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LUNG CANCER (H BORGHAEI, SECTION EDITOR)

Emerging Trends in the Management of Brain Metastases from Non-small Cell Lung Cancer

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Abstract

Purpose of Review To summarize current approaches in the management of brain metastases from non-small cell lung cancer (NSCLC).

Recent Findings Local treatment has evolved from whole-brain radiotherapy (WBRT) to increasing use of stereotactic radiosurgery (SRS) alone for patients with limited (1–4) brain metastases. Trials have established post-operative SRS as an alternative to adjuvant WBRT following resection of brain metastases. Second-generation TKIs for *ALK* rearranged NSCLC have demonstrated improved CNS penetration and activity. Current brain metastasis trials are focused on reducing cognitive toxicity: hippocampal sparing WBRT, SRS for 5–15 metastases, pre-operative SRS, and use of systemic targeted agents or immunotherapy.

Summary The role for radiotherapy in the management of brain metastases is becoming better defined with local treatment shifting from WBRT to SRS alone for limited brain metastases and post-operative SRS for resected metastases. Further trials are warranted to define the optimal integration of newer systemic agents with local therapies.

Keywords Radiotherapy · Stereotactic radiosurgery · SRS · Stereotactic radiation therapy · SRT · Brain metastases · Immunotherapy · Targeted therapy · Whole brain radiotherapy · WBRT · Non-small cell lung cancer

Introduction

Brain metastases are a common diagnosis and source of morbidity for patients with non-small cell lung cancer (NSCLC). Of the 220,000 new cases of NSCLC diagnosed annually, an estimated 57% will present with metastatic disease including 20% with brain metastases at diagnosis [1, 2]. In addition, among locally advanced NSCLC patients treated with multimodal therapy, brain metastases represent a commons site of distant relapse in 30–55% of patients [3–5].

The management of patients with brain metastases has evolved from whole-brain radiotherapy (WBRT) alone to combinations of locally directed therapies including surgical resection and/or stereotactic radiosurgery (SRS) with or without WBRT. WBRT involves daily fractionated radiation therapy to the entire brain parenchyma to treat both microscopic and macroscopic brain metastases. While WBRT reduces development of distant brain metastases, presumably due to sterilization of subclinical disease, it comes at the cost of cognitive toxicity [6–8, 9••]. SRS, typically delivered in a single fraction, utilizes highly conformal dose distributions to treat metastases while sparing uninvolved brain parenchyma. Approaches have been refined over time due to concerns that both radiotherapy and progression of brain metastases can lead to neurologic deterioration. The purpose of this review is to summarize recent developments in the management of brain metastases with an emphasis on NSCLC.

Prognostic Indices

The median survival of patients with brain metastases has historically been estimated at 2–6 months [10–12]. However, patients with brain metastases represent a heterogeneous group, and extended survival has been observed in certain patient subsets (such as *epidermal growth factor receptor* (*EGFR*) mutated or *anaplastic lymphoma kinase* (*ALK*) re-

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arranged NSCLC) [13]. Prognostic indices have been refined over time with improved options for local and systemic therapy.

The Radiation Therapy Oncology Group (RTOG) utilized a recursive partitioning analysis (RPA) to analyze factors associated with survival from three brain metastasis trials from 1979 to 1993 including 1200 patients [14]. Three classes were defined based on age, performance status, and status of the primary tumor. Patients with the longest survival (Class 1, median survival of 7.1 months) included those with age < 65 years, Karnofsky performance status (KPS) ≥ 70, and controlled primary with brain only site of metastases. Similarly, the RTOG identified three classes of prognostic groups following surgical resection based on age, KPS, controlled primary disease, and extent of surgical resection [15].

While the original RTOG GPA allowed stratification of homogenous patient groups for trials and improved prognostication, it required the subjective estimation of control of systemic disease and did not account for the number of brain metastases. To address these limitations the Graded Prognostic Assessment (GPA), was developed in 1998 from 1960 patients in the RTOG database [16]. The GPA is a four-point index (with higher scores indicating more favorable prognoses) and includes age, KPS, number of brain metastases, and presence or absence of extracranial metastases. The GPA was found to be more prognostic than other indices (including the RPA) and less subjective.

