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Review

Management of patients with brain metastases from NSCLC without a genetic driver alteration: upfront radiotherapy or immunotherapy?

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***Abstract*:** Lung cancer is the second most common cancer and the most common cause of cancer-related death in the United States. Brain metastases (BM) are detected in 21% of patients with lung cancer at the time of diagnosis and are the sole metastatic site in 35% of patients with stage IV disease. The best upfront therapy for non-small-cell lung cancer depends on both tumor programmed death 1 ligand-1 (PD-L1) expression and the presence or absence of a targetable genetic alteration in genes such as epidermal growth factor receptor and anaplastic lymphoma kinase. In the absence of a targetable genetic alteration, options include chemotherapy, immune checkpoint inhibitors (ICIs), and ICI combined with chemotherapy. Upfront local therapy followed by systemic therapy is the current standard of care for the management of BM, and may include whole brain radiotherapy, stereotactic radiosurgery (SRS), or craniotomy for surgical resection followed by consolidative SRS. This paradigm is effective in achieving local control, but it remains unclear if this approach is necessary for every patient. Prospective and retrospective data suggest that ICIs with or without chemotherapy can have activity against BM; however, appropriately selecting patients who are able to safely forgo local therapy and start an ICI-based treatment remains a challenge. To be considered for upfront ICI-based therapy, a patient should be free of neurologic symptoms, lesions should be small and not located in a critical region of the central nervous system, if corticosteroids are indicated the requirement should be low (prednisone 10 mg/d or less), and PD-L1 expression should be high. The decision to proceed with upfront ICI without local therapy to BM should be made in a multidisciplinary fashion and patients should undergo frequent surveillance imaging so that salvage local therapy can be administered when necessary. Prospective clinical trials are needed to validate this approach before it can be widely adopted.

Keywords: brain metastases, immune checkpoint inhibitor, immunotherapy, non-small-cell lung cancer, radiotherapy, stereotactic radiosurgery

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Brain metastases in non-small-cell lung cancer

Lung cancer is the second most common cancer and the most common cause of cancer-related death in the United States. Annually, lung cancer causes more deaths than breast, prostate, and pancreatic cancer combined, and 2.5 times more deaths than colorectal cancer.[1] Non-small-cell lung cancer (NSCLC) is the most common lung cancer subtype accounting for approximately 83% of all cases, with adenocarcinoma and squamous cell carcinoma (SCC) accounting for approximately 55% and 30% of NSCLCs, respectively.[2]

To select the best first-line treatment for each patient with newly diagnosed advanced NSCLC, the tumor must be evaluated for predictive biomarkers, including programmed death 1 ligand-1 (PD-L1) expression by immunohistochemistry and activating genetic alterations amenable to targeted therapy by next-generation sequencing, colloquially referred to as driver alterations or driver mutations. Targetable genetic alterations are detected in less than half of patients with newly diagnosed advanced NSCLC. Examples include numerous epidermal growth factor receptor (*EGFR*) mutations (exon 19 deletion, exon 21 L858R, T790M), v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) mutations, human epidermal growth factor receptor 2 (*HER2*) mutations, Kirsten rat sarcoma viral oncogene homolog (*KRAS*) G12C mutations, mesenchymal–epithelial transition (*MET*) factor exon 14 skipping mutations, anaplastic lymphoma kinase (*ALK*) fusions, neurotrophic tyrosine receptor kinase (*NTRK*) fusions, rearranged during transfection (*RET*) fusions, and ROS proto-oncogene 1 (*ROS1*) fusions.[3] Patients with a targetable genetic alteration often benefit from oral tyrosine kinase inhibitor therapy. Many of these agents have excellent central nervous system (CNS) penetration, a tolerable side effect profile, and are efficacious in the treatment of both extracranial and intracranial metastatic disease. In the absence of a targetable genetic alteration, appropriate medical therapy involves the administration of chemotherapy, immune checkpoint inhibitors (ICIs), or ICI with chemotherapy.[4] In tumors with PD-L1 expression $\geqslant$50%, monotherapy with pembrolizumab (anti-PD-1), atezolizumab (anti-PD-L1), or cemiplimab (anti-PD-1) can be an effective and durable treatment.[5–7] For most patients, tumors without targetable genetic alterations and either low (1–49%) or absent (<1%) PD-L1 expression, combination ICI with chemotherapy is typically used as first-line therapy.[8]

Lung cancer is among the most common causes of intracranial metastatic disease accounting for 20% of all patients with brain metastases (BM).[9,10] BM are detected in 21% of patients with lung cancer at the time of lung cancer diagnosis and the CNS is the sole site of metastatic disease in 35% of patients with stage IV lung cancer. Multiple interventions are available for the upfront treatment of BM for patients without a targetable genetic alteration including systemic therapy, whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), and craniotomy for surgical resection. Given the high prevalence of BM in the lung cancer patient population and the high potential for severe morbidity or mortality due to BM, determining the best intervention or combination of interventions for each individual patient requires careful consideration of patient and tumor attributes such as size and number of BM, PD-L1 status, and the presence or absence of neurological symptoms. This review will summarize the evidence for the management of BM in patients with NSCLC without a targetable genetic alteration.

