Expanding the Spectrum of Radiation Necrosis After Stereotactic Radiosurgery (SRS) for Intracranial Metastases From Lung Cancer

A Retrospective Review

Akanksha Sharma, MD, Luke J. Mountjoy, DO,† Richard J. Butterfield, BS,‡ Nan Zhang, MS,‡ Helen J. Ross, MD,† Steven E. Schild, MD,§ Terence T. Sio, MD, MS,§ Thomas B. Daniels, MD,§ Harshita R. Paripati, MD,† Maciej M. Mrugala, MD, PhD,* Sujay A. Vora, MD,§ Naresh P. Patel, MD,‖ Richard S. Zimmerman, MD,‖ Jonathan B. Ashman, MD,§ and Alyx B. Porter, MD†*

Objective: Radiation therapy (RT) is the primary treatment of intracranial metastasis (ICM) from lung cancer (LC). Radiation necrosis (RN) has been reported post-RT with an incidence of 5% to 24%. We reviewed the spectrum of imaging changes in patients treated with RT for ICM from LC in an effort to identify potential risk factors for RN.

Methods: We reviewed 63 patients with LC and ICM who received RT (radiosurgery [stereotactic radiosurgery] with/without whole brain radiation therapy) at our institution between 2013 and 2018. Data evaluated included demographics, tumor type, ICM burden and location, chemotherapy, surgery, and RT details as well as treatment choices and outcomes.

Results: Of the 63 patients, clinical and radiographic criteria for RN were noted in 24 (38%) as early as 2 months and as late as 5 years posttreatment. Six patients required surgical resection due to refractory symptoms revealing pathology-proven RN and occasionally tumor. Patients were significantly more likely to develop RN if they had surgical resection of an ICM (45.8% vs. 20.5%, $P = 0.05$). No differences were found in location, size, or genetic profile of lesions. In total, 80% of patients received treatment for symptoms and/or radiographic change. This was generally a combination of steroids, bevacizumab, laser interstitial thermal treatment, or surgical resection. Most patients required >1 treatment modality.

Conclusions: This review of outcomes of RT for ICM in LC demonstrates a higher rate of RN than previously reported in the literature in those having had a surgical resection plus stereotactic radiosurgery. Our observation of RN as late as 5 years post-RT for ICM necessitates clinician awareness.

Key Words: radiation necrosis, intracranial metastases, lung cancer, stereotactic radiosurgery

(*Am J Clin Oncol* 2020;43:128–132)

BACKGROUND

Intracranial metastases (ICMs) are the most common brain tumors, representing half of all intracranial tumors diagnosed with 170,000 new cases annually.[1] Lung cancer (LC), specifically non–small cell lung cancer (NSCLC), is the most common source of ICM.[2] Significant advances in treatment in the last 2 decades have led to improvements in survival rates, which also translate into increasing incidence and prevalence of ICM.[3]

Management of ICM often requires multidisciplinary care, with a combination of resection for isolated and/or symptomatic lesions and radiation therapy (RT). Whole brain radiation therapy (WBRT) had been a mainstay for the management of ICM but has been associated with a significant burden of neurotoxicity.[4] Advances in stereotactic radiosurgery (SRS) in addition to several randomized controlled trials comparing WBRT and SRS for the control of limited disease has resulted in the increased use of SRS for the treatment of ICM. Overall survival outcomes may be unchanged with the use of SRS, with less neurotoxicity and improved quality of life.[5–7] Increasingly, tumors with various different genetic mutations may also be treated with immunotherapy with significant intracranial efficacy, which can further delay the need for WBRT.[8,9]

Radiation necrosis (RN) is a delayed toxicity of therapy that has had a reported incidence of 5% to 24%.[10–13] It has been described to occur as early as several weeks after to up to 24 months from treatment.[14] RN results in significant burden to the patient and also on the health care system, as morbidity from neurological symptoms can lead to expensive imaging, prolonged treatment and hospitalizations.[15,16] In addition, RN is a dose-limiting toxicity, influencing treatment choices going forward for the patient.