With the recognition that prognostic factors for brain metastases may vary with primary diagnosis and tumor biology, and was therefore not granular enough, the diagnosis-specific GPA (DS-GPA) was developed [17, 18]. Individual prognostic scores with varying combinations of prognostic variables were constructed for NSCLC, small cell lung cancer, melanoma, breast cancer, renal cell carcinoma, and GI cancers. The DS-GPA for NSCLC includes age, KPS, number of brain metastases, and presence of extracranial metastases.

The most recent update of the GPA for lung cancer incorporates molecular markers into the algorithm (Lung-molGPA) [19••]. The presence of *EGFR* or *ALK* gene alterations is associated delayed onset of brain metastases and protracted survival compared to those without alterations [13]. In the modified Lung-molGPA, the most favorable group including *EGFR* or *ALK* positive patients demonstrates a median survival approaching 4 years from the time of brain metastasis diagnosis [19••].

Surgical Resection and Post-operative SRS

Three of four randomized controlled trials demonstrated that intensification of local therapy with surgical resection in addition to WBRT resulted in improved survival among patients with a single brain metastasis [20–23]. Conversely, high rates of tumor bed recurrence have been observed with surgical resection of brain metastases without adjuvant therapy with estimates approaching 50–60% at 12 months [8, 24, 25•, 26]. Randomized trials have further demonstrated improved local control with WBRT following surgical resection of brain metastases [8, 24]. However, lack of an appreciable survival benefit to adjuvant WBRT [8, 24, 27] and recognized neurocognitive toxicity of WBRT [9••] have led to an interest in post-op SRS to resection cavities with either single fraction [28, 29] or multiple fraction regimens [30].

The Alliance N107C trial randomized patients with a resected brain metastasis and cavity less than 5.0 cm in maximal dimension to post-operative SRS (12–20 Gy × 1) versus WBRT [31••]. There were no significant differences in overall survival (12.2 vs. 11.6 months, respectively, HR [95% CI] = 1.07 [0.76–1.50], $p = 0.70$), but there was less cognitive decline for patients receiving SRS. Median cognitive deterioration free survival (greater than 1 SD decline from baseline in at least one of six cognitive tests) in SRS patients was 3.7 months compared to 3.0 months among WBRT patients (HR [95% CI] = 0.47 [0.35–0.63], $p < 0.0001$). Whether a less than 1-month margin is clinically meaningful is debatable. However, the authors observed that for long-term survivors (≥ 12 months), cognitive deterioration was less frequent after SRS than after WBRT at 3 (27 vs. 89%, $p = 0.00016$), 6 (46 vs. 88%, $p = 0.0025$), 9 (48 vs. 81%, $p = 0.020$), and 12 months (60 vs. 91%, $p = 0.0188$) respectively. This cognitive benefit of SRS over WBRT was in spite of inferior control of brain metastasis (40.7 vs. 81.5% $p = 0.003$), a finding largely due to the increased incidence of distant brain relapse without WBRT. Further, duration of functional independence was longer after SRS (median not yet reached) than after WBRT (14 months; $p = 0.034$). Another single institution phase III trial of patients with surgically resected brain metastases randomized to post-op SRS versus observation with a primary endpoint of local control found freedom from local recurrence at 12 months was improved among the SRS arm (72 vs. 43%) [25•].

Taken together, these landmark trials suggest that post-operative SRS to the resection cavity can be considered a standard of care where technically feasible. However, concern for dural-based leptomeningeal patterns of recurrence along the surgical tract has been described with post-op SRS to resection cavities [32]. Expert consensus guidelines on post-operative clinical target volumes were recently published but require refinement [33]. As discussed below, pre-operative SRS is an emerging concept with theoretical benefits of decreased radionecrosis and leptomeningeal recurrence secondary to delineation and treatment of an intact metastasis.