Local CNS therapy for treatment of NSCLC BM

Chemotherapy alone for NSCLC with BM results in inadequate intracranial response rates and poor survival. This led to the inclusion of local therapy – which includes radiotherapy and surgery – as a key element of routine care. The evolution of modern local therapy practices initially centered around local control of large or symptom-producing lesions and progressed to include treatment of all BMs identified on advanced imaging. Clinical trials evaluating the efficacy of craniotomy for surgical resection and WBRT were conducted concurrently and eventually culminated in craniotomy for surgical resection followed by consolidative radiotherapy as the standard of care for select patients. The introduction of SRS further revolutionized the local management of BM and now has supplanted WBRT in most cases.

Surgical management

Between 1990 and 1998, Patchell and colleagues published two studies that set the new standard for surgical BM management. While not specific to lung cancer, patients with a solitary, large, and symptomatic BM were randomized to either WBRT alone or craniotomy for surgical resection followed by WBRT. In all, 37 of the 48 enrolled patients (77%) had NSCLC, and those who underwent surgical resection with postoperative WBRT consolidation experienced a longer median overall survival (OS) (40 *versus* 15 weeks, $p < 0.01$) and a more durable response of functional independence (38 *versus* 8 weeks, $p < 0.005$).[11] These data highlight the uniqueness of the CNS in that unlike other organs in the body, a single metastasis in the CNS can severely impair function that is restored with local treatment in many cases. Moreover, preserving CNS function can improve survival.

A second important study randomized 95 patients with a solitary, large, and symptomatic BM to either craniotomy for surgical resection alone or surgery followed by WBRT. This study showed that postoperative WBRT provided better protection against tumor recurrence both at the surgical site, termed local recurrence (10% recurrence with WBRT *versus* 46% without WBRT, $p < 0.001$), and at other sites in the CNS, termed distant CNS recurrence (14% *versus* 37%, $p < 0.01$). While this combined modality approach did not improve the duration of functional independence compared to surgery alone, it reduced the number of deaths attributable to neurological causes (14% *versus* 44%, $p = 0.003$) and improved median OS (115 *versus* 81 weeks; RR 2.62, 95% CI 1.03–6.64; $p = 0.003$, $N = 82$).[12]

These data form the basis of modern methods for local control of BM. Surgery continues to be offered for relief of focal neurological deficits and management of patients with severe mass effect or impending herniation because no other therapy has demonstrated equal efficacy for these specific indications. Surgery is then followed by postoperative consolidative radiation with SRS directed at the surgical bed in nearly all cases (the replacement of WBRT with SRS is discussed below) to reduce the rates of local recurrence and improve survival.[13–15] In addition to intervening on surgical urgencies and emergencies including other CNS-specific complications such as symptomatic hydrocephalus, a surgical approach might be needed for patients in whom the diagnosis of BM is in question and tissue is required for a pathologic diagnosis.

Radiation management

Because chemotherapy alone was insufficient for local and distant CNS control and craniotomy for resection was limited by lesion size, number, and location, a new approach to the management of NSCLC with BM was needed to improve cancer outcomes. WBRT had been an established treatment for BM for several decades, but it was not until 1997 when Gaspar and colleagues used recursive partitioning analysis (RPA) of 1200 patients from three consecutive RTOG trials to show that an appropriately selected patient population could have a median survival of 7.1 months. Key criteria defining this population included patients who were less than 65 years of age, had a Karnofsky performance status (KPS) of at least 70, and controlled primary systemic disease. Based on these data, WBRT became the standard of care treatment for BM regardless of primary tumor type.[16–18]

After the widespread adoption of WBRT, two CNS-specific complications were observed. First, options to achieve local control of BM recurrence after prior WBRT were limited because only a small subset of patients can tolerate a repeat of WBRT and surgical resection is a viable option for only a minority of BM.[19,20] Second, because patients were living longer with improved systemic and CNS-directed therapy, the neurocognitive side effects of WBRT – decreased memory, executive function, and fine motor skills – became more apparent and dramatically reduced quality of life for many patients.[21,22] Despite the capacity of WBRT to reduce symptoms of BM and prolong life while sparing some patients the need for invasive surgery, it was clear that novel modalities to administer local therapy were needed, which led to the introduction of SRS in the management of BM.

