factors for patients with alk-rearranged non–small-cell lung cancer and brain metastasis. *J Clin Oncol*. 2016;34(2):123–129.
19. Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol*. 2014;15(4):387–395.
20. Liu Y, Alexander BM, Chen YH, et al. Salvage whole brain radiotherapy or stereotactic radiosurgery after initial stereotactic radiosurgery for 1-4 brain metastases. *J Neurooncol*. 2015;124(3):429–437.
21. Gondi V, Pugh SL, Tome WA, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. *J Clin Oncol*. 2014;32(34):3810–3816.
22. Kondziolka D, Parry PV, Lunsford LD, et al. The accuracy of predicting survival in individual patients with cancer. *J Neurosurg*. 2014;120(1):24–30.
23. Lin NU, Claus E, Sohl J, et al. Sites of distant recurrence and clinical outcomes in patients with metastatic triple-negative breast cancer: high incidence of central nervous system metastases. *Cancer*. 2008;113(10):2638–2645.
24. Dyer MA, Kelly PJ, Chen YH, et al. Importance of extracranial disease status and tumor subtype for patients undergoing radiosurgery for breast cancer brain metastases. *Int J Radiat Oncol Biol Phys*. 2012;83(4):e479–e486.
25. Barnholtz-Sloan JS, Yu C, Sloan AE, et al. A nomogram for individualized estimation of survival among patients with brain metastasis. *Neuro Oncol*. 2012;14(7):910–918.
26. Borgelt B, Gelber R, Kramer S, et al. The palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys*. 1980;6(1):1–9.
27. Brown PD, Asher AL, Ballman KV, et al. NCCTG N0574 (Alliance): A phase III randomized trial of whole brain radiation therapy (WBRT) in addition to radiosurgery (SRS) in patients with 1 to 3 brain metastases. *J Clin Oncol*. 2015;33(suppl):abstr LBA4.
28. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA*. 2006;295(21):2483–2491.
29. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol*. 2011;29(2):134–141.
30. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA*. 1998;280(17):1485–1489.
31. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol*. 2009;10(11):1037–1044.
32. American Society for Radiation Oncology. 2014 Choosing Wisely List. Available at: https://www.astro.org/Patient-Care/

Patient-Education/2014-Choosing-Wisely-List/. Accessed May 3, 2016.