SRS for Intact Lesions

A paradigm for single fraction SRS dosing was established in an RTOG 90-05 dose escalation trial which found acceptable rates of toxicity among patients with previously treated, recurrent primary or metastatic brain tumors: 24 Gy for tumors ≤ 2 cm, 18 Gy for tumors between 2.1 and 3.0 cm, and 15 Gy for tumors between 3.1 and 4 cm [34]. The multi-institutional phase III RTOG 95-08 trial evaluated the incremental benefit of intensification of local therapy with SRS compared to WBRT alone for patients with limited (1–3) brain metastases. For all patients, SRS resulted in improved local control of treated lesions (82 vs. 71%, $p = 0.01$). Moreover, in a finding conceptually congruent with the survival benefit observed with the addition of resection to WBRT, a pre-specified subgroup analysis demonstrated that the addition of SRS led to improved survival among patients with a single brain metastasis (median 6.4 (SRS + WBRT) vs. 4.9 months (WBRT alone), $p = 0.0393$)).

While SRS has been traditionally used for limited (i.e., 1–4) brain metastases, the maximum number of brain metastases appropriate for treatment is not well established [35]. A multi-institutional prospective study from Japan enrolled 1194 patients with up to 10 brain metastases treated with SRS alone. Patients with a single brain metastasis demonstrated the longest survival (median 13.9 months [95% CI = 12.0–15.6), consistent with findings for this population seen in the aforementioned trials. However, in this non-inferiority study, no significant survival difference was observed among patients with 2–4 brain metastases (median 10.8 months [9.4–12.4]) compared to those with 5–10 brain metastases (10.8 months [95% CI = 9.1–12.7], $p < 0.0001$ for non-inferiority) [36•]. Long-term follow-up (median 46.3 months) of this observational study demonstrated no significant differences in minimental status exam score or post-SRS complication rates among the three groups [37]. A trial led by the NCIC plans to accrue 206 patients with 5–15 brain metastases (< 30 cm^3 total volume) and randomize to SRS (volume-based dosing) or WBRT and memantine (ClinicTials.gov identifier NCT03075072). Overall and cognitive deterioration-free survivals are the co-primary endpoints [38].

SRS Vs. Surgical Resection

Though both surgery and radiosurgery offer a survival benefit for patients with single brain metastasis, there is limited data to suggest the superiority of either modality or guide choice between neurosurgical resection and SRS where patients do not have a clear indication for surgical decompression or require histology. One randomized trial compared SRS to surgical resection, and WBRT accrued only 64 patients and found overall survival to be comparable. One year local control favored radiosurgery (96.8 vs. 82%, $p = 0.06$) but did not reach statistical significance [39]. A recent secondary analysis of the EORTC 22952 trial of SRS or neurosurgery plus or minus WBRT demonstrated comparable local control between SRS and surgical resection, with early control favoring SRS and long-term control favoring surgical resection [26]. While a multi-institutional retrospective analysis of 213 patients with brain metastases larger than 2 cm found improved local control with the addition of surgery to SRS [40], there are no head-to-head randomized trials comparing a benefit of surgery to SRS. Radiation dose reduction [34] necessitated with increasing target size may explain the decrement in local control for larger brain metastases. It is unclear whether alterative fractionation schemes such as hypofractionated fractionated stereotactic radiotherapy might improve local control for this cohort. There are varying dose/fractionation regimens in this context, and further study is required to define an optimal approach [30, 41].

Evolving Role of WBRT

Adjuvant WBRT

The role for advjuant WBRT after resection or SRS is evolving. Several randomized trials evaluated the role of adjuvant whole brain radiation for limited brain metastases [6–8, 9••]. Among the four major trials evaluating SRS with or without WBRT, all yielded consistent results, finding that WBRT increased intracranial control (both treated and new sites) but not overall survival (Table 1). The addition of WBRT reduces the rate of distant recurrence by approximately half, while local control of treated brain metastases is improved by an absolute value of approximately 15–30%. The improvement in local control without an associated survival benefit has been attributed to the efficacy of salvage therapies [6–8, 9••]. Of note, these trials were not powered to detect a survival difference. The EORTC 22952 trial was the largest of the four trials and unique in enrolling both patients who received surgical resection and those who received SRS [8]. Alliance N0574, the most recent trial, utilized a comprehensive list of neurocognitive and quality of life tests for the primary endpoint of cognitive deterioration. The rate of cognitive deterioration (in at least one test) at 3 months was lower among SRS patients compared to SRS + WBRT patients (63.5 vs. 91.7%, respectively, $p < 0.001$) [9••].