In clinical practice, the diagnosis is often presumed and ascertained after a careful review of the imaging, treatment history, and clinical presentation. Establishing a diagnosis of RN remains problematic. While a pathologic diagnosis is the gold standard, it is not always clinically feasible or safe to obtain a biopsy or resection in these patients. Historically, positron emission tomography (PET) and single-photon emission computerized tomography imaging were used to attempt delineation of RN from tumor progression (TP).[17–19] Advanced imaging techniques such as perfusion magnetic resonance imaging (MRI) and PET-MRI have emerged as additional tools for noninvasive diagnosis of RN.[20] Diagnostic accuracy remains paramount given nuances in management and prognostication, but we are still quite limited in achieving this. In clinical practice, the determination is usually established by multidisciplinary discussion and serial monitoring with a combination of the methods discussed above.

As treatment and management of cancer becomes increasingly individualized and precise, it is more important to understand the factors that predispose to RN and which factors may be protective.

From the Departments of *Neurology; †Hematology/Oncology; ‡Biostatistics; §Radiation Oncology; and ‖Neurosurgery, Mayo Clinic Arizona.
The authors declare no conflicts of interest.
Reprints: Alyx B. Porter, MD, 5777 E Mayo Blvd, Phoenix, AZ 85054. E-mail: porter.alyx@mayo.edu.

ISSN: 0277-3732/20/4302-0128
DOI: 10.1097/COC.0000000000000642

Previous studies have suggested that increased RN rates may be seen with larger tumor sizes, higher doses of radiation, low conformity indexes, prior radiation, and fractionation (of larger lesions).[12–14,21,22] LC has been independently considered to be a risk, and several mutations have also been linked to higher rates of RN, including HER2, ALK, and BRAFV600E.[22] Certain immunotherapies have also been associated with an increased risk of local inflammation and RN when used pre-SRS, peri-SRS, and also post-SRS, although the mechanisms remain unclear.[23] In this era of individualized medicine, further understanding is needed regarding risk factors for RN.

In this retrospective study we reviewed a cohort of LC patients treated for ICM treated with SRS at our institution. We sought to confirm previously described risk factors in our cohort and identify any novel factors that predisposed patients to develop RN. We recorded treatment strategies and outcomes in cases where a clinical diagnosis of RN was made.

METHODS

Patient Inclusion

A retrospective review was conducted with approval of our institutional review board. All adult patients presenting with LC who received RT for ICM between 2013 and 2018 were eligible for inclusion. Patients could have received SRS at an outside institution if radiation records were available and if they had a follow-up MRI at our institution. Patients who had WBRT alone were excluded; however, we included cases where both WBRT and SRS had been given.

Data Collection

Patient and treatment characteristics obtained through a detailed chart review included the following: age, sex, performance status, primary pathology, date of diagnosis, tumor characteristics, and the type of systemic treatment (including cytotoxic chemotherapy, immunotherapy, or targeted therapy) used before or during radiation. Treatment for clinically presumed or confirmed RN, if present, and outcomes of that treatment were also recorded.

Treatment Delivery

SRS was delivered using a Linac-based frameless technique with 6 MV photons and the Exactrac system for image guidance. Immobilization was achieved with a thermoplastic mask. CT simulation was performed at 1 mm slice thickness through the entire head typically with intravenous contrast. CT images were then fused to high resolution treatment planning MRI images obtained at 1 mm slice thickness using an axial T-weighted spoiled gradient sequence. Collimation technique utilized based on the size and shape of the lesion included circular cones, dynamic multileaf collimation, or volumetric modulated arc therapy. Dose selection was based on tumor size, location, resection status, and history of prior cranial radiation. It was typically prescribed to the 80% isodose line. The majority of patients were treated with single fraction SRS, with doses ranging from 1500 to 2700 cGy. Multifractionated (stereotactic radiotherapy [SRT]) cases were also included, with a range of 2100 to 3600 cGy over 3 to 5 fractions. WBRT was given over 10 fractions, with doses ranging from 2200 to 4500 cGy. In the majority of cases (13/19), WBRT preceded SRS/SRT and SRS/SRT was used at time of progressive or recurrent disease. Patients generally had a repeat MRI 4 to 12 weeks after RT and were subsequently followed with repeat MRI scans every 3 months at least, sooner if symptomatic.