33. Sahgal A, Aoyama H, Kocher M, et al. Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: individual patient data meta-analysis. *Int J Radiat Oncol Biol Phys*. 2015;91(4):710–717.
34. Arvold ND, Catalano PJ. Local therapies for brain metastases, competing risks, and overall survival. *Int J Radiat Oncol Biol Phys*. 2015;91(4):718–720.
35. Aoyama H, Tago M, Shirato H, Japanese Radiation Oncology Study Group I. Stereotactic radiosurgery with or without whole-brain radiotherapy for brain metastases: secondary analysis of the JROSG 99-1 randomized clinical trial. *JAMA Oncol*. 2015;1(4):457–464.
36. Sahgal A. Point/counterpoint: Stereotactic radiosurgery without whole-brain radiation for patients with a limited number of brain metastases: the current standard of care? *Neuro Oncol*. 2015;17(7):916–918.
37. Mehta MP. The controversy surrounding the use of whole-brain radiotherapy in brain metastases patients. *Neuro Oncol*. 2015;17(7):919–923.
38. Mehta MP, Tsao MN, Whelan TJ, et al. The American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based review of the role of radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys*. 2005;63(1):37–46.
39. Tsao MN, Rades D, Wirth A, et al. Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): an American Society for Radiation Oncology evidence-based guideline. *Pract Radiat Oncol*. 2012;2(3):210–225.
40. Bhangoo SS, Linskey ME, Kalkanis SN, American Association of Neurologic Surgeons, Congress of Neurologic Surgeons. Evidence-based guidelines for the management of brain metastases. *Neurosurg Clin N Am*. 2011;22(1):97–104, viii.
41. Grandhi R, Kondziolka D, Panczykowski D, et al. Stereotactic radiosurgery using the Leksell Gamma Knife Perfexion unit in the management of patients with 10 or more brain metastases. *J Neurosurg*. 2012;117(2):237–245.
42. University of California, San Francisco. Neurocognitive outcomes in patients treated with radiotherapy for five or more brain metastases (NAGKC 12-01). In: *ClinicalTrials.gov [Internet]*. Bethesda, MD: National Library of Medicine (US). 2012-[cited 2015 Nov 2]. Available from: http://clinicaltrials.gov/show/NCT01731704. NLM Identifier: NCT01731704.
43. MD Anderson Cancer Center. A prospective phase iii trial to compare stereotactic radiosurgery versus whole brain radiation therapy. In: *ClinicalTrials.gov [Internet]*. Bethesda, MD: National Library of Medicine (US). 2012-[cited 2015 Nov 2]. Available from: http://clinicaltrials.gov/show/NCT01592968. NLM Identifier: NCT01592968.
44. Nath SK, Lawson JD, Simpson DR, et al. Single-isocenter frameless intensity-modulated stereotactic radiosurgery for simultaneous treatment of multiple brain metastases: clinical experience. *Int J Radiat Oncol Biol Phys*. 2010;78(1):91–97.
45. Huang Y, Chin K, Robbins JR, et al. Radiosurgery of multiple brain metastases with single-isocenter dynamic conformal arcs (SIDCA). *Radiother Oncol*. 2014;112(1):128–132.
46. Thomas EM, Popple RA, Wu X, et al. Comparison of plan quality and delivery time between volumetric arc therapy (RapidArc) and Gamma Knife radiosurgery for multiple cranial metastases. *Neurosurgery*. 2014;75(4):409–417;discussion 417-408.
47. Thomas A, Niebanck M, Juang T, et al. A comprehensive investigation of the accuracy and reproducibility of a multitarget single isocenter VMAT radiosurgery technique. *Med Phys*. 2013;40(12):121725.
