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Symptomatic radiation necrosis in brain metastasis patients treated with stereotactic radiosurgery and immunotherapy

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ABSTRACT

Objectives: The association of symptomatic radiation necrosis (RN) with stereotactic radiosurgery (SRS) and immune checkpoint inhibitors (ICIs) in brain metastases patients has been incompletely explored. We aim to discuss the incidence, risk factors, and prognosis of symptomatic RN in patients treated with these modalities.
Patients and methods: We retrospectively evaluated the incidence of symptomatic RN among all patients with brain metastases treated with both SRS and an ICI at a single academic center. Risk factors for the development of symptomatic RN were determined, along with median overall survival (OS) stratified by the development of RN.
Results: Between 2010 and 2016, 57 brain metastases patients were treated with both SRS and an ICI. Only 4 (7%) developed symptomatic RN. Symptomatic RN lesions were more likely to be located in the cerebral cortex ($p = 0.019$) and be associated with a primary renal cell carcinoma ($p = 0.032$). Median OS was 32 months for those who developed symptomatic RN and 29 months for all other patients ($p = 0.16$).
Conclusion: Treatment of brain metastases with both SRS and an ICI is an effective modality that poses mild risk for developing symptomatic RN when compared to the risk of RN from SRS alone.

1. Introduction

Brain metastases are the most common malignancy affecting the central nervous system [1]. They occur in at least 9–17% of patients with a solid-organ cancer and are particularly common in patients with melanoma, non-small cell lung cancer, and breast cancer [1]. Brain metastases are traditionally treated with surgery, stereotactic radiosurgery (SRS), whole brain radiotherapy and/or chemotherapy, but increasingly immune checkpoint inhibitors (ICIs) are also being used as part of systemic treatment [2,3]. The anti-CTLA-4 inhibitors, ipilimumab and tremelimumab, as well as anti-PD-1 antibodies, nivolumab and pembrolizumab, have shown promise as adjuvants for treating melanoma brain metastases [4–10]. Nivolumab and durvalumab, an anti-PD-L1 antibody, are being used as adjuvants for treating non-small cell lung cancer brain metastases [11]. Within the last two years, the FDA has granted approval of nivolumab, pembrolizumab and durvalumab for the treatment of several metastatic cancers.

Combining ICIs and stereotactic radiosurgery (SRS) to treat brain metastases may improve survival, but it may also increase risk of radiation necrosis (RN). A recent study examining melanoma brain metastases treated with SRS with or without ipilimumab found that those treated with ipilimumab had a higher incidence of RN (6%–8% for patients treated with ipilimumab versus 0% for those treated without ipilimumab, $p = 0.005$) [12]. Other studies have found that up to 37.5% of patients treated with SRS and an ICI developed RN, while only 4.7% of patients treated with SRS alone did [13]. Notably, all published studies on the risk of RN in patients treated with ICIs have defined RN on the basis of radiographic findings with/without histopathologic confirmation.

The association between ICIs and symptomatic RN – defined as characteristic RN imaging findings in addition to clinical symptoms requiring intervention – has yet to be reported. Symptomatic RN is a more clinically relevant outcome because, unlike broadly-defined radiographic RN, symptomatic RN represents true treatment-associated morbidity. Further, the most common treatment for symptomatic RN, corticosteroids, may interfere with the primary mechanism of action of ICIs, thereby reducing the effectiveness of systemic treatment. An improved understanding of the risk factors for symptomatic RN in patients receiving SRS and ICIs for brain metastases may help avoid treatment-related morbidity.

In this study, we performed a retrospective single-center consecutive case series review to evaluate the incidence of symptomatic RN

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in patients with brain metastases treated with both SRS and an ICI. Our study examined the risk factors for, and prognosis of, symptomatic RN in these patients.

2. Materials and methods

2.1. Patient data

Patients undergoing Gamma Knife SRS for the treatment of brain metastases at Northwestern Memorial Hospital between 2010 and 2016 were retrospectively identified from a radiosurgery treatment database. Patient identifiers were cross-referenced with medical records in the Enterprise Data Warehouse to identify patients who received ICIs at our institution during their treatment course. Patients who underwent SRS at our institution but received systemic therapy elsewhere with incomplete records were excluded. Radiation treatment records, oncology treatment records, and radiology reports were reviewed for each patient. GammaPlan treatment records were reviewed to identify radiosurgical treatment doses and volumes. This study was approved by the Northwestern University Institutional Review Board.

