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Controversies in the Therapy of Brain Metastases: Shifting Paradigms in an Era of Effective Systemic Therapy and Longer-Term Survivorship

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Opinion statement

With the development of therapies that improve extracranial disease control and increase long-term survival of patients with metastatic cancer, effective treatment of brain metastases while minimizing toxicities is becoming increasingly important. An expanding arsenal that includes surgical resection, whole brain radiation therapy, radiosurgery, and targeted systemic therapy provides multiple treatment options. However, significant controversies still exist surrounding appropriate use of each modality in various clinical scenarios and patient populations in the context of cancer care strategies that control systemic disease for increasingly longer periods of time. While whole brain radiotherapy alone is still a reasonable and standard option for patients with multiple metastases, several randomized trials have now revealed that survival is maintained in patients treated with radiosurgery or surgery alone, without upfront whole brain radiotherapy, for up to four brain metastases. Indeed, recent data even suggest that patients with up to 10 metastases can be treated with radiosurgery alone

without a survival detriment. In an era of dramatic advances in targeted and immune therapies that control systemic disease and improve survival but may not penetrate the brain, more consideration should be given to brain metastasis-directed treatments that minimize long-term neurocognitive deficits, while keeping in mind that salvage brain therapies will likely be more frequently required. Less toxic therapies now also allow for concurrent delivery of systemic therapy with radiosurgery to brain metastases, such that treatment of both extracranial and intracranial disease can be expedited, and potential synergies between radiotherapy and agents with central nervous system penetration can be harnessed.

Introduction

Brain metastases are a common cause of morbidity and mortality in cancer patients and occur in approximately 10 % of all cancer patients, with the highest incidence in patients with lung cancer, followed by renal, melanoma, breast, and colorectal cancers [1–3]. The incidence of brain metastases is thought to be increasing with improved imaging techniques for detection and better local and systemic therapies that prolong survival [4]. Because most systemic therapies poorly penetrate the blood-brain barrier or are inactive in the central nervous system (CNS) microenvironment [5], surgery and radiation therapy have been the mainstays of treatment for brain metastases.

Whole brain radiation therapy (WBRT) was historically the standard of care with the goal of short-term palliation, until an early study demonstrated the potential survival benefit of more intensive local therapy with surgery in patients with limited brain metastases [6]. The introduction of stereotactic radiosurgery (SRS) to target individual metastases with ablative high-dose radiotherapy has since made an aggressive approach accessible for patients who are not otherwise surgical candidates, including those with multiple lesions, lesions in inaccessible locations, and other contraindications. Although no randomized data comparing resection and radiosurgery exist, radiosurgery results appear similar in properly selected patients, and it is now a generally preferred approach.

Localized therapy with radiosurgery treats identified brain metastases with a substantially higher radiation dose than is safe with WBRT, which is limited by risk to the normal brain. The use of radiosurgery is motivated not only by the goal of improving tumor control but also by diminished risk of neurocognitive effects from normal brain exposure [7, 8••]. Treatment with radiosurgery also generally allows faster initiation or less interruption of needed systemic therapies, which now have the potential to increase long-term survivorship with metastatic cancer [9, 10••, 11••]. Thus, SRS is now increasingly used in the treatment of brain metastases, both in the first-line setting as an alternative to surgery or WBRT, and in the adjuvant and salvage settings. There is level I evidence that radiosurgery alone in the first-line setting is appropriate for patients with 1–4 brain metastases [7, 12, 13••, 14], and additional data suggest it is appropriate for many patients with greater than four lesions [15••]. Neurosurgical resection is of particular value in confirming the diagnosis, removing large lesions that cannot be treated well with radiosurgery, and relieving symptoms and mass effect.

Motivated by advances in systemic therapies that are not fully active in the CNS but are increasing long-term survival, there is a need to develop optimal strategies to control brain disease while limiting treatment toxicities for patients who develop recurrence after local therapy. Repeat radiosurgery to new lesions appears appropriate, with use of surgery when needed [16–18, 19•, 20•, 21]. Development of systemic agents capable of stabilizing CNS disease remains a subject of active investigation and is beyond the scope of this review.