48. Hsu F, Carolan H, Nichol A, et al. Whole brain radiotherapy with hippocampal avoidance and simultaneous integrated boost for 1-3 brain metastases: a feasibility study using volumetric modulated arc therapy. *Int J Radiat Oncol Biol Phys*. 2010;76(5):1480–1485.
49. Arvold ND, Pinnell NE, Mahadevan A, et al. Steroid and anticonvulsant prophylaxis for stereotactic radiosurgery: Large variation in physician recommendations [published online Nov 10 2015]. *Pract Radiat Oncol*. 2015. doi:10.1016/j.prro.2015.11.004.
50. Kwon AK, Dibiase SJ, Wang B, et al. Hypofractionated stereotactic radiotherapy for the treatment of brain metastases. *Cancer*. 2009;115(4):890–898.
51. Rajakesari S, Arvold ND, Jimenez RB, et al. Local control after fractionated stereotactic radiation therapy for brain metastases. *J Neurooncol*. 2014;120(2):339–346.
52. Soffietti R, Ruda R, Trakul N, et al. Point/counterpoint: Is stereotactic radiosurgery needed following resection of brain metastasis? *Neuro Oncol*. 2016;18(1):12–15.
53. Soltys SG, Adler JR, Lipani JD, et al. Stereotactic radiosurgery of the postoperative resection cavity for brain metastases. *Int J Radiat Oncol Biol Phys*. 2008;70(1):187–193.
54. Jagannathan J, Yen CP, Ray DK, et al. Gamma Knife radiosurgery to the surgical cavity following resection of brain metastases. *J Neurosurg*. 2009;111(3):431–438.
55. Kelly PJ, Lin YB, Yu AY, et al. Stereotactic irradiation of the postoperative resection cavity for brain metastasis: a frameless linear accelerator-based case series and review of the technique. *Int J Radiat Oncol Biol Phys*. 2012;82(1):95–101.
56. Choi CY, Chang SD, Gibbs IC, et al. Stereotactic radiosurgery of the postoperative resection cavity for brain metastases: prospective evaluation of target margin on tumor control. *Int J Radiat Oncol Biol Phys*. 2012;84(2):336–342.
57. Atalar B, Modlin LA, Choi CY, et al. Risk of leptomeningeal disease in patients treated with stereotactic radiosurgery targeting the postoperative resection cavity for brain metastases. *Int J Radiat Oncol Biol Phys*. 2013;87(4):713–718.
58. Ojerholm E, Lee JY, Thawani JP, et al. Stereotactic radiosurgery to the resection bed for intracranial metastases and risk of leptomeningeal carcinomatosis. *J Neurosurg*. 2014;121(Suppl):75–83.
59. Minniti G, Esposito V, Clarke E, et al. Multidose stereotactic radiosurgery (9 Gy × 3) of the postoperative resection cavity for treatment of large brain metastases. *Int J Radiat Oncol Biol Phys*. 2013;86(4):623–629.
60. Wang CC, Floyd SR, Chang CH, et al. Cyberknife hypofractionated stereotactic radiosurgery (HSRS) of resection cavity after excision of large cerebral metastasis: efficacy and safety of an 800 cGy × 3 daily fractions regimen. *J Neurooncol*. 2012;106(3):601–610.
61. M.D. Anderson Cancer Center. Resection bed post-surgical stereotactic radiosurgery (SRS). In: *ClinicalTrials.gov [Internet]*. Bethesda, MD: National Library of Medicine (US). 2009-[cited 2015 Nov 2]. Available from: http://clinicaltrials.gov/show/NCT00950001. NLM Identifier: NCT00950001.
62. Alliance for Clinical Trials in Oncology. Stereotactic radiosurgery or whole-brain radiation therapy in treating patients with brain metastases that have been removed by surgery. In:

ClinicalTrials.gov [Internet]. Bethesda, MD: National Library of Medicine (US). 2011-[cited 2015 Nov 2]. Available from: http://clinicaltrials.gov/show/NCT01372774. NLM Identifier: NCT01372774.

63. Patel KR, Burri SH, Asher AL, et al. Comparing preoperative with postoperative stereotactic radiosurgery for resectable brain metastases: a multi-institutional analysis. *Neurosurgery*. 2015. [Epub ahead of print].
64. Gondi V, Paulus R, Bruner DW, et al. Decline in tested and self-reported cognitive functioning after prophylactic cranial irradiation for lung cancer: pooled secondary analysis of Radiation Therapy Oncology Group randomized trials 0212 and 0214. *Int J Radiat Oncol Biol Phys*. 2013;86(4):656–664.
65. Monaco EA III, Faraji AH, Berkowitz O, et al. Leukoencephalopathy after whole-brain radiation therapy plus radiosurgery versus radiosurgery alone for metastatic lung cancer. *Cancer*. 2013;119(1):226–232.
66. Li J, Bentzen SM, Li J, et al. Relationship between neurocognitive function and quality of life after whole-brain radiotherapy in patients with brain metastasis. *Int J Radiat Oncol Biol Phys*. 2008;71(1):64–70.
67. Soffietti R, Kocher M, Abacioglu UM, et al. A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results. *J Clin Oncol*. 2013;31(1):65–72.
68. Brown PD, Pugh S, Laack NN, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. *Neuro Oncol*. 2013;15(10):1429–1437.
69. NRG Oncology. Memantine hydrochloride and whole-brain radiotherapy with or without hippocampal avoidance in reducing neurocognitive decline in patients with brain metastases. In: *ClinicalTrials.gov [Internet]*. Bethesda, MD: National Library of Medicine (US). 2015-[cited 2015 Nov 2]. Available from: http://clinicaltrials.gov/show/NCT02360215. NLM Identifier: NCT02360215.
70. Rapp SR, Case LD, Peiffer A, et al. Donepezil for irradiated brain tumor survivors: a phase iii randomized placebo-controlled clinical trial. *J Clin Oncol*. 2015;33(15):1653–1659.
71. Ropper AH, Samuels MA. Intracranial neoplasms and paraneoplastic disorders. In: Ropper AH, Samuels MA, eds. *Adams and Victor's Principles of Neurology*. 10th ed. New York, NY: McGraw-Hill; 2014.
72. Nonoguchi N, Miyatake S, Fukumoto M, et al. The distribution of vascular endothelial growth factor-producing cells in clinical radiation necrosis of the brain: pathological consideration of their potential roles. *J Neurooncol*. 2011;105(2):423–431.
73. Chao ST, Ahluwalia MS, Barnett GH, et al. Challenges with the diagnosis and treatment of cerebral radiation necrosis. *Int J Radiat Oncol Biol Phys*. 2013;87(3):449–457.
74. Stockham AL, Tievsky AL, Koyfman SA, et al. Conventional MRI does not reliably distinguish radiation necrosis from tumor recurrence after stereotactic radiosurgery. *J Neurooncol*. 2012;109(1):149–158.
75. Mitsuya K, Nakasu Y, Horiguchi S, et al. Perfusion weighted magnetic resonance imaging to distinguish the recurrence of metastatic brain tumors from radiation necrosis after stereotactic radiosurgery. *J Neurooncol*. 2010;99(1):81–88.
76. Horky LL, Hsiao EM, Weiss SE, et al. Dual phase FDG-PET imaging of brain metastases provides superior assessment of recurrence versus post-treatment necrosis. *J Neurooncol*. 2011;103(1):137–146.
77. Lin NU, Lee EQ, Aoyama H, et al. Response assessment criteria for brain metastases: proposal from the RANO group. *Lancet Oncol*. 2015;16(6):e270–e278.
78. Du Four S, Wilgenhof S, Duerinck J, et al. Radiation necrosis of the brain in melanoma patients successfully treated with ipilimumab, three case studies. *Eur J Cancer*. 2012;48(16):3045–3051.
79. Liebner DA, Walston SA, Cavaliere R, et al. Radiation necrosis mimicking rapid intracranial progression of melanoma metastasis in two patients treated with vemurafenib. *Melanoma Res*. 2014;24(2):172–176.
80. Parker GM, Dunn IF, Ramkissoon SH, et al. Recurrent radiation necrosis in the brain following stereotactic radiosurgery. *Pract Radiat Oncol*. 2015;5(3):e151–e154.
81. Levin VA, Bidaut L, Hou P, et al. Randomized double-blind placebo-controlled trial of bevacizumab therapy for radiation necrosis of the central nervous system. *Int J Radiat Oncol Biol Phys*. 2011;79(5):1487–1495.
82. Alliance for Clinical Trials in Oncology.Corticosteroids + bevacizumab vs. corticosteroids + placebo (best) for radionecrosis after radiosurgery for brain metastases. In: *ClinicalTrials.gov [Internet]*. Bethesda, MD: National Library of Medicine (US). 2015-[cited 2015 Nov 2]. Available from: http://clinicaltrials.gov/show/NCT02490878. NLM Identifier: NCT02490878.
83. Torres-Reveron J, Tomasiewicz HC, Shetty A, et al. Stereotactic laser induced thermotherapy (LITT): a novel treatment for brain lesions regrowing after radiosurgery. *J Neurooncol*. 2013;113(3):495–503.
84. Tsao MN, Lloyd N, Wong RK, et al. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. *Cochrane Database Syst Rev*. 2012;4:CD003869.
85. Mehta MP, Paleologos NA, Mikkelsen T, et al. The role of chemotherapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol*. 2010;96(1):71–83.
86. Welsh JW, Komaki R, Amini A, et al. Phase II trial of erlotinib plus concurrent whole-brain radiation therapy for patients with brain metastases from non-small-cell lung cancer. *J Clin Oncol*. 2013;31(7):895–902.
87. Sperduto PW, Wang M, Robins HI, et al. A phase 3 trial of whole brain radiation therapy and stereotactic radiosurgery alone versus WBRT and SRS with temozolomide or erlotinib for non-small cell lung cancer and 1 to 3 brain metastases: Radiation Therapy Oncology Group 0320. *Int J Radiat Oncol Biol Phys*. 2013;85(5):1312–1318.
88. Margolin K, Atkins B, Thompson A, et al. Temozolomide and whole brain irradiation in melanoma metastatic to the brain: a phase II trial of the Cytokine Working Group. *J Cancer Res Clin Oncol*. 2002;128(4):214–218.
89. Cao KI, Lebas N, Gerber S, et al. Phase II randomized study of whole-brain radiation therapy with or without concurrent temozolomide for brain metastases from breast cancer. *Ann Oncol*. 2015;26(1):89–94.
90. National Cancer Institute. Whole-brain radiation therapy with or without lapatinib ditosylate in treating patients with brain metastasis from HER2-positive breast cancer.

In: *ClinicalTrials.gov [Internet]*. Bethesda, MD: National Library of Medicine (US). 2012-[cited 2015 Jul 27]. Available from: http://clinicaltrials.gov/show/NCT01622868. NLM Identifier: NCT01622868.