Patient demographics including age, gender, primary tumor type, prior systemic treatments, prior cranial radiation treatments, and time from diagnosis to SRS were obtained from the medical record. Tumor treatment volume and dose for each lesion were obtained from the radiation treatment records. ICI treatment and timing relative to SRS was obtained from the oncology and medication administration records. Each patient was treated with at least one dose of one of the following ICIs: nivolumab, ipilimumab, pembrolizumab, durvalumab, and tremelimumab. Nivolumab was administered at 2 or 3 mg/kg every 2 weeks. Ipilimumab was administered at 3 or 10 mg/kg every 3 weeks. Pembrolizumab was administered at 2 mg/kg every 3 or 4 weeks. Durvalumab alone was administered at 10 mg/kg every 2 weeks. Durvalumab and MEDI6469 (an agonistic anti-OX40 antibody) combined were administered at 10 mg/kg and 2 mg/kg respectively every 2 weeks. Durvalumab and tremelimumab combined were administered at 1500 or 750 mg, and 75 mg respectively every 4 weeks. Time to tumor progression after SRS treatment and overall survival were obtained from the medical record.

Suspected cases of RN were identified based on reports in the oncology, radiation oncology, or neurosurgery medical records, or radiology records demonstrating tumor progression with the suggestion of RN. Cases were identified by searching records for the following keywords: “radiation necrosis,” “radionecrosis,” “radiation-induced changes,” “radiation injury,” “pseudoprogression” or “treatment-related imaging changes” following SRS. Brain MRIs of suspected RN cases were reviewed by the senior author for visual confirmation of tumor changes. Symptomatic RN cases were identified when three criteria were met: (1) radiographic findings were confirmed by the senior author to represent RN, (2) the patient experienced new or progressive symptoms that were attributable to the progressing lesion (s), and (3) treatment with corticosteroids, bevacizumab, or surgical resection (with pathology confirming radionecrosis) only resulted in improvement of symptoms without further radiographic progression of the lesion. No patients were excluded from analysis.

2.2. Statistical analysis

The primary end point was development of symptomatic RN. Time to development of RN was measured from the date of SRS to the date of the last MRI showing suspected RN prior to RN treatment. Overall survival (OS) was calculated as the time from treatment to either death or last follow-up prior to data closure on June 1, 2018. Median OS was determined using the Kaplan-Meier method with differences assessed by the log-rank test. Treatment and tumor characteristics for patients between patient groups were compared with a Kruskal-Wallis 1-way ANOVA test. Differences were considered statistically significant for $p < 0.05$.

Table 1
Patient demographics and tumor characteristics.

Characteristic	Median [IQR]	No. of patients (%) N = 57
Age (yrs)	66 [60-73]	
Sex		
Male		34 (60%)
Female		23 (40%)
Ethnicity		
White		40 (70%)
Black		1 (2%)
Asian		1 (2%)
Other		15 (26%)
Primary tumor		
Melanoma		25 (44%)
Lung		23 (40%)
Renal cell		8 (14%)
Breast		1 (2%)
No. of BM treated per SRS	2 [1–4]	
No. of SRS treatments per patient	1 [1–2]	
No. of total BM treated per patient	5 [2–8]	
Marginal SRS dose (Gy)	20 [18–20]	
Immune Checkpoint Inhibitor		
Nivolumab		33 (58%)
Ipilimumab		18 (32%)
Pembrolizumab		12 (21%)
Durvalumab		1 (2%)
Durvalumab + Tremulimumab		1 (2%)
Durvalumab + MEDI6469		1 (2%)
Relative timing of ICI and SRS		
ICI administered prior to SRS		5 (9%)
Days between ICI and SRS	195 [185–306]	
ICI administered during SRS		7 (12%)
ICI administered after SRS		45 (79%)
Days between SRS and ICI	141 [32–406]	
WBRT prior to SRS		3 (5%)
Receiving chemotherapy		32 (56%)

3. Results

3.1. Treatment

A total of 387 irradiated metastastic lesions in 57 patients treated with ICIs were analyzed. Patient demographics and tumor characteristics are displayed in Table 1. The patients’ median age at diagnosis of brain metastases was 66 years (interquartile range [IQR] 60–73), 23 (40%) were female, and the median number of brain metastases treated with SRS per patient was 5 (IQR 2–8). Among treated patients 25 (44%) had a primary diagnosis of melanoma, 23 (40%) had lung cancer, 8 (14%) had renal cell carcinoma and 1 (2%) had breast cancer.