In this review, we discuss controversies involving (1) the appropriate use of radiotherapy, radiosurgery, and surgery for initial treatment of brain metastases; (2) post-resection management of brain metastases; (3) salvage therapy for new or recurrent brain metastases following prior treatment; and (4) combination systemic and CNS-directed radiation therapy.

Is there a benefit to aggressive local management of individual brain metastases?

Whole brain radiotherapy was traditionally the standard of care for brain metastasis, before routine use of modern brain imaging and the demonstration that therapy of individual gross lesions might be beneficial. The Radiation Therapy Oncology Group (RTOG) conducted randomized trials in the 1970s to test a variety of WBRT regimens and demonstrated median survivals of 15–18 weeks [22]. The poor survival outcomes observed may be related to the limited efficacy in controlling gross disease with palliative doses of radiation given to the whole brain, as well as the lack of effective therapies to control metastatic disease. Patients treated with WBRT experience significant short-term quality-of-life toxicities of fatigue and hair loss, and a proportion will develop meaningful long-term decline in neurocognitive function [7, 8••, 13••, 23, 24].

The desire to improve outcomes for patients with brain metastases led to trials testing alternative radiotherapy dosing [25], as well as the value of surgical resection for select patients. Patchell et al. demonstrated in a proof of principal randomized trial that intensive management with definitive local therapy (surgical resection), when added to WBRT for a single brain metastasis, significantly improved local control and survival, with median overall survival (OS) increased to 40 weeks from 15 weeks with WBRT alone [6]. The RTOG randomized trial 9508 investigated the similar question of adding SRS as aggressive local management to WBRT for patients with 1–3 brain metastases and found improved survival for the subgroup of patients with a single metastasis (6.5 months WBRT + SRS vs. 4.9 months WBRT only, $P = 0.04$) and improved performance status for all patients [26].

Radiosurgery alone, without whole brain radiotherapy, is an appropriate treatment option

In response to concerns about the risk of neurocognitive deficits associated with WBRT [24, 27, 28], the question arose of whether WBRT was necessary for lesions treatable by radiosurgery. Four randomized studies [7, 12, 13••, 14] have confirmed similar survival outcomes if WBRT is omitted, with a tradeoff of reduced side effects and risks balanced against a reduction in failure elsewhere in the brain when the whole organ is treated (Table 1). While local and distant intracranial recurrences and need for salvage therapy are reduced with WBRT in these studies, WBRT appears only to moderate but not eliminate these risks. For example, the incidence of new lesions was reduced from 48 to 33 % at 2 years in patients treated with radiosurgery or surgery followed by adjuvant WBRT in the European Organization for Research and Treatment of Cancer (EORTC) 22952-26001 randomized trial [14], but the median survival was similar at 10.9 versus 10.7 months. The absence of a resulting survival benefit is likely the result of successful salvage therapy, as well as the competing risk of death from other causes.

These randomized trials testing the value of WBRT also assessed quality of life and/or neurocognitive endpoints [7, 8••, 13••, 14, 29] and generally confirmed

Table 1. Randomized studies of radiosurgery with or without whole brain radiotherapy for brain metastases