91. Lin NU, Freedman RA, Ramakrishna N, et al. A phase I study of lapatinib with whole brain radiotherapy in patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer brain metastases. *Breast Cancer Res Treat*. 2013;142(2): 405–414.
92. Tsimberidou AM, Letourneau K, Wen S, et al. Phase I clinical trial outcomes in 93 patients with brain metastases: the MD Anderson Cancer Center experience. *Clin Cancer Res*. 2011; 17(12):4110–4118.
93. Lin NU, Lee EQ, Aoyama H, et al. Challenges relating to solid tumour brain metastases in clinical trials, part 1: patient population, response, and progression. A report from the RANO group. *Lancet Oncol*. 2013;14(10):e396–e406.
94. Lin NU, Wefel JS, Lee EQ, et al. Challenges relating to solid tumour brain metastases in clinical trials, part 2: neurocognitive, neurological, and quality-of-life outcomes. A report from the RANO group. *Lancet Oncol*. 2013;14(10):e407–e416.
95. Ellingson BM, Bendszus M, Boxerman J, et al. Consensus recommendations for a standardized brain tumor imaging protocol in clinical trials. *Neuro Oncol*. 2015;17(9):1188–1198.
96. Preusser M, Berghoff AS, Schadendorf D, et al. Brain metastasis: opportunity for drug development? *Curr Opin Neurol*. 2012;25(6): 786–794.
97. Zhang L, Zhang S, Yao J, et al. Microenvironment-induced PTEN loss by exosomal microRNA primes brain metastasis outgrowth. *Nature*. 2015;527(7576):100–104.
98. van Tellingen O, Yetkin-Arik B, de Gooijer MC, et al. Overcoming the blood-brain tumor barrier for effective glioblastoma treatment. *Drug Resist Updat*. 2015;19:1–12.
99. Lin NU, Amiri-Kordestani L, Palmieri D, et al. CNS metastases in breast cancer: old challenge, new frontiers. *Clin Cancer Res*. 2013;19(23):6404–6418.
100. Camidge DR. Taking aim at ALK across the blood-brain barrier. *J Thorac Oncol*. 2013;8(4):389–390.
101. Shi W, Dicker AP. CNS metastases in patients with non–small-cell lung cancer and ALK gene rearrangement. *J Clin Oncol*. 2016; 34(2):107–109.
102. Grossman SA, Reinhard CS, Loats HL. The intracerebral penetration of intraventricularly administered methotrexate: a quantitative autoradiographic study. *J Neurooncol*. 1989;7(4): 319–328.
103. Burch PA, Grossman SA, Reinhard CS. Spinal cord penetration of intrathecally administered cytarabine and methotrexate: a quantitative autoradiographic study. *J Natl Cancer Inst*. 1988; 80(15):1211–1216.
104. Lockman PR, Mittapalli RK, Taskar KS, et al. Heterogeneous blood-tumor barrier permeability determines drug efficacy in experimental brain metastases of breast cancer. *Clin Cancer Res*. 2010;16(23):5664–5678.
105. Morikawa A, Peereboom DM, Thorsheim HR, et al. Capecitabine and lapatinib uptake in surgically resected brain metastases from metastatic breast cancer patients: a prospective study. *Neuro Oncol*. 2015;17(2):289–295.
106. Parrish KE, Sarkaria JN, Elmquist WF. Improving drug delivery to primary and metastatic brain tumors: strategies to overcome the blood–brain barrier. *Clin Pharmacol Ther*. 2015;97(4):336–346.
107. Lin NU, Gabrail NY, Sarantopoulos J, et al. Evaluation of CNS and peripheral antitumor activity of ANG1005 in patients with brain metastases from breast tumors and other advanced solid tumors. *ASCO Meeting Abstracts*. 2014;32(15_suppl):2523.