Defining Cohorts That May Benefit from Adjuvant WBRT

While survival for patients with brain metastases is usually measured in months, uncontrolled systemic disease remains the proximate cause of death in the majority of patients with

Table 1 Summary of local recurrence and survival across trials of adjuvant whole brain radiotherapy for limited (1–4) brain metastases

Trial	Local brain recurrence (%)[a]		Distant brain recurrence (%)[a]		Median overall survival (months)	
	SRS alone	SRS + WBRT	SRS alone	SRS + WBRT	SRS alone	SRS + WBRT
JROSG-99 (Aoyama et al.) [6]	27.5	11.3	63.7	41.5	8.0	7.5
MDACC (Chang et al.) [7]	33	0	55	27	15.2	5.7
EORTC 22952 (Kocher et al.) [8]	31	19	48	33	10.7	10.9
Alliance N0574 (Brown et al.) [9••]	27.2	9.9	30.1	7.7	10.4	7.4

SRS stereotactic radiosurgery, *WBRT* whole brain radiotherapy

[a] Estimates at 12 months, except for EORTC 22952 where estimates are at 24 months

brain metastases [42, 43]. This competing risk of death from extracranial disease has been used to explain the lack of observable survival benefit from enhanced intracranial control afforded by WBRT. Alternatively, the lack of survival benefit has also been attributed to the efficacy of salvage therapies. Given that trials randomizing patients to WBRT versus observation were not powered to detect an overall survival difference, there has been interest in defining a cohort of patients that may benefit from aggressive intracranial control.

A secondary analysis of the JROSG-99 trial suggested improved survival with the addition of WBRT to SRS among NSCLC patients with favorable diagnosis-specific graded prognostic assessment scores at baseline (median survival of 16.7 vs. 10.6 months, respectively, $p = 0.04$, HR [95% CI] = 1.92 [1.01–3.78]) [6]. This supports the hypothesis that patients at increased risk of death from intracranial disease may benefit from improved intracranial control with WBRT. However, two subsequent secondary analyses of randomized controlled trials (EORTC 22952 [44] and Alliance N0574 [45]) failed to replicate this survival benefit to WBRT among NSCLC patients with favorable diagnosis-specific graded prognostic assessment scores at baseline. In addition, the exploratory analysis of the EORTC 22952 trial found no benefit to WBRT among all patients with controlled extracranial disease (HR [95% CI] = 0.70 [0.45–1.11], $p = 0.133$) [44]. Definitive interpretation of these analyses is hampered by the limitations of unplanned analyses, but it remains possible that biologic differences among the populations may be responsible for the discordant findings (such as increased prevalence of *EGFR* mutated NSCLC among the Japanese [46, 47]). Taken together, these studies support SRS alone with close surveillance by MRI as a preferred treatment approach for the majority of patients with limited brain metastases to spare neurocognitive effects without a decrement in survival.

Is Active Treatment Preferable to Best Supportive Care?