Study (accrual years)	Eligibility	Treatment/ arms	Local control	Distant IC recurrence	Neurologic death	Median OS (months)
JROSG 99-1 [12] (1999–2003)	1–4 brain metastases, <3 cm diameter, KPS ≥ 70	1: WBRT + SRS (n = 65) 2: SRS only (n = 67)	1: 88.7 %[a] 2: 72.5 % (1-year actuarial rate)	1: 41.5 %[b] 2: 63.7 % (1-year actuarial rate)	1: 22.8 %[c] 2: 19.3 %	1: 7.5[d] 2: 8.0
MDACC [7] (2001–2007)	1–3 brain metastases, KPS ≥ 70	1: WBRT + SRS (n = 28) 2: SRS only (n = 30)	1: 100 %[e] 2: 67 % (1-year actuarial rate)	1: 27 %[f] 2: 55 % (1-year actuarial rate)	1: 25 %[g] 2: 27 %	1: 5.7[h] 2: 15.2
EORTC 22952-26001 [14] (1996–2007)	1–3 brain metastases, WHO PS 0–2	1: WBRT + SRS (n = 99) 2: SRS only (n = 100)	1: 81 %[i] 2: 69 % (2-year cumulative incidence)	1: 33 %[j] 2: 48 % (2-year cumulative incidence)	1: 28 %[k] 2: 44 %	1: 10.7[l] 2: 10.9

JROSG Japanese Radiation Oncology Study Group, *MDACC* MD Anderson Cancer Center, *EORTC* European Organisation for Research and Treatment of Cancer, *KPS* Karnofsky performance status, *WHO PS* World Health Organization performance status, *WBRT* whole brain radiation therapy, *SRS* stereotactic radiosurgery, *IC* intracranial, *OS* overall survival

[a] $P = 0.002$

[b] $P = 0.003$

[c] $P = 0.64$

[d] $P = 0.42$

[e] $P = 0.012$

[f] $P = 0.02$

[g] $P = 0.15$

[h] $P = 0.003$

[i] $P = 0.04$

[j] $P = 0.023$

[k] $P < 0.002$ (includes patients treated initially with either surgery or radiosurgery)

[l] $P = 0.89$ (includes patients treated initially with either surgery or radiosurgery)

superior outcomes with stereotactic radiotherapy alone. It had been proposed that early WBRT may decrease neurocognitive deficits from the development of new, symptomatic intracranial disease [30, 31] and thereby be of value. However, these randomized trials suggest better quality of life with omission of WBRT [7, 8••, 13••, 14], although one showed a higher incidence of drop in mini-mental status score over 2 years following treatment with SRS alone [29]. Our own data suggest that with routine imaging follow-up every 3 months for the first 2 years and then at longer intervals, most new intracranial disease is not symptomatic when detected. Even when new lesions are associated with neurologic deficits, most symptoms are reversed or at least improved with treatment [20•]. As such, SRS without WBRT is increasingly used in the management of brain metastases, with level I evidence supporting this approach for patients with up to four metastases based on similar survival outcomes and reduced treatment morbidity.

Should treatment with radiosurgery alone be used for all patient populations with 1–4 brain metastases?

Despite the results of randomized trials showing no survival benefit overall with addition of WBRT for 1–4 brain metastases, individual patients may choose this option to reduce the incidence of new brain lesions while accepting the risks of treatment toxicity. Prognostic groupings based on diagnosis have been proposed to help stratify patients and select appropriate treatments [32]. Although data are limited, it is hypothesized that there may be subgroups of patients who might have improved outcomes with the addition of WBRT based on their histology or other individual factors [33•]. Conversely, an individual patient data meta-analysis of three randomized trials of SRS with or without WBRT (discussed above) suggested an OS benefit with SRS alone in patients age 50 or younger [34•].

The decision may become more nuanced as more effective systemic therapies increase the prospects of long-term cancer survival for subgroups of patients, raising anew the issue of balance between brain recurrence over time and the long-term neurocognitive risks of therapy. Limited data are available about long-term survivors, but one series suggested that WBRT may not be meaningfully effective in eradicating distant disease, with distant intracranial failure rates at 5 years of 74.5 % for SRS alone and 61.8 % with the addition of WBRT ($P = 0.07$) [35]. Until more data are available, the approach may best be individualized based upon the patient's wishes.