SRS was originally intended as a modality of radiotherapy that delivers a high and very precisely collimated dose of radiation to CNS lesions in a single fraction. RTOG 9508 assessed the efficacy of an SRS boost following WBRT – that is, a standard dose of WBRT followed by SRS solely to the site of disease – in patients with 1–3 BM and found that when compared with WBRT alone, this approach decreased both local recurrence and tumor size at 3 months, improved KPS, and resulted in less steroid use over the subsequent 24 months. The SRS boost did not increase toxicity and it was therefore concluded that SRS used either with WBRT or as salvage therapy upon CNS recurrence was a safe treatment for BM.[23] Although a subgroup analysis of the RTOG 9508 cohort revealed that patients with SCC histology experienced a worse survival than patients with adenocarcinoma histology, other investigators have not identified a difference in survival between patients with different NSCLC subtypes.[23,24] In patients with 2–4 BM, WBRT with an SRS boost resulted in better duration of local control than WBRT alone. The median time to local recurrence for WBRT alone was 6 months (95% CI: 3.5–8.5) and for WBRT plus SRS was 36 months (95% CI: 15.6–57).[25] However, neither study was able to demonstrate a survival benefit with the addition of the SRS boost.

Although an SRS boost did not appear to improve survival, numerous other benefits quickly became

apparent. First, treatment could be completed in a single day with minimal disruption to the delivery of systemic therapies while administering higher doses of radiation to BM than were possible with WBRT. Second, SRS was effective in the treatment of both radiosensitive and radioresistant pathologies with minimal injury to surrounding healthy tissue and therefore fewer side effects. Third, with the advancement and widespread availability of advanced neuroimaging capabilities – magnetic resonance imaging (MRI) as the preferred imaging modality, and high-resolution computed tomography when MRI is not available or safe – it was now possible to detect and use SRS to treat BM before they became symptomatic. This approach was assessed in 52 patients who received standard of care (WBRT after the detection of a symptomatic BM) and 80 patients who underwent routine surveillance by MRIs of the brain every 3 months to detect and treat new or re-growing metastases while they were clinically occult. Although surveillance imaging did not improve survival, it did reduce rates of death due to neurological causes (16% *versus* 48%, $p = 0.009$). This approach is ideal for patients with NSCLC because approximately 50% of patients with BM at time of diagnosis are asymptomatic.[26] This study provides support for the implementation of screening and surveillance CNS imaging at diagnosis and during treatment for metastatic NSCLC and forms the basis for standard of care at many institutions.

As the benefits of SRS over WBRT became more evident – namely easier implementation, less time required, and fewer neurocognitive side effects without a difference in survival – the time had come to redefine the role of WBRT in the treatment of BM. A retrospective analysis of 2319 patients from 2 prospectively collected databases showed that SRS alone for 11–20 BM *versus* 5–10 BM was not unfavorable in carefully selected patients, namely those with modified RPA classes 1, 2A, and 2B.[27] WBRT *versus* SRS *versus* WBRT plus SRS were evaluated in a meta-analysis that analyzed 763 patients from five randomized clinical trials. This study included 202 patients (26%) treated with WBRT alone, 196 patients (26%) treated with SRS alone, and 365 patients (48%) treated with WBRT plus SRS. The analysis showed that WBRT plus SRS achieved better local control than SRS alone (HR: 2.05, 95% CI: 1.36–3.09, $p = 0.0006$) or WBRT alone (HR: 1.84, 95% CI: 1.26–2.740, $p = 0.002$) without a difference in grade $\geqslant 2$ adverse events or OS.[28] Irrespective of both the primary tumor type and the presence or absence of targetable genetic alterations, this finding has been recapitulated in multiple studies. The JROSG 99-1 trial randomized patients with 1–4 BM to either SRS alone or WBRT plus SRS and showed that the distant CNS recurrence rate was 63.7% in the SRS group compared with 41.5% in the WBRT group ($p = 0.03$).[29] Brown *et al.*[30] strengthened the evidence for SRS over WBRT in a study of patients with 1 to 3 BM that showed that SRS alone resulted in less cognitive deterioration at 3 months (63.5% *versus* 91.7% of patients with cognitive deterioration, $p < 0.001$) than SRS plus WBRT. SRS therefore became the first-line radiotherapy for BM in patients not requiring WBRT (e.g. patients with innumerable BM) or craniotomy for surgical resection.