Outcomes

The primary endpoint was presumptive RN based on clinical and radiographic criteria. RN is challenging to distinguish from TP based on imaging alone, but the diagnosis could only be pathologically confirmed in 6 cases where the patients went for surgical resection. Our focus in this "real-world" evaluation was therefore on presumptive RN and presumptive TP, which was defined as changes on imaging with/without clinical symptoms where concern was raised by the neuroradiologist or the primary treating specialists of RN versus TP. RANO guidelines were used by the neuroradiologists to define complete response, partial response, stable disease, and progression for each MRI performed after RT. Perfusion MRI and PET-CT was also used in several cases to try to ascertain between tumor and necrosis, but these measures are still not strongly founded in evidence. For our study, we reviewed the notes of the radiation oncologist, oncologist, neurooncologist, or the multidisciplinary tumor board to determine the clinical stance on a particular case. Often, presumptive RN coexisted with presumptive TP and was recorded as such in cases where the clinical team and the tumor board could not reach a definite clinical opinion on RN versus TP. Generally, presumptive RN versus presumptive TP was confirmed by following the clinical course and assessing response to the treatment given, fluctuations on imaging, and long-term outcomes. For each case, we evaluated for any correlation between RN or TP and the tumor/treatment variables.

Statistical Methods

Patients' demographics, clinical characteristics, tumor characteristics, and treatment modalities were compared between patients with RN and patients without RN using Wilcoxon rank sum test or the Fisher exact test when applicable. Within the cohort of patients with RN, outcomes were then compared between patients receiving RN-directed treatment and those not receiving RN-directed treatment using Fisher exact test. RN was treated as time-varying variable—before patients who developed RN, they actually contributed to the risk set of the non-RN group and after patients developed the condition they contributed to the risk set of the RN group. Kaplan-Meier curve using the time-varying predictor—RN were generated and log rank test was used to test if the survival distribution between patients who developed RN and those who did not developed RN differed significantly. All hypotheses were 2-sided with $P < 0.05$ considered statistically significant. Analyses were performed in SAS version 9.4 (SAS Institute; Cary, NC).

RESULTS

Patient Demographics

A total of 63 patients were included; 24 of which had RN (38%). Patient demographics and performance status were comparable between the groups (Table 1). Patients with RN appeared to

TABLE 1. Patient Characteristics at Presentation

	n (%)		
Characteristics	**Radiation Necrosis (N = 24)**	**No Radiation Necrosis (N = 39)**	***P***
Age median (range)	64 (48-79)	67 (54-81)	0.09
Female	15 (62.5)	27 (69.2)	0.59
ECOG score median (range)	0 (0-3)	1 (0-3)	0.84
Pathology			
Small cell	0 (0)	5 (12.8)	0.15
NSCLC	24 (100)	34 (87.2)	
Squamous	3 (12.5)	2 (5.9)	0.64
Adenocarcinoma	21 (87.5)	32 (94.1)	

NSCLC indicates non–small cell lung cancer.

TABLE 2. Lesion Characteristics

Characteristics	Radiation Necrosis (N = 24)	No Radiation Necrosis (N = 39)	*P*
Lesion size (cm), mean (SD)	1.5 (1.0)	1.2 (1.0)	0.17
Lesion size (cm), range	0.4-3.8	0.2-3.5	
No. lesions, median (range)	3 (1-14)	2 (1-19)	0.20
Edema present, n (%)	20 (83.3)	22 (56.4)	0.03

be younger at onset of disease 64 versus 67, but this was not statistically significant ($P = 0.09$). 92% of all patients had NSCLC. No patient in the RN cohort had a diagnosis of SCLC and only 5 patients free of RN had SCLC. There were no differences in the incidence of RN between squamous carcinoma and adenocarcinoma histology ($P = 0.64$). However, the majority of patients with NSCLC had adenocarcinoma. The molecular mutational status and PD-L1 tumor proportional score was not readily available on all patients. In total, 18 of 24 (75%) patients in the RN cohort had unknown molecular mutation characteristics with 29 of 39 (74%) unknown in the non-RN cohort. PD-L1 was unknown in 14 of 24 (58%) and 29 of 39 (74%) patients in the RN and non-RN cohorts, respectively. Where available, there was no statistical difference in the molecular mutational status or PD-L1 tumor proportional score between cohorts.