Clearly, WBRT is necessary when there are too many lesions to target individually with safety, especially as the cumulative incidence of toxicity is expected to increase as more lesions are treated. Diffuse processes such as leptomeningeal disease require WBRT. In addition, bulky disease above 3 cm in size not planned for surgical resection is generally less effectively treated with SRS given dose constraints [36]. Small cell lung cancer is considered to be most optimally treated with WBRT not only because it may generally be a diffuse process with significant subclinical disease but also because it is radiosensitive, and the dose administered has a high chance of controlling disease.

Research is underway to minimize the neurocognitive toxicity of WBRT, although no strategy has yet been confirmed to be of meaningful benefit [37]. Hippocampal-sparing radiotherapy techniques have been promising with only limited recurrence in the under-dosed region [38•]. Drugs such as memantine and donepezil used in Alzheimer's disease may also be of modest benefit [39–41].

Is radiosurgery alone an appropriate choice for greater than four brain metastases?

Retrospective and prospective studies suggest the appropriateness of this approach, although the value has not been assessed in a phase III trial. Several retrospective studies demonstrated that survival is not impaired when treating patients with five or more metastases with SRS alone [42–44]. A recent multi-

institutional prospective observational study from the Japanese Leksell Gamma Knife Society, JLGK0901, evaluated patients with 1–10 brain metastases treated with radiosurgery alone [15••]. The study was confined to small volume disease, with the largest tumor limited to <10 mL in volume and <3 cm in longest diameter, and the cumulative volume of all lesions limited to ≤15 mL. No differences in OS, local recurrence, distant failure, or neurological death were seen between patients with 2–4 brain metastases and those with 5–10 metastases treated with SRS alone. In the group of patients with 5–10 lesions, 8 % were treated with salvage WBRT, 43 % with repeat radiosurgery, and 19 % developed leptomeningeal failure, compared to 10, 42, and 13 %, respectively, in the group with 2–4 lesions for whom radiosurgery is considered established standard management. Thus, while randomized data are still needed to guide management of multiple brain metastases, existing data suggest that SRS alone may be a reasonable approach for select patients seeking to avoid WBRT who present with small volume disease up to 10 metastases.

When should surgical resection be considered?

Although no randomized trials comparing surgery and radiosurgery have been successfully completed, retrospective studies have suggested similar survival outcomes in patients with a single brain metastasis. As surgery with post-operative radiotherapy compared with radiosurgery results in similar local control, it is expected that survival outcomes would also be similar [45–47]. Surgery is typically favored for large, symptomatic lesions, as it can provide immediate relief of mass effect and perilesional edema while limiting requirement of steroids [48, 49]. In addition, radiosurgery is less likely to be effective for lesions larger than 3 cm in size, as the dose that may be safely administered is limited [36]. Surgery is used when pathologic confirmation of metastatic disease is desired, as even in patients with known primary cancer, a new brain mass represents non-metastatic disease in approximately 10 % of cases [6]. Pathologic confirmation of recurrent disease is also an indication for surgical resection and is discussed in a later section.

Optimal post-resection therapy: whole brain radiotherapy or radiosurgery?

Radiotherapy is usually recommended after surgical resection of metastatic disease, as local recurrence is high in this situation where wide margins are generally not safely attained. An early randomized trial assessed the value of WBRT after surgical resection of brain metastasis [50] (Table 2). The addition of WBRT improved local and distant intracranial control and freedom from neurologic death, although no improvement in OS was noted (median OS ~40–50 weeks). In particular, resection bed failure was reduced from 46 to 10 % ($P < 0.001$). Similarly, the randomized EORTC 22952-26001 study, in which two of the four arms evaluated surgical resection followed by WBRT versus observation, demonstrated reduced local relapse (59 to 27 %, $P < 0.001$) and distant intracranial relapse (42 to 23 %, $P = 0.008$) but no difference in OS with WBRT [14] (Table 2). As these trials confirm high target lesion failure rates after surgical resection in

Table 2. Select studies of surgical resection with adjuvant radiotherapy for brain metastases