Although SRS had become the preferred method for administering radiotherapy in most cases, prospective data were needed to define the maximum number of BM that could be safely treated with SRS. In 2020, data from a prospective phase III trial showed that SRS could be administered to patients with up to 15 BM. In this study of 72 patients with 4–15 nonmelanoma BM randomized to SRS or WBRT, median OS (10.4 months for SRS and 8.4 months for WBRT, $p = 0.45$) and rates of local control (100% for SRS *versus* 96% for WBRT) were similar between the two groups, but SRS caused fewer neurocognitive symptoms with the expected trade-off of higher rates of distant CNS recurrence, likely due to persistence of radiographically invisible micrometastatic disease not treated by SRS alone.[31] Based on institutional expertise and anecdotal experience, some institutions may apply SRS to more than 15 lesions. To approximate the maximum number of lesions that can be safely treated with single fraction SRS, our institution performed a retrospective study that suggested beyond 25 lesions the cumulative whole-brain radiation exposure is equivalent to approximately 4 Gy, which is the currently acceptable threshold for any single fraction irradiation of healthy brain tissue.[32] However, there are currently no published data that measure the neurocognitive consequences of single fraction 4 Gy to the whole brain.

Although SRS is now the preferred modality of local therapy in most cases because it causes lower rates of adverse events associated with other forms of local therapy, it is associated with an increased risk of radiation necrosis. This is a phenomenon in

which treated lesions may enlarge radiographically and acquire surrounding edema leading to a decrease in neurological function for nonmalignant reasons. It can be seen radiographically in up to 17% of patients surviving beyond 12 months and become symptomatic in about 5% of patients. Symptoms of radiation necrosis, should they occur, can be treated with steroids, bevacizumab, laser interstitial therapy, or surgical resection.[33–35]

Overall, the superior toxicity profile, equivalent efficacy for local control, capability for recurrent use as both a standalone treatment for new BM at previously untreated sites and in combination with CNS-penetrating therapy, and ability to precisely target lesions that are not amenable to surgery due to their location (in particular, proximity to critical neurological structures) have made SRS the recommended form of radiotherapy for BM in most cases.[36–42] The trade-off of using SRS without WBRT is the loss of control of micrometastatic disease leading to higher rates of distant CNS recurrence, but in the authors' opinion, the ability to salvage these sites with SRS at the time of recurrence makes this compromise worth the reduction in toxicity from WBRT in many cases.

Systemic therapy for treatment of NSCLC BM

Although local therapy for BM is effective, it remains unclear whether it is necessary for all patients. The possibility of omitting local therapy for BM that are small and asymptomatic in patients who are expected to experience a long-term response to systemic therapy regimen has enormous potential benefit. Omission of radiotherapy in those who have a good systemic therapy option may spare patients the acute and chronic neurocognitive dysfunction from WBRT, radiation necrosis from SRS, and added cost of local therapy, thereby leading to an improvement in quality of life and avoidance of potentially life-threatening complications without compromising intracranial disease control.[21,22,43] This section will summarize the data that support the use of systemic therapy (including chemotherapy with or without bevacizumab, ICI alone, and ICI with chemotherapy) for patients with BM.

Activity of chemotherapy alone and with bevacizumab for treatment of NSCLC BM

Before the era of immune checkpoint blockade and targeted therapy, systemic treatment for NSCLC BM relied upon a backbone of conventional platinum-based chemotherapy with the later addition of bevacizumab, a monoclonal antibody that inhibits vascular endothelial growth factor. Platinum-based chemotherapies, such as cisplatin and carboplatin, are active against NSCLC when combined with a microtubule inhibitor (e.g., paclitaxel and vinorelbine), topoisomerase inhibitor (e.g., etoposide), or the methotrexate derivative pemetrexed, depending on the histologic subtype.[44–47] These chemotherapy combinations have some efficacy in the treatment of BM but a theoretical concern for decreased efficacy in the BM population due to poor CNS penetration prompted CNS-specific assessment of response rates and survival. In a study of 107 patients with BM, an intracranial objective response rate (ORR) of 30% ($N = 43/107$) was observed in patients with lung cancer.[46] One study of 26 patients with treatment-naive BM from NSCLC who were treated with cisplatin and paclitaxel, and either gemcitabine ($N = 15$, 58%) or vinorelbine ($N = 11$, 42%) showed that intracranial *versus* extracranial ORRs may be similar (intracranial ORR 38%), but with a dismal median OS of only 21.4 weeks.[45] To improve the efficacy of chemotherapy for BM, carboplatin and paclitaxel were evaluated in combination with bevacizumab in 67 patients and showed a global ORR of 63% and intracranial ORR of 61% with a median progression-free survival (PFS) of 6.7 months and OS of 16.0 months.[48] Although chemotherapy alone or with bevacizumab is active in some patients with NSCLC, responses are seldom durable leading to poor OS.