Lesion Characteristics

The lesion characteristics are outlined in Table 2. There was no trend for larger lesion size and mean number of lesions in the RN cohort. Patients with RN had a higher incidence of pretreatment cerebral edema ($P = 0.03$). There were no differences in the location of ICMs and a large portion had lesions in > 1 location—63% in RN cohort and 49% in non-RN cohort. There were 5 cerebellar ICMs and 2 basal ganglia ICMs in total.

TABLE 3. Tumor Treatment Modalities

Treatment	n (%) Radiation Necrosis (N = 24)	n (%) No Radiation Necrosis (N = 39)	*P*
Type of radiation			
Any SRS/SRT (dose ranges in cGy)	23 (95.8) (1400-3600)	38 (97.4) (1500-2700)	1.00
Any WBRT (dose ranges in cGy)	5 (20.8) (2200-3600)	14 (35.9) (2500-4500)	0.26
Average number of radiation treatments	1.3 (0.5)	1.7 (0.7)	
Systemic chemotherapy			0.61
None	4 (16.7)	8 (20.5)	
Cytotoxic only*	9 (37.5)	13 (33.3)	
Immunotherapy only†	4 (16.7)	2 (5.1)	
Targeted therapy only‡	2 (8.3)	5 (12.8)	
Combination therapies	5 (20.8)	11 (28.2)	
Surgical resection	11 (45.8)	8 (20.5)	0.05

*Platinum/pemetrexed, platinum/taxane, platinum/etoposide.
†Pembrolizumab, atezolizumab, nivolumab.
‡Erlotinib, osimertinib, afatinib, crizotinib, alectinib.
SRS indicates stereotactic radiosurgery; SRT, stereotactic radiotherapy; WBRT, whole brain radiation therapy.

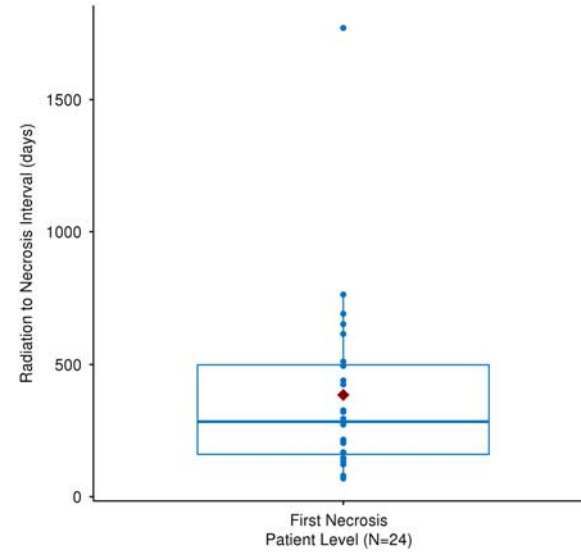

FIGURE 1. Time to development of first RN following treatment with SRS. full color online

Treatment Characteristics

The different tumor treatment modalities between cohorts are outlined in Table 3. The majority of patients had undergone systemic treatment before receiving intracranial radiation (81%). There was no difference in systemic treatment regimens, including targeted and immunotherapies, or interval from metastasis development to radiation between cohorts. There was also no correlation between radiation type or dose and RN development.

The median time to development of RN after radiation was 10.3 months. There was a wide range of RN development (2.2 to 59 mo) indicating that patients could be at risk for RN several years after radiation exposure (Fig. 1).

Surgical resection followed by SRS appeared to be associate with RN greater than SRS alone (45.8% vs. 20.5%, $P = 0.05$). Patients who underwent surgical resection were more likely to have a larger median lesion size (2.7 cm [0.5 to 3.8] vs. 0.6 cm [0.2 to 2.6] $P < 0.0001$] and increased incidence of edema (94.7% vs. 54.5%, $P = 0.001$) compared with those with no surgery. No patient who underwent surgical resection received WBRT compared with 20.5% of patients who did not have surgery ($P = 0.05$). There did not appear to be a difference in type of systemic therapy (ie, cytotoxic chemotherapy, immunotherapy, or targeted therapy) used in patients that had received surgical resection versus no surgery ($P = 0.77$). When comparing surgical resection to no surgical resection there was no difference in the median age (67 [53 to 79] vs. 66.0 [48 to 81], $P = 0.92$), gender (female 63.2% vs. 68.2%, $P = 0.77$), or median radiation dose (2200 cGy [1800 to 7300] vs. 2850 cGy [1500 to 7300] $P = 0.09$). The indication for surgical resection was either large size, symptoms secondary to local mass effect, or need for a pathologic diagnosis. The interval from surgery to radiation was between 2 and 4 weeks in most cases.