Study (accrual/treatment years)	Eligibility	Treatment/arms	Local recurrence	Distant IC recurrence	Median OS
Prospective					
Patchell et al., 1990 [6] (1985–1988)	Single resectable brain metastasis, KPS ≥ 70	1: Surgery + WBRT 36 Gy (n = 25, median follow-up 40 weeks) 2: WBRT only (n = 23, median follow-up 15 weeks)	1: 20 %[a] 2: 52 %	1: 20 %[b] 2: 13 %	1: 40 weeks[c] 2: 15 weeks
Patchell et al., 1998 [50] (1989–1997)	Single completely resected brain metastasis, KPS ≥ 70	1: Surgery + WBRT 50.4 Gy (n = 49, median follow-up 48 weeks) 2: Surgery only (n = 46, median follow-up 43 weeks)	1: 10 %[d] 2: 46 %	1: 14 %[e] 2: 37 %	1: 48 weeks[f] 2: 43 weeks
EORTC 22952-26001 [14] (1996–2007) 10.7 months[i] 2: 10.9 months	1–3 brain metastases, WHO PS 0–2	1: Surgery + WBRT 30 Gy (n = 81) 2: Surgery only (n = 79)	1: 27 %[g] 2: 59 %	1: 23 %[h] 2: 42 %	1:
Brennan et al. [51•] (2004–2009)	1–2 brain metastases, KPS ≥ 70	Surgery + tumor bed SRS (n = 39 patients/40 lesions, median dose 18 Gy, median follow-up 12 months)	15 %	44 %	14.7 months
Retrospective					
Hwang et al. [52] (1999–2008) 15.0 months[j] 2: 6.8 months	No prior SRS/WBRT, additional synchronous metastases allowed	1: Surgery + tumor bed SRS (n = 25) 2: Surgery + WBRT (n = 18) (not randomized, retrospectively evaluated)	1: 0 % 2: 25 % (crude rate)	1: 33 % 2: 25 % (crude rate)	1:
Jensen et al. [53] (2001–2009)	No prior WBRT, additional synchronous metastases allowed	Surgery + tumor bed SRS (n = 106 patients/112 lesions, median dose 17 Gy)	19.7 % (1-year K-M estimate)	64.6 % (1- year K-M estimate)	10.9 months
Prabhu et al. [54] (2007–2010)	No prior cranial RT, additional synchronous metastases allowed	Surgery + tumor bed SRS (n = 62 patients/64 lesions, median dose 18 Gy, median follow-up 9.7 months)	22 % (1-year K-M estimate)	51 % (1-year K-M estimate)	13.4 months
Minniti et al. [55] (2005–2012)	Single brain metastasis, >3 cm, no prior WBRT	Surgery + tumor bed SRS (n = 101 patients, 9 Gy ×3, median follow-up 16 months)	7 % (1-year K-M estimate)	50 % (1-year K-M estimate)	17 months
Atalar et al. and Choi et al. [56•, 57•]				DF: 54 %	17 months

Table 2. (Continued)

Study (accrual/treatment years)	Eligibility	Treatment/arms	Local recurrence	Distant IC recurrence	Median OS
(1998–2011)	No prior WBRT, additional synchronous metastases allowed	Surgery + tumor bed SRS (n = 165 patients/175 lesions, median follow-up 12.4 months)	10 % (1-year cumulative incidence)	LMD: 11 % (1-year cumulative incidence)	
Ojerholm et al. [58] (2007–2013)	No prior WBRT, additional synchronous metastases allowed	Surgery + tumor bed SRS (n = 91 patients/96 lesions, median dose 16 Gy, median follow-up 9.8 months)	18 % (crude rate)	DF: 64 % LMD: 14 % (crude rate)	22.3 months

EORTC European Organization for Research and Treatment of Cancer, *KPS* Karnofsky performance status, *WHO PS* World Health Organization performance status, *WBRT* whole brain radiation therapy, *SRS* stereotactic radiosurgery, *RT* radiation therapy, *K-M* Kaplan-Meier, *IC* intracranial, *DF* distant failure, *LMD* leptomeningeal disease, *OS* overall survival