ICIs alone for management of BM

Soon after ICIs were introduced into NSCLC treatment, it became clear that dramatic and durable systemic responses could be achieved. But the persistent concern about CNS penetration resulting in poor intracranial response and OS led to the exclusion of patients with active or untreated BM from nearly all large, randomized trials of ICIs, complicating the assessment of ICI activity against active BM. However, with numerous post hoc analyses of large trials it soon became apparent that nearly every ICI that is active extracranially in NSCLC also has at least some CNS activity. In a pooled analysis of four pivotal trials that compared the PD-1 inhibitor pembrolizumab with chemotherapy beyond first-line therapy (KEYNOTE-001, -010, -024, and -042) in PD-L1-positive tumors, pembrolizumab dramatically improved survival in

patients with BM. Patients with tumors who were with PD-L1 tumor proportion score (TPS) of ⩾ 50% derived the greatest benefit from pembrolizumab monotherapy with a median OS of 19.7 months (95% CI: 12.1−31.4) *versus* 9.7 months (95% CI: 7.2–19.4) for those treated with chemotherapy alone, but any PD-L1 positivity conferred a survival benefit if treated with pembrolizumab with a median OS of 13.4 months (95% CI: 10.4–18.0) *versus* 10.3 months (95% CI: 8.1–13.3) for those treated with chemotherapy.[49]

Similar to pembrolizumab, nivolumab, another anti-PD-1 therapy, has activity in NSCLC BM. In an expanded access program with 1588 patients (26% with BM) from 153 medical centers throughout Italy who had progressed after at least one prior therapy, 1-year OS in the BM subgroup was 43%, which was similar to the entire cohort (48%), as were disease control rates (40% *versus* 44%) and ORR (17% *versus* 18%). Patients were limited to 10 mg/d of prednisone or equivalent.[50]

The efficacy of atezolizumab, an anti-PD-L1 therapy, has also demonstrated benefit in patients with BM. A pooled safety analysis was conducted on five trials with either a single-arm design with atezolizumab alone or a two-arm design with atezolizumab *versus* docetaxel in both the recurrent and first-line settings (PCD4989g, BIRCH, FIR, POPLAR, and OAK). Of the 1452 patients evaluated, 79 had BM that required treatment before enrollment. In the OAK subgroup, atezolizumab conferred an OS benefit for patients with BM with a HR of 0.54 (95% CI: 0.31–0.94). Atezolizumab was associated with a nonsignificant reduction in the risk of developing new BM (HR: 0.42, 95% CI: 0.15–1.18).[51,52]

The combination of anti-PD-1 (nivolumab) and anti-CTLA-4 (ipilimumab) has been well studied in other malignancies and is also effective for the treatment of BM in patients with NSCLC. CheckMate-227 was a factorial study design with four treatment groups and two primary endpoints (OS and PFS) comparing ipilimumab/nivolumab with histology-appropriate chemotherapy, both for PD-L1-positive tumors. Of the 135 patients with BM combined between the ipilimumab/nivolumab ($N = 69$) and chemotherapy ($N = 66$) arms ipilimumab/nivolumab conferred an OS benefit (HR: 0.57, 95% CI: 0.38–0.85).[53,54]

Overall, subgroup analyses of large, randomized trials suggest that ICIs are an effective treatment for NSCLC with BM, heterogeneity within the subgroup of patients with BM at the time of enrollment and the requirement in nearly every trial that patients receive local therapy prior to initiating systemic therapy pose a major challenge in interpreting the efficacy of ICIs to treat BM in these post hoc analyses. For example, some studies permitted patients to receive steroids at ⩽10 mg/d prednisone or equivalent, and others required patients to be off steroids entirely before enrollment. Additionally, all patients were treated on a clinical trial and therefore had a good performance status, which is not representative of the real-world treatment setting for many patients with BM from NSCLC. To address the heterogeneity within clinical trial subgroup analyses, several groups have retrospectively evaluated patients who received upfront ICI (Table 1). Although these trials are heterogeneous and some patients included in these analyses had received local therapy, these data suggest that upfront ICIs administered without local therapy can be effective as primary treatment for BM for a subset of patients.

To our knowledge, only one trial has prospectively evaluated the safety and activity of ICI alone in the management of asymptomatic, untreated BM. A prospective phase II study for ICI-naive patients with NSCLC with BM evaluated the activity of pembrolizumab alone. Patients could have any number of BM, provided they were less than 2.0 cm in size, untreated or progressing despite radiotherapy, and without neurological symptoms. The primary endpoint was the BM response rate in PD-L1-positive patients, which was found to be approximately 30% ($N = 11/37$). Patients with PD-L1 <1% or PD-L1 unevaluable were evaluated in a separate cohort ($N = 5$); however, no intracranial responses were observed. The median time to response was 1.8 months (IQR: 1.7–2.4), median PFS was 1.9 months (95% CI: 1.8–3.7), median intracranial PFS was 2.3 months, and median OS was 9.9 months (95% CI: 7.5–29.8), with an estimated 1-year OS of 40% (95% CI: 30–64%) and 2-year OS of 34% (95% CI: 21–54%). The systemic toxicity profile of patients treated with pembrolizumab was consistent with other studies of anti-PD-1 therapy. The neurological toxicity profile was mostly grade 1–2 adverse events except for grade 3 cognitive dysfunction, seizure, and stroke in one patient each, all deemed unrelated to study drug. Six patients experienced a discordant response to pembrolizumab – three patients experienced CNS progression despite

Table 1. Summary of retrospective and prospective studies of ICI for treatment of BM due to NSCLC.