For patients with limited life expectancy and/or poor performance status, best supportive care with corticosteroids alone is reasonable. The QUARTZ phase III non-inferiority trial randomized patients with NSCLC unsuitable for SRS or surgical resection to WBRT (20 Gy in 5 fractions) + best supportive care versus best supportive care alone. Quality-adjusted life-years (QALY) represented the primary endpoint, and non-inferiority was defined by a threshold of seven QALY days. The majority (63%) of patients had uncontrolled extracranial disease and 38% had poor performance status (KPS < 70). There was no difference in overall survival between groups (HR [95% CI] = 1.06 [0.90–1.26]), and the difference between mean QALYs was 4.7 days ([90% CI] = − 12.7–3.3) in favor of WBRT (46.4 QALY days for WBRT, 41.7 QALY days for best supportive care alone). The median survival of the entire cohort was 8 weeks, which is substantially less than historic estimates of 4–6 months for patients with brain metastases [11, 12]. Although the trial did not technically meet the non-inferiority criteria (lower bound of confidence interval of 12.7 days is greater than pre-specified 7 days), the findings suggests that patients with NSCLC and expected limited survival are unlikely to benefit from WBRT. As discussed in previous, there is wide heterogeneity in prognosis for patients with brain metastases (i.e., median survival from first treatment for ALK rearranged lung cancer metastatic to brain = 45 months [13]), and these results are not generalizable for patients with better performance statuses or resection.

Targeted Systemic Therapy

Limited penetration of the blood-brain barrier by systemic agents [48] has traditionally limited the role for systemic therapy to treat brain metastases. The advent of targeted systemic agents for *EGFR* mutated or *ALK* rearranged NSCLC has renewed interest in utilizing systemic therapy to treat brain metastases [49–53].

Epidermal Growth Factor Receptor (EGFR) Mutated

Approximately 15% of patients with NSCLC in the USA harbor activating *EGFR* mutations, for which *EGFR*

tyrosine kinase inhibitors (TKI) have demonstrated superiority over first line chemotherapy for advanced stage disease [49, 54, 55]. Recently, three phase II trials have reported front-line treatment with first-generation *EGFR*-TKI (erlotinib or gefitinib) among NSCLC patients with *EGFR* mutations and brain metastases [56–58]. Objective CNS response rates were 58.3–87.8% and median overall survival ranged from 15.9 to 21.9 months. Pre-specified secondary analysis of the phase III trials LUX-3 and LUX-6 comparing second-generation *EGFR* TKI afatinib to chemotherapy demonstrated increased time to progression (extracranial or intracranial) with afatinib compared to chemotherapy among patients with asymptomatic brain metastases (8.2 vs. 5.4 months, HR = 0.50, p = 0.0297) [59]. Although evaluation of intracranial metastases was performed per protocol, intracranial response was not recorded as a separate endpoint and intracranial response rates were not reported. However, a recent multi-institutional analysis demonstrated inferior overall survival with up-front *EGFR*-TKI use and deferral of brain radiotherapy [60•]. In multivariable analysis, both up-front SRS (HR [95% CI] = 0.39 [0.26–0.58]) and up-front WBRT (0.70 [0.50–0.98]) were associated with improved survival compared to up-front *EGFR*-TKI. A randomized trial of SRS followed by *EGFR*-TKI versus *EGFR*-TKI followed by SRS at time of progression is required to define the optimal sequencing of systemic and local therapies for *EGFR*-mutated NSCLC.

Anaplastic Lymphoma Kinase (ALK) Rearranged

Approximately 5% of patients with NSCLC in the USA will have rearrangements in the ALK gene resulting in constitutive kinase activity [61, 62]. First-generation *ALK* TKI crizotinib has demonstrated superiority to first-line chemotherapy [63, 64], and second-generation *ALK* TKIs ceritinib and alectinib have demonstrated efficacy among patients developing resistance to crizotinib [65, 66, 67•]. Brain metastases at diagnosis of *ALK* rearranged NSCLC are frequent (approximately 30%), and the brain is a common site of progression while on crizotinib (approximately 20% of those patients without brain metastases at diagnosis) [68]. Acquired resistance and poor blood-brain permeability of crizotinib have been mechanisms used to describe these findings [68, 69]. However, in the ASCEND-4 trial, ceritinib demonstrated an intracranial response rate of 72.7% compared to 27.3% in the chemotherapy arm among previously untreated patients. Likewise, the alectinib demonstrated a 75% intracranial response rate after crizotinib resistance with a median duration of response of 11.1 months in a phase II trial [70].