[a] $P < 0.02$

[b] $P = 0.52$

[c] $P < 0.01$

[d] $P < 0.001$

[e] $P < 0.01$

[f] $P = 0.39$

[g] $P < 0.001$

[h] $P = 0.008$

[i] $P = 0.89$ (includes patients treated initially with either surgery or radiosurgery)

[j] $P = 0.08$

addition to expected distant brain recurrences, it is currently a standard of care to follow surgical resection with post-operative WBRT [49, 59, 60].

However, with the increasing use of SRS alone as the local therapy for brain metastases and association of WBRT with significant neurocognitive toxicities [7, 8••, 23, 24], post-operative SRS is now commonly administered as an alternative to post-operative WBRT [61, 62], with the goal of reducing the very high risk of recurrence in the operative bed. While no randomized trials comparing post-operative WBRT and SRS have been reported to date, this approach is supported by the studies discussed above demonstrating no detriment in survival when WBRT is omitted following SRS alone or surgical resection. Prospective and retrospective data summarized in Table 2 suggest that post-operative SRS is associated with local recurrence rates of 10–20 % and distant brain failure rates of 30–60 %, which are similar to outcomes with radiosurgery alone, and that survival is not adversely affected. Thus, while post-operative WBRT is currently the standard of care for resected brain metastases based on level I evidence, post-operative SRS is increasingly used to avoid or delay neurocognitive toxicities from WBRT. Ongoing prospective randomized studies comparing post-operative SRS versus WBRT or observation (NCCTG N107C, ClinicalTrials.gov.: NCT01372774; MD Anderson, ClinicalTrials.gov.: NCT00950001) should help identify which patients would benefit most from each approach, based on factors such as histology, tumor size and location, performance status, and extracranial disease status.

Is repeated radiosurgery for new brain metastases an appropriate management strategy?

Limited data exist to guide management of new brain metastases (distant brain failure) that appear after initial therapy [63], an occurrence expected to increase in incidence with longer survival following initial diagnosis of brain metastases. Options include salvage surgery, WBRT, and repeat SRS. Surgical resection in the salvage setting is valuable for pathologic confirmation of recurrence or for large, symptomatic lesions [21, 64, 65]. Studies of salvage surgery for recurrent lesions previously treated with surgical resection or radiosurgery have demonstrated median OS of 9–12 months following salvage surgery and minimal operative morbidity and mortality, although recurrences following salvage surgery were frequent in the absence of adjuvant radiotherapy [64–67]. As discussed in the previous section, resection is now typically followed by post-operative radiotherapy due to high operative bed recurrence rates with surgery alone [50].

Salvage WBRT even if the patient has received prior WBRT may be considered. Studies describing outcomes of whole brain re-irradiation have noted symptomatic improvement in 30–70 % of patients, minimal toxicity, and median OS following re-irradiation of 4–5 months [68–70]. Salvage WBRT following initial focal therapy is commonly practiced and was used for 16 % of patients in the JROSG 99-1 randomized study [12] and 31 % of patients in the EORTC 22952-26001 randomized study [14] who were initially treated with SRS or surgery alone. The "need" for later WBRT should not be considered a reliable metric of success of stereotactic therapy, as criteria for selecting salvage therapy are not well established and vary greatly among treatment teams.

More recently, mirroring the increased use of SRS in the initial setting, salvage SRS is now more widely employed, following both prior WBRT [71–73, 74•] and prior radiosurgery [16–18, 19•, 20]. In both settings, survival does not appear to be impaired by the use of salvage radiosurgery, with median OS of 8–13 months from the time of salvage SRS and 17–25 months from brain metastasis diagnosis [19•, 20•, 71–73]. Although there has been concern that once distant brain failure has occurred, it is likely that further lesions will rapidly develop resulting in adverse clinical outcomes, we have shown in a retrospective data set that patients who received three or more sessions of radiosurgery had favorable survival from diagnosis (32.5 months) [20•]. While selection factors are certainly responsible for this favorable survival outcome, the data suggest that repeated use of radiosurgery is appropriate for many patients.