Study Design	Treatment	Patients with BM*	Patients on steroids	Patients with local therapy within 2 months	Patients with PD-L1 ⩾1%[a]	ORR (%)	iORR (%)	PFS (months, 95% CI)	iPFS (months, 95% CI)	OS (months, 95% CI)	Ref
Retrospective	Nivolumab	100% (*N* = 5)	0%	0%	–	40	40	–	–	–	Li *et al.*[55]
Retrospective	Nivolumab	40% (*N* = 19)	–	79% (*N* = 15)	–	11	0[†]	2.0	–	NR	Abdulhaleem *et al.*[56]
Retrospective	Nivolumab	100% (*N* = 43)	–	16% (*N* = 7)	–	14	11	2.8 (1.8–5.3)	3.9 (2.8–11.1)	NR	Scoccianti *et al.*[57]
Retrospective	Any anti-PD-(L)1	25% (*N* = 255)	27.4% (*N* = 69)	–	62% (*N* = 51)	21	27	1.7 (1.5–2.1)	–	8.6 (6.8–12.0)	Vogelbaum *et al.*[15]
Prospective[‡]	Pembrolizumab	100% (*N* = 42)	–	–	88.1% (*N* = 37)	19	30	1.9 (1.8–3.7)	2.3 (1.9–NR)	9.9 (7.5–29.8)	Borghaei *et al.*[53], Hellmann *et al.*[54]
Retrospective	Pembrolizumab ± chemotherapy	22% (*N* = 131)	22% (*N* = 29)	48% (*N* = 63)	–	–	31[‡]	9.2	–	18.3	Sun *et al.*[58]
Prospective[⁂]	Atezolizumab + Chemotherapy	100% (*N* = 40)	55% (*N* = 22)	0%	50% (*N* = 20)	40	40	8.9 (6.7–13.8)	6.9 (4.7–11.9)	13.6 (9.7–NR)	Powel *et al.*[59], Paz-Ares *et al.*[60]

*N represents the total number of patients with BM.
[a]Denominator includes only patients with known PD-L1 status.
[†]CNS response only evaluable for 12 of the 19 patients with BM.
[‡]Response rates and survival are listed only for patients in cohort 1, which included all 37 PD-L1-positive patients.
[‡]Denominator includes only patients treated with pembrolizumab alone (*N* = 13).
[⁂]Global ORR and PFS not reported. ORR and PFS describe extracranial ORR and PFS.
OS, PFS, iPFS, ORR, and iORR apply only to patients with BM unless otherwise specified.
BM, brain metastases; iORR, intracranial ORR; iPFS, intracranial PFS; NR, not reached; ORR, objective response rate; OS, overall survival; PD-L1, programmed death 1 ligand-1; PFS, progression-free survival.

extracranial response, and another three patients experiencing CNS response despite extracranial progression. This was the first prospective study to demonstrate efficacy of ICI monotherapy for the management of untreated and asymptomatic BM.[61,62] Although PD-L1 was not routinely measured in BMs in this study, theoretically discordant PD-L1 expression between intracranial and extracranial sites is one possible explanation for discordant responses. However, literature assessing PD-L1 expression at multiple sites are conflicted. For example, one study demonstrated discordance between BM and systemic disease sites in up to 20% cases while another study showed no significant difference in PD-L1 expression between BM and primary lung tumor.[63,64] Therefore, additional studies are needed to better understand mechanisms of discordant responses to ICI-based therapy, which could improve future patient selection approaches for upfront ICI-based therapy. It is also important to recognize that although the activity of pembrolizumab in lung cancer BM can be robust, the intracranial response rate is inferior to that which is observed in studies of SRS. This emphasizes the vital importance of closely monitoring patients treated with upfront ICI alone to allow ample time for salvage local therapy, should upfront ICI therapy fail to control intracranial disease.