108. Jamal-Hanjani M, Spicer J. Epidermal growth factor receptor tyrosine kinase inhibitors in the treatment of epidermal growth factor receptor–mutant non–small cell lung cancer metastatic to the brain. *Clin Cancer Res*. 2012;18(4):938–944.
109. Clarke JL, Pao W, Wu N, et al. High dose weekly erlotinib achieves therapeutic concentrations in CSF and is effective in leptomeningeal metastases from epidermal growth factor receptor mutant lung cancer. *J Neurooncol*. 2010;99(2): 283–286.
110. Grommes C, Oxnard GR, Kris MG, et al. "Pulsatile" high-dose weekly erlotinib for CNS metastases from EGFR mutant non-small cell lung cancer. *Neuro Oncol*. 2011;13(12):1364–1369.
111. Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. *Lancet Oncol*. 2012;13(5):459–465.
112. Heller KN, Pavlick AC, Hodi FS, et al. Safety and survival analysis of ipilimumab therapy in patients with stable asymptomatic brain metastases. *ASCO Meeting Abstracts*. 2011;29(15_suppl):8581.
113. Italian Network for Tumor Biotherapy Foundation. A study of fotemustine (FTM) vs FTM and ipilimumab (IPI) or IPI and nivolumab in melanoma brain metastasis (NIBIT-M2). In: *ClinicalTrials.gov [Internet]*. Bethesda, MD: National Library of Medicine (US). 2015-[cited 2015 Nov 2]. Available from: http://clinicaltrials.gov/show/NCT02460068. NLM Identifier: NCT02460068.
114. Bristol-Myers Squibb. A multi-center phase 2 open-label study to evaluate safety and efficacy in subjects with melanoma metastatic to the brain treated with nivolumab in combination with ipilimumab followed by nivolumab monotherapy (CheckMate 204). In: *ClinicalTrials.gov [Internet]*. Bethesda, MD: National Library of Medicine (US). 2014-[cited 2015 Jun 22]. Available from: http://clinicaltrials.gov/show/NCT02320058. NLM Identifier: NCT02320058.
115. Besse B, Lasserre SF, Compton P, et al. Bevacizumab safety in patients with central nervous system metastases. *Clin Cancer Res*. 2010;16(1):269–278.
116. Lin NU, Gelman RS, Younger WJ, et al. Phase II trial of carboplatin (C) and bevacizumab (BEV) in patients (pts) with breast cancer brain metastases (BCBM). *ASCO Meeting Abstracts*. 2013; 31(15_suppl):513.
117. Besse B, Le Moulec S, Mazières J, et al. Bevacizumab in patients with nonsquamous non–small cell lung cancer and asymptomatic, untreated brain metastases (BRAIN): a nonrandomized, phase ii study. *Clin Cancer Res*. 2015;21(8): 1896–1903.
118. Centre Hospitalier Intercommunal Creteil. Comparison of two therapeutic strategies in patients with non-squamous non-small cell lung cancer (NSCLC) with asymptomatic brain metastases (METAL2). In: *ClinicalTrials.gov [Internet]*. Bethesda, MD: National Library of Medicine (US). 2014-[cited 2015 Nov 2]. Available from: http://clinicaltrials.gov/show/NCT02162537. NLM Identifier: NCT02162537.
119. Stricker T, Arteaga CL. Drug-resistant brain metastases: a role for pharmacology, tumor evolution, and too-late therapy. *Cancer Discov*. 2015;5(11):1124–1126.
120. Brastianos PK, Carter SL, Santagata S, et al. Genomic characterization of brain metastases reveals branched