Because of the lack of prospective evidence in the management of new/recurrent brain metastases following initial therapy, current clinical practice guidelines recommend individualizing treatment based on patient factors [63]. It is clear that with improvements in systemic therapy, a higher proportion of patients are likely to require salvage therapy for new or recurrent brain metastases during their lifetimes. Additional prospective studies are needed to identify patients who would benefit most from the various approaches, taking into consideration the risks of long-term toxicities and potential need for multiple brain treatments for long-term survivors.

Can systemic therapy be given concurrently with brain metastasis-directed therapy?

While most systemic therapies have limited CNS penetration, it may be beneficial to deliver systemic therapy concomitantly with brain radiotherapy in cases of active extra- and intracranial disease, as well as when agents with better CNS penetration are used to enhance anti-tumor effect in the brain. Concurrent delivery of systemic therapy and WBRT has been avoided due to concerns of increased neurotoxicity and worsening myelosuppression [75–80]. Even partial brain fractionated radiotherapy delivered to a significant area of brain has been shown to result in substantial myelosuppression, likely the result of exposure of a large proportion of circulating blood that flows through the brain [81, 82]. As a result, WBRT often results in an interruption or delay in systemic therapy of well over a month.

Radiosurgery is attractive as a treatment option that may not require interruption or delay in initiation of needed systemic therapies. Our retrospective analysis demonstrates no evidence of enhanced neurotoxicity and myelosuppression with concurrent systemic therapy (conventional chemotherapy, targeted therapy, or immune therapy) and brain SRS. Patients with a new diagnosis of primary cancer with brain metastasis may derive particular benefit from early concurrent systemic and brain-directed therapy [11••].

The development of targeted and immune systemic therapies may also provide new opportunities to improve outcomes and treatment tolerability [9]. A recent phase II study demonstrated that WBRT could be safely given concurrently with erlotinib with no increase in neurotoxicity [83•]. Recent studies evaluating combined treatment with SRS and BRAF inhibitors for melanoma brain metastases suggest no increased toxicity [84, 85], despite increased radiodermatitis noted with larger volume radiation combined with BRAF inhibition [86, 87]. Intriguingly, very

long-term survival has been demonstrated for patients with anaplastic lymphoma kinase (ALK)-rearranged non-small cell lung cancer (NSCLC) treated with highly effective ALK inhibitors along with brain management with radiosurgery or WBRT [10••]. For those beginning inhibitor therapy at or after the diagnosis of brain metastasis, median survival was 54.8 months from brain metastasis discovery, whereas it was still favorable at 28.4 months for those who developed brain metastasis while on inhibitor therapy. Over this prolonged period of survival, patients frequently required additional brain therapy, emphasizing that agents that improve systemic control but rarely penetrate the blood-brain barrier fully will create a cadre of patients who survive long enough to require several treatments to the brain.

Several ongoing prospective studies are evaluating combinations of WBRT or SRS with targeted or immune therapies primarily for lung cancer, breast cancer, and melanoma patients [9]. Thus, recent developments in systemic therapies, as well as increasing use of SRS for brain metastases, now allow for concurrent systemic and CNS-directed therapy, which will hopefully result in fewer interruptions in systemic therapy, as well as improved CNS disease control. Concurrent therapy may be particularly important for harnessing the potential abscopal effect of immune therapy [88, 89], and several recent studies have demonstrated improved outcomes with combined immune therapy and SRS for melanoma brain metastases [90•, 91•, 92•]. The efficacy of checkpoint inhibitor therapy for disease within the immune privileged CNS requires further investigation.

Compliance with Ethical Standards

Conflict of Interest

Colette J. Shen declares that she has no conflict of interest.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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