ICIs with chemotherapy for management of BM

A common first-line treatment regimen for patients with metastatic NSCLC includes combining ICI with chemotherapy, which is based on data from several large, randomized trials. Among these trials, both KEYNOTE-189 and -407 permitted enrollment of patients with asymptomatic untreated BM <1.5 cm and without a corticosteroid requirement. In a pooled analysis of all patients with BM enrolled in KEYNOTE-021, -189, and -407, in which pembrolizumab with chemotherapy was compared to chemotherapy alone, ICI therapy was effective in patients with BM regardless of PD-L1 status. Patients with BM treated with pembrolizumab plus chemotherapy exhibited a median OS of 18.8 months (95% CI: 13.8–25.9) *versus* 7.6 months (95% CI: 5.4–10.9) for those treated with chemotherapy alone.[49,59]

CheckMate-9LA was a large study that evaluated chemotherapy alone with combination anti-PD-1/anti-CTLA-4 plus chemotherapy. Of the 122 patients (17%) with BM in the study, ipilimumab/nivolumab/chemotherapy provided a substantial survival advantage with a median OS of 19.9 months (95% CI: 12.4–25.6) *versus* 7.9 months (95% CI: 5.0–10.7) compared to chemotherapy alone.[60,65]

A single-arm phase II trial (ATEZO-BRAIN) is prospectively evaluating the use of atezolizumab plus chemotherapy for upfront management of patients with non-squamous NSCLC and untreated, asymptomatic BM. Of the 40 patients enrolled so far, 42.5% were receiving $\leqslant 4$ mg/d of dexamethasone, a higher equivalent dose than the 10 mg/d of prednisone equivalent that is typically considered acceptable with checkpoint inhibitor administration.[66] This combination seems to be safe and effective with 16 (40%) patients having achieved an intracranial ORR (including 4 complete responses), and an observed median intracranial PFS of 6.9 months (95% CI: 4.7–11.9) and median OS of 13.6 months (9.7–NR). Similar to the trial of pembrolizumab monotherapy for untreated BM, a discordant response was observed in four patients.[67,68] Currently, there is strong evidence to support the use of ICI in combination with chemotherapy for patients with NSCLC and BM. This trial, which is the first trial of ICI with chemotherapy for NSCLC with untreated BM, is ongoing but preliminary data suggest that this combination is efficacious and safe.

Concurrent immunotherapy and local therapy for BM

Despite the durable CNS activity of ICI therapy in a subset of patients with NSCLC, there is insufficient evidence to shift the treatment paradigm of upfront local therapy to systemic therapy for every patient and the standard of upfront SRS followed by ICI therapy remains. An important avenue of research involves the concurrent administration of ICI with radiotherapy, which has been repeatedly demonstrated in numerous murine models of cancer to create synergy between immunotherapy and radiotherapy and may improve outcomes for patients with BM.[69–71] However, it is possible that when SRS is combined with ICI the risk for toxicity (particularly radiation necrosis) increases, and this has been one of the focal points for evaluating the safety of this combination. In addition to assessing safety of SRS with ICI upfront (SRS + ICI), several investigators have evaluated both the efficacy and safety of this approach compared to SRS alone or ICI alone.[33–35,72]

Safety data are available from one prospective single-arm phase I/II single institution study of ipilimumab/nivolumab with SRS to be administered within 7 days of ICI initiation. Dose-limiting toxicities (DLT), which were defined as >15% intracranial toxicity (grade >3 hypophysitis or neurologic toxicity) or >30% extracranial toxicity (grade >4 laboratory or dermatologic toxicity, or grade >3 non-laboratory or non-dermatologic toxicity). At the time this data were reported, 13 patients were enrolled and 10 were evaluable for a DLT. Only one patient had experienced a DLT and thus the stopping criteria were not met, suggesting that anti-PD-1/anti-CTLA-4 plus SRS for the treatment of BM may be safe.[55]

Retrospective studies that have attempted to determine whether SRS + ICI confers a survival advantage have yielded mixed results. The most dramatic example is an analysis of 80 patients with BM from NSCLC treated with SRS + ICI (defined as having received ICI within 30 days of SRS) and 235 patients with BM from NSCLC treated with SRS alone and showed a median OS of 40 months *versus* 8 months (HR for OS of 0.285, 95% CI: 0.19–0.43; HR for local control of 0.12, 95% CI: 0.01–0.57).[56] On the contrary, a large retrospective series of 150 patients with BM from NSCLC ($N=100$ treated with SRS + ICI and $N=50$ treated with SRS alone) did not observe a difference in OS.[57]

Whether SRS + ICI provides a local control benefit over SRS alone also remains unclear. In the same series of 150 patients, SRS + ICI reduced the risk of local CNS recurrence at both 6 and 12 months (HR: 0.32, 95% CI: 0.14–0.73; $p=0.007$) and was not associated with a difference in rate of radiation necrosis, but also did not reduce distant CNS recurrence.[57] An analysis of 85 patients with NSCLC – 39 were treated with SRS + ICI and 46 were treated with SRS followed by chemotherapy – did not find that SRS + ICI resulted in better local control than SRS monotherapy. They found the lesional response rate and time to maximal response were not different between the two groups; however, patients were not divided by PD-L1 status and survival was not different between the two groups. Although it remains unclear whether SRS + ICI confers a survival or recurrence benefit, most studies did not observe a difference in radiation necrosis or neurological complications between groups suggesting that this combination may be safe.