Amidst the 24 patients diagnosed with RN there were 35 individual instances of RN, that is, 35 instances where there was clinical and/or radiographic concern for RN. Time to first necrosis ranged from 2 months to 5 years, as illustrated in Figure 1. In 24 of 35 instances, the patient was clinically symptomatic prompting the decision to treat. Five of the 35 patients received treatment based on radiographical changes alone—notably, this treatment

Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

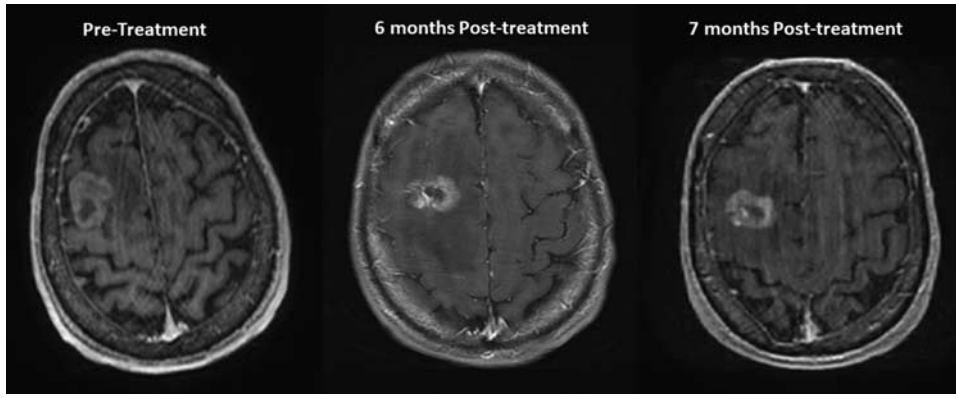

FIGURE 2. Pathologically proven RN in a patient previously treated with SRS for a solitary metastasis.

modality generally to be reirradiation, suggesting that these were cases where TP was strongly suspected.

RN-directed treatment was given in 28 of 35 (80%) of these instances. Treatment resulted in clinical improvement in 21 of 28 (75%) instances, and patients who had >1 line of treatment tended to have better clinical response. Steroids were used in 15 of 28 cases, either alone or combine with laser interstitial thermal treatment (LITT) (3/28), bevacizumab (4/28), or surgery (3/28), with improvement in 10 of 15 cases (67%). LITT combined with either steroids or reirradiation was beneficial in 4 of 5 cases. Reirradiation was the treatment choice when there was lack of clarity as to whether the situation represented disease progression or RN, and a mixture of both appeared to be likely. Bevacizumab was beneficial in 4 of 4 cases, but was never administered alone as primary treatment for RN. In 6 instances, surgical resection was done because of symptoms refractory to steroids—all 6 had pathology-proven RN and 3 of 6 had a mixture of tumor and RN. Surgical resection resulted in improvement in 3 of 6 patients, but 2 of 6 patients were left with increased neurological morbidity and passed away in the postoperative period. The imaging from one of these patients is included as Figure 2. There was no difference in overall survival between the patient groups, with at least 1 instance of RN with a median survival of 17 months in both groups.

DISCUSSION

RN remains a challenging diagnosis to confirm and with improving rates of overall survival emerges as a priority area for additional study. Our retrospective review reveals the spectrum of experience and treatment for patients with LC and RN. In this study we reviewed 63 patients with a goal of evaluating the rate of clinical RN, factors that increased risk of developing RN, and observing outcomes once a diagnosis had been established. In the majority of cases, the treating clinician was left to rely on imaging features and clinical assessment to guide treatment in addition to serial observation. Surgical resection (resulting in pathologic confirmation) was performed in only a small percentage of our patients.