Future Directions

Pre-operative SRS

Early data suggests that pre-operative SRS followed by surgical resection within 48 h [71] may be an alternative to post-operative SRS with a lower observed incidence of both leptomeningeal recurrence and radionecrosis [32]. Further, multi-institution analyses have demonstrated lower rates of leptomeninigeal recurrence and radionecrosis among pre-operative SRS compared to post-operative SRS [72] and comparable rates of leptomeningeal recurrence among pre-operative SRS compared to post-operative WBRT [73]. Investigators hypothesize that pre-operative SRS has the theoretical advantages of a better-defined tumor volume, a smaller margin volume, and pre-operative sterilization of the surgical field. Further prospective study is required before this treatment paradigm is adopted into practice. Pre-operative SRS compared to post-operative SRS is the subject of a current phase II trial concept by NRG oncology (NRG-BN1605) [74].

Hippocampal Sparing WBRT

Injury to the neural stem cell component of the hippocampus has been hypothesized to play a role in radiation-induced cognitive decline [75]. WBRT with conformal avoidance of the hippocampus preserved memory and quality of life compared to historic controls in a single arm phase II study [76]. A randomized phase III trial of memantine and WBRT with or without hippocampal avoidance is currently accruing through NRG Oncology (NRG-CC001, ClinicalTrials.gov Identifier NCT02360215).

Immunotherapy

Immune checkpoint inhibitors, including those targeting the programmed death 1 (PD-1) signaling pathway, are being rapidly adopted into clinical practice for a variety of solid and hematologic malignancies. Currently, three monoclonal antibodies (pembrolizumab, nivolumab, and atezolizumab) targeting the PD-1 pathway are approved for either first-line or subsequent therapy in advanced NSCLC [77]. However, data regarding the safety and efficacy of immunotherapy for patients with brain metastases are limited. The Checkmate 017 and 057 phase III trials that demonstrated the efficacy of nivolumab as second-line therapy for NSCLC included patients with asymptomatic brain metastases and did not reveal serious neurologic complications [78, 79]. A phase II trial of pembrolizumab for untreated melanoma or NSCLC brain metastases documented response in 6 of 18 patients with NSCLC without serious adverse events [80]. There are

several ongoing clinical trials that seek to test the efficacy of immunotherapy, either alone or in combination with radiotherapy in the management of brain metastases (ClinicTrials.gov identifiers NCT02085070, NCT02681549, NCT02978404, NCT03366376, NCT02858869, NCT03325166, NCT02696993, NCT02831959, NCT01454102, NCT02320058, NCT02374242, NCT02621515).

Conclusions

The role and technique of radiotherapy in the management of brain metastases continues to be refined. Several well-designed trials suggest preservation of neurocognitive function with SRS alone in limited (1–4) brain metastases and post-operative SRS alone for resected brain metastases. Radiosurgery alone may be reasonable for well-selected patients with up to 10 brain metastases. Recent secondary analyses have been unable to reliably identify a cohort of patients with limited brain metastases and favorable prognoses, who may derive a survival benefit to adjuvant WBRT in addition to SRS.

The use of SRS to the resection cavity results in acceptable local control with less neurocognitive toxicity compared to adjuvant WBRT. However, optimal technique and sequencing have yet to be defined, and there may be an elevated risk of dural-based leptomeningeal recurrence in the setting of post-operative SRS. Choice of local therapy may be influenced by improved prognostic models for NSCLC patients with brain metastases. The Lung-molGPA accounts for *EGFR* or *ALK* mutational status with the most favorable groups demonstrating median survival on the order of 4 years.

Although there is evidence to suggest improved CNS activity for targeted systemic agents (such as second generation tyrosine kinase inhibitors for *ALK* rearranged NSCLC), there is insufficient evidence to defer local therapy and treat with upfront systemic therapy. Future trials are exploring ways to mitigate neurocognitive toxicity such as the use of WBRT with hippocampal avoidance, use of SRS for more than limited (5–15) brain metastases, pre-operative SRS, and the use of targeted systemic agents to control asymptomatic brain metastases.

Compliance with Ethical Standards

Conflict of Interest Thomas M. Churilla and Stephanie E. Weiss declare that they have no conflict of interest.

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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