evolution and potential therapeutic targets. *Cancer Discov*. 2015; 5(11):1164–1177.

121. Paik PK, Shen R, Won H, et al. Next-generation sequencing of stage iv squamous cell lung cancers reveals an association of PI3K aberrations and evidence of clonal heterogeneity in patients with brain metastases. *Cancer Discov*. 2015;5(6): 610–621.
122. Steeg PS. Perspective: the right trials. *Nature*. 2012;485(7400): S58–S59.
123. Boggs DH, Robins HI, Langer CJ, et al. Strategies to prevent brain metastasis in high-risk non-small-cell lung cancer: lessons learned from a randomized study of maintenance temozolomide versus observation. *Clin Lung Cancer*. 2014; 15(6):433–440.
124. Palmieri D, Duchnowska R, Woditschka S, et al. Profound prevention of experimental brain metastases of breast cancer by temozolomide in an MGMT-dependent manner. *Clin Cancer Res*. 2014;20(10):2727–2739.
125. Heon S, Yeap BY, Lindeman NI, et al. The impact of initial gefitinib or erlotinib versus chemotherapy on central nervous system progression in advanced non-small cell lung cancer with EGFR mutations. *Clin Cancer Res*. 2012;18(16):4406–4414.
126. Pivot X, Manikhas A, Zurawski B, et al. CEREBEL (EGF111438): 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. *J Clin Oncol*. 2015;33(14):1564–1573.
127. National Comprehensive Cancer Network. Central Nervous System Cancers (Version 1.2015). 2015; http://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed May 3, 2016.
128. Lin X, DeAngelis LM. Treatment of brain metastases. *J Clin Oncol*. 2015;33(30):3475–3484.
129. Arvold ND, Oh KS, Niemierko A, et al. Brain metastases after breast-conserving therapy and systemic therapy: incidence and characteristics by biologic subtype. *Breast Cancer Res Treat*. 2012;136(1):153–160.
130. Bendell JC, Domchek SM, Burstein HJ, et al. Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. *Cancer*. 2003;97(12): 2972–2977.
131. Lin NU, Dieras V, Paul D, et al. Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. *Clin Cancer Res*. 2009;15(4):1452–1459.
132. Bachelot T, Romieu G, Campone M, et al. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. *Lancet Oncol*. 2013;14(1):64–71.
133. Cortes J, Dieras V, Ro J, et al. Afatinib alone or afatinib plus vinorelbine versus investigator's choice of treatment for HER2-positive breast cancer with progressive brain metastases after trastuzumab, lapatinib, or both (LUX-Breast 3): a randomised, open-label, multicentre, phase 2 trial. *Lancet Oncol*. 2015;16(16):1700–1710.
134. Freedman RA, Gelman RS, Wefel JS, et al. Translational Breast Cancer Research Consortium (TBCRC) 022: a phase ii trial of neratinib for patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases. *J Clin Oncol*. 2016;34(9):945–952.
135. Awada A, Colomer R, Inoue K, et al. Neratinib plus paclitaxel vs trastuzumab plus paclitaxel in previously untreated metastatic ERBB2-positive breast cancer: the NEfERT-T randomized clinical trial. *JAMA Oncol*. 2016. doi: 10.1001/jamaoncol.2016.0237.
136. Bartsch R, Berghoff AS, Vogl U, et al. Activity of T-DM1 in Her2-positive breast cancer brain metastases. *Clin Exp Metastasis*. 2015;32(7):729–737.
137. Lim E, Lin NU. Updates on the management of breast cancer brain metastases. *Oncology (Williston Park)*. 2014;28(7): 572–578.
138. Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012;13(11):1087–1095.
139. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med*. 2015;372(1):30–39.
140. GlaxoSmithKline. Study to evaluate treatment of dabrafenib plus trametinib in subjects with braf mutation-positive melanoma that has metastasized to the brain. In: *ClinicalTrials.gov [Internet]*. Bethesda, MD: National Library of Medicine (US). 2013-[cited 2015 Nov 2]. Available from: http://clinicaltrials.gov/show/NCT02039947. NLM Identifier: NCT02039947.
141. University of Pittsburgh. Phase II study of cobimetinib in combination with vemurafenib in active melanoma brain metastases (CoBRIM-B). In: *ClinicalTrials.gov [Internet]*. Bethesda, MD: National Library of Medicine (US). 2014-[cited 2015 Nov 2]. Available from: http://clinicaltrials.gov/show/NCT02230306. NLM Identifier: NCT02230306.
142. Kluger HM, Goldberg S, Sznol M, et al. Safety and activity of pembrolizumab in melanoma patients with untreated brain metastases. *J Clin Oncol*. 2015;33(suppl):abstr 9009.
143. Fuerst ML. Pembrolizumab induces responses in melanoma patients with brain mets. In *Cancer Network [Internet]*. Published 2015 Nov 22. Cited 18 Feb 2016. Available from: http://www.cancernetwork.com/smr-2015/pembrolizumab-induces-responses-melanoma-patients-brain-mets.
144. Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med*. 2013; 369(2):122–133.
145. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N Engl J Med*. 2015;372(21):2006–2017.
146. Bearz A, Garassino I, Tiseo M, et al. Activity of Pemetrexed on brain metastases from non-small cell lung cancer. *Lung Cancer*. 2010;68(2):264–268.
147. Ceresoli GL, Cappuzzo F, Gregorc V, et al. Gefitinib in patients with brain metastases from non-small-cell lung cancer: a prospective trial. *Ann Oncol*. 2004;15(7):1042–1047.
148. Wu YL, Zhou C, Cheng Y, et al. Erlotinib as second-line treatment in patients with advanced non-small-cell lung cancer and asymptomatic brain metastases: a phase II study (CTONG-0803). *Ann Oncol*. 2013;24(4):993–999.
149. Dempke WC, Edvardsen K, Lu S, et al. Brain metastases in NSCLC: are TKIs changing the treatment strategy? *Anticancer Res*. 2015; 35(11):5797–5806.
150. Zhang I, Zaorsky NG, Palmer JD, et al. Targeting brain metastases in ALK-rearranged non-small-cell lung cancer. *Lancet Oncol*. 2015;16(13):e510–e521.
151. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med*. 2013;368(25):2385–2394.