In our cohort, we identified RN in 38% of patients after SRS, which appears higher than what has previously been reported.[12,13,24] We suspect that contributors to this higher rate include increased survival in patients from radiation and treatment in this current era, closer surveillance in terms of imaging post-treatment, and possibly a greater rate of identification of RN given additional awareness of this complication in recent years. We have also found a wide interval for development of RN ranging between 2 to 60 months post-SRS treatment, suggesting that our institution may be considering and demonstrating the diagnosis of RN more often in cases, especially in long-term survivors who present with changes in previously treated areas. Interestingly, we found a correlation between RN in patients who had SRS performed to the operative cavity, that is, those who had surgery before SRS. Understanding the role of SRS after surgery remains challenging, and this raises questions on how the collapsed area postsurgery is actually targeted and mapped for SRS treatment. On our review of the literature, we did not find that there has been much exploration yet on how surgical injury impacts brain tissue specifically in metastatic disease and how the combination of radiation may further influence this at a microscopic level. It is reasonable to assume that local injury and disruption in the blood brain barrier leads to a heightened inflammation. Animal models have demonstrated an influx of macrophages to an area surgically injured in the cerebral cortex.[25] In addition, there is evidence that extensive neovascularization also takes place in the injured area in the early period, in an effort by the brain to create a scar over its injury.[26] Longer term evaluation has demonstrated that these new endothelial constructs may often be suboptimal in construction and more prone to degeneration and injury.[25,26] We wonder if these deficits in the vascular network result in fragility and vulnerability to the effects of radiation. Additional research would be needed to understand if there may be a "safer" period after surgery for the radiation treatment. At this point, we rely on markers of external wound healing to guide treatment decisions, but clearly additional information is needed on what is happening on the deeper level that impacts necrosis. The implications of these findings are essential to our understanding as clinicians caring for this patient population.

Our analysis also demonstrates the importance of empiric treatment for RN. Patients who received treatment appeared to do better clinically and radiographically. Symptomatic RN has a significant burden on the patient and the system of treatment options offered carry varying degrees of risk. Surgical resection had the highest risk of unfavorable outcomes in our review. This highlights the fact that pathologic confirmation may not be in the patients' best interest. Steroids, dexamethasone specifically, was effective for the majority of patients. We also highlight the utility of 2 lesser-used treatments, LITT and bevacizumab. Both showed efficacy in the treatment of RN, but of course in a limited number of patients.

There are many limitations of this study as a result of its retrospective nature. We were not able to confirm previously reported risk factors contributing RN. Specifically, we found no significant differences regarding radiation dose or lesion size. We did not have genetic characteristics or PD-L1 status on the majority of patients at the time of analysis. We did not see a

relationship between the use of immunotherapy and increased rates. The combination of surgical resection followed by SRS appeared to increase the risk of RN compared with SRS alone. With the improvement in overall survival in patients with metastatic LC and emerging treatment options, prospective studies are needed to clarify the scope of neurological morbidity that can occur as a result of extended survival.

CONCLUSION

Our study suggests that RN occurred at a frequency similar to previous SRS studies except for the patient who had surgery followed by SRS. On the basis of the findings, it appears the combination of resection plus SRS resulted in more RN then SRS alone. With advances in therapies, patients with ICMs are living longer potentially leading to a higher incidence, thus clinicians must remain vigilant in consideration of RN, even years from the initial treatment. Prospective study of RN incidence and response to treatment is needed. Early and aggressive treatment of RN may have implications on quality of life and survival. Nonsurgical treatments such as LITT and bevacizumab in conjunction with steroids appeared beneficial.