In general, retrospective studies of SRS + ICI are very heterogeneous and difficult to interpret because the average number of treated and untreated lesions per patient, total volume of lesions treated, and the definition of concurrent SRS + ICI therapy are variable. For example, some studies considered ICI administration within 30 days of SRS to be concurrent therapy, while others strictly adhered to a 7-day cutoff, and others yet to a 3-month cutoff. Taken together, it is unclear exactly how to define concurrent therapy, and therefore challenging to draw a conclusion about the efficacy of SRS + ICI. Importantly, there are no published studies comparing SRS + ICI with ICI alone. Prospective trials are required to evaluate the efficacy of SRS + ICI *versus* either SRS alone or ICI alone, and to confirm that SRS + ICI does not increase the risk of delayed occurrence of radiation necrosis when compared with SRS alone.

Discussion

Here we reviewed the data supporting the use of local therapy, ICI alone, ICI with chemotherapy, and SRS + ICI in patients with BM from NSCLC without a targetable genetic alteration. Because most targeted therapies result in excellent CNS penetration and high extracranial and intracranial ORR, the majority of patients with BM from NSCLC that harbor a targetable genetic alteration often proceed directly to systemic therapy with deferral of local therapy for BM until intracranial progression.[15] However, the management of BM in patients with NSCLC without targetable genetic alterations is more challenging because the available systemic therapies (including platinum-based chemotherapy alone or with bevacizumab, ICI alone, or ICI with chemotherapy) typically have lower intracranial and extracranial response rates than can be expected with targeted therapies.

Despite the lack of randomized data, in the authors' opinion. there are two scenarios in which upfront ICI-based therapy might be considered for treatment of NSCLC BM without the use of upfront local therapy. These include (1) patients who might be expected to have an excellent and durable response to treatment and (2) patients with innumerable asymptomatic BM making SRS an unrealistic option and for which WBRT would be required for local therapy, provided the BMs are asymptomatic and no larger than 1 cm.

The phase II trial of pembrolizumab for untreated BM showed that upfront ICI alone allowed some patients to forgo local therapy entirely, reserving SRS for salvage local therapy without a clinically significant increase in neurologic adverse events.[62] The ongoing phase II trial of atezolizumab plus chemotherapy for a similar patient population also suggests that deferring local therapy and proceeding directly to systemic therapy with ICI plus chemotherapy is safe and effective in the appropriate patient population; however, this approach is still an undergoing evaluation and is not yet ready to be introduced into routine clinical practice for most patients.[68] Because response rates to ICI alone are inferior to SRS, even in a biomarker-selected population, patients treated with upfront ICI alone require frequent serial imaging for close monitoring of BM. At our institution, patients undergo repeat CNS imaging every 6 weeks until disease stability is confirmed after which imaging is obtained less frequently. This approach will enable early detection of lesions that are not responding to ICI therapy and allow ample time to administer salvage local therapy before neurological symptoms occur. Because this approach is novel and deviates from a decade-long paradigm of local therapy followed by systemic therapy, the decision to proceed with upfront ICI therapy alone must be made in a multidisciplinary fashion.

Conclusions

The optimal management for patients with BM from NSCLC without a targetable genetic alteration is actively evolving as systemic therapy options improve. The standard treatment for most patients is still SRS followed by systemic therapy with ICI and with or without platinum-based chemotherapy, but in select cases we recommend consideration of upfront ICI-containing systemic therapy with deferral of local therapy. The latter appears to be safe and effective when applied to an appropriate patient; thus, the use of specific selection criteria is the key, and this treatment approach should only be chosen after a multidisciplinary discussion. Concurrent SRS + ICI shows promise, but the benefit of this approach has not been confirmed prospectively. Clinical trials are needed for additional safety and efficacy evaluation of upfront ICI-containing regimens compared to upfront SRS, as well as to determine the ideal patient selection criteria for each therapeutic approach with the ultimate goal of optimizing quality of life, decreasing neurological morbidity, and improving OS in patients with metastatic NSCLC with BM.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contribution(s)

Ross D. Merkin: Conceptualization; Writing – original draft; Writing – review & editing.

Veronica L. Chiang: Conceptualization; Writing – original draft; Writing – review & editing.

Sarah B. Goldberg: Conceptualization; Supervision; Writing – original draft; Writing – review & editing.

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