152. Kodama T, Hasegawa M, Takanashi K, et al. Antitumor activity of the selective ALK inhibitor alectinib in models of intracranial metastases. *Cancer Chemother Pharmacol*. 2014;74(5):1023–1028.

153. Gadgeel SM, Gandhi L, Riely GJ, et al. Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): results from the dose-finding portion of a phase 1/2 study. *Lancet Oncol*. 2014;15(10):1119–1128.

154. Kim DW, Mehra R, Tan DS, et al. Activity and safety of ceritinib in patients with ALK-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial. *Lancet Oncol*. 2016. doi: 10.1016/S1470-2045(15)00614.2.

155. Ou SI, Ahn JS, De Petris L, et al. Alectinib in crizotinib-refractory ALK-rearranged non-small-cell lung cancer: a phase ii global study. *J Clin Oncol*. 2016;34(7):661–668.

156. Novartis. A phase II Study to evaluate the efficacy and safety of oral ceritinib in patients with ALK-positive NSCLC metastatic to the brain and/or to leptomeninges (Ascend-7). In: *ClinicalTrials.gov [Internet]*. Bethesda, MD: National Library of Medicine (US). 2015-[cited 2015 Nov 2]. Available from: http://clinicaltrials.gov/show/NCT02336451. NLM Identifier: NCT02336451.

157. Hoffmann-La Roche. ALEX study: a randomized, phase III study comparing alectinib with crizotinib in treatment-naive anaplastic lymphoma kinase-positive advanced non-small cell lung cancer participants. In: *ClinicalTrials.gov [Internet]*. Bethesda, MD: National Library of Medicine (US). 2014-[cited 2015 Nov 2]. Available from: http://clinicaltrials.gov/show/NCT02075840. NLM Identifier: NCT02075840.

158. Yale University. MK-3475 in melanoma and NSCLC patients with brain metastases. In: *ClinicalTrials.gov [Internet]*. Bethesda, MD: National Library of Medicine (US). 2014-[cited 2015 Jun 22]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02085070. NLM Identifier: NCT02085070.

159. Bristol-Myers Squibb. Study of nivolumab (BMS-936558) in combination with gemcitabine/cisplatin, pemetrexed/cisplatin, carboplatin/paclitaxel, bevacizumab maintenance, erlotinib, ipilimumab or as monotherapy in subjects with stage IIIB/IV non-small cell lung cancer (NSCLC) (CheckMate 012). In: *ClinicalTrials.gov [Internet]*. Bethesda, MD: National Library of Medicine (US). 2011-[cited 2016 Feb 18]. Available from: http://clinicaltrials.gov/show/NCT01454102. NLM Identifier: NCT01454102.

160. Yale University. Pembrolizumab plus bevacizumab for treatment of brain metastases in metastatic melanoma or non-small cell lung cancer. In: *ClinicalTrials.gov [Internet]*. Bethesda, MD: National Library of Medicine (US). 2016-[cited 2016 Feb 18]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02681549. NLM Identifier: NCT02681549.

161. Guerrieri M, Wong K, Ryan G, et al. A randomised phase III study of palliative radiation with concomitant carboplatin for brain metastases from non-small cell carcinoma of the lung. *Lung Cancer*. 2004;46(1):107–111.

162. Ushio Y, Arita N, Hayakawa T, et al. Chemotherapy of brain metastases from lung carcinoma: a controlled randomized study. *Neurosurgery*. 1991;28(2):201–205.

163. Antonadou D, Paraskevaidis M, Sarris G, et al. Phase II randomized trial of temozolomide and concurrent radiotherapy in patients with brain metastases. *J Clin Oncol*. 2002;20(17):3644–3650.

164. Verger E, Gil M, Yaya R, et al. Temozolomide and concomitant whole brain radiotherapy in patients with brain metastases: a phase II randomized trial. *Int J Radiat Oncol Biol Phys*. 2005;61(1):185–191.

165. Knisely JP, Berkey B, Chakravarti A, et al. A phase III study of conventional radiation therapy plus thalidomide versus conventional radiation therapy for multiple brain metastases (RTOG 0118). *Int J Radiat Oncol Biol Phys*. 2008;71(1):79–86.

166. Neuhaus T, Ko Y, Muller RP, et al. A phase III trial of topotecan and whole brain radiation therapy for patients with CNS-metastases due to lung cancer. *Br J Cancer*. 2009;100(2):291–297.