REFERENCES

1. Ostrom QT, Gittleman H, Truitt G, et al. CBTRUS Statistical Report: primary brain and other central nervous system tumors diagnosed in the United States in 2011-2015. *Neuro Oncol*. 2018;20(suppl_4):iv1–iv86.
2. Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. *Curr Oncol Rep*. 2012;14:48–54.
3. Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. *Nature*. 2018;553:446–454.
4. Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a Randomized Clinical Trial. *JAMA*. 2016;316:401–409.
5. Brown PD, Ballman KV, Cerhan JH, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2017;18:1049–1060.
6. Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol*. 2014;15:387–395.
7. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA*. 2006;295:2483–2491.
8. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2018;378:113–125.
9. Shaw AT, Gandhi L, Gadgeel S, et al. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. *Lancet Oncol*. 2016;17:234–242.
10. Chao ST, Ahluwalia MS, Barnett GH, et al. Challenges with the diagnosis and treatment of cerebral radiation necrosis. *Int J Radiat Oncol Biol Phys*. 2013;87:449–457.
11. Chin LS, Ma L, DiBiase S. Radiation necrosis following gamma knife surgery: a case-controlled comparison of treatment parameters and long-term clinical follow up. *J Neurosurg*. 2001;94:899–904.
12. Minniti G, Clarke E, Lanzetta G, et al. Stereotactic radiosurgery for brain metastases: analysis of outcome and risk of brain radionecrosis. *Radiat Oncol*. 2011;6:48.
13. Sharma M, Jia X, Ahluwalia M, et al. First follow-up radiographic response is one of the predictors of local tumor progression and radiation necrosis after stereotactic radiosurgery for brain metastases. *Cancer Med*. 2017;6:2076–2086.
14. Shaw E, Scott C, Souhami L, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. *Int J Radiat Oncol Biol Phys*. 2000;47:291–298.
15. Sharma A, Mrugala MM, Low J. Neuro-oncologists have spoken—the role of bevacizumab in the inpatient setting. A clinical and economic conundrum. *Neuro-Oncology Practice*. 2018;6:30–36.
16. Rahman M, Hoh BL. Avastin in the treatment for radiation necrosis: exciting results from a recent randomized trial. *World Neurosurg*. 2011;75:4–5.
17. Schwartz RB, Holman BL, Polak JF, et al. Dual-isotope single-photon emission computerized tomography scanning in patients with glioblastoma multiforme: association with patient survival and histopathological characteristics of tumor after high-dose radiotherapy. *J Neurosurg*. 1998;89:60–68.
18. Mitsuya K, Nakasu Y, Horiguchi S, et al. Perfusion weighted magnetic resonance imaging to distinguish the recurrence of metastatic brain tumors from radiation necrosis after stereotactic radiosurgery. *J Neurooncol*. 2010;99:81–88.
19. Sugahara T, Korogi Y, Tomiguchi S, et al. Posttherapeutic intraaxial brain tumor: the value of perfusion-sensitive contrast-enhanced MR imaging for differentiating tumor recurrence from nonneoplastic contrast-enhancing tissue. *AJNR Am J Neuroradiol*. 2000;21:901–909.
20. Chao ST, Suh JH, Raja S, et al. The sensitivity and specificity of FDG PET in distinguishing recurrent brain tumor from radionecrosis in patients treated with stereotactic radiosurgery. *Int J Cancer*. 2001;96:191–197.
21. Lehrer EJ, Peterson JL, Zaorsky NG, et al. Single versus multifraction stereotactic radiosurgery for large brain metastases: an international meta-analysis of 24 trials. *Int J Radiat Oncol Biol Phys*. 2019;103:618–630.
22. Miller JA, Bennett EE, Xiao R, et al. Association between radiation necrosis and tumor biology after stereotactic radiosurgery for brain metastasis. *Int J Radiat Oncol Biol Phys*. 2016;96:1060–1069.
23. Martin AM, Cagney DN, Catalano PJ, et al. Immunotherapy and symptomatic radiation necrosis in patients with brain metastases treated with stereotactic radiation. *JAMA Oncol*. 2018;4:1123–1124.
24. Wang TJ, Saad S, Qureshi YH, et al. Does lung cancer mutation status and targeted therapy predict for outcomes and local control in the setting of brain metastases treated with radiation? *Neuro Oncol*. 2015;17:1022–1028.
25. Frontczak-Baniewicz M, Walski M. New vessel formation after surgical brain injury in the rat's cerebral cortex I. Formation of the blood vessels proximally to the surgical injury. *Acta Neurobiol Exp (Wars)*. 2003;63:65–75.
26. Frontczak-Baniewicz M, Chrapusta SJ, Sulejczak D. Long-term consequences of surgical brain injury - characteristics of the neurovascular unit and formation and demise of the glial scar in a rat model. *Folia Neuropathol*. 2011;49:204–218.

Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.