Thirty-three patients were treated with nivolumab, 18 with ipilimumab, 12 with pembrolizumab, and 3 with durvalumab (1 in combination with tremelimumab, 1 in combination with MEDI6469, and 1 alone). Brain metastases were treated with a median marginal radiation dose of 20 Gy (range 10–20 Gy) targeted at the 50% isodose line. Thirteen patients also received whole-brain radiotherapy, 3 of whom received it prior to SRS. Thirty-two patients received at least one chemotherapy agent before or after receiving immunotherapy. Forty-five patients underwent SRS before receiving their first dose of an ICI, 7 underwent SRS while receiving an ICI, and 5 underwent SRS after receiving their last dose of an ICI.

3.2. Outcomes

Of the 57 patients treated with both an ICI and SRS, 4 (7%) developed symptomatic RN (Table 2). Two patients were treated for 2

Table 2
Treatment characteristics.

	Symptomatic RN		p Value
	Y	N	
Median SRS dose (Gy)	18	20	0.69
ICI			
Nivolumab	2	31	0.75
Ipilimumab	2	16	0.42
Pembrolizumab	1	11	0.84
Durvalumab	1	0	< **0.01**
Durvalumab + Tremelimumab	0	1	0.79
Durvalumab + MEDI6469	0	1	0.79
Relative timing of treatments			
ICI prior to SRS	1	4	0.24
Median Interval (days)	356	190	0.15
ICI during SRS	0	7	0.45
ICI after SRS	3	42	0.84
Median Interval (days)	188	137.5	0.43
Primary tumor			
Melanoma	2	23	0.80
Lung	0	23	0.09
Renal cell	2	6	**0.03**
Breast	0	1	0.79
Location of metastasic lesions			
Cerebral cortex	6	198	**0.02**
Cerebellum	0	62	0.28
Brainstem	0	5	0.78
Basal ganglia	0	5	0.78
Thalamus	0	2	0.86
Other	0	2	0.86
Unspecified	0	107	0.13

separate radionecrotic lesions each; the other 2 patients were treated for 1 radionecrotic lesion each (Table 3). Of the 387 total tumors treated with SRS, 6 (1.6%) developed symptomatic RN. The median time to development of symptomatic RN following SRS was 150 days (range 13–363 days). Three of the 4 patients treated for symptomatic RN received their first dose of ICI after receiving SRS; the other patient completed his last ICI dose 71 days before receiving SRS. Two (50%) patients treated for symptomatic RN received nivolumab, 2 (50%) received ipilimumab, 1 (25%) received pembrolizumab and 1 (25%) received durvalumab alone. 31 (58.5%) patients who did not have symptomatic RN received nivolumab, 16 (30.1%) received ipilimumab, 11 (20.7%) received pembrolizumab, 1 (1.89%) received durvalumab combined with tremelimumab and 1 (1.89%) received durvalumab combined with MEDI6469. Patients who were treated for symptomatic RN were more likely than all others to have received durvalumab alone ($p = 0.00012$).

The median SRS dose used to treat symptomatic RN lesions was 18 Gy while the median dose used to treat all other lesions was 20 Gy ($p = 0.69$). Of the 6 lesions treated for symptomatic RN, all were found in the cerebral cortex. Of the 381 other lesions whose locations were clearly specified, 198 (72.2%) were found in the cerebral cortex. Lesions treated for symptomatic RN were more likely to occur in the cerebral cortex than were all other lesions ($p = 0.019$), though this association did not persist in multivariate logistic regression ($p = 0.98$).

The median OS for all 57 patients was 32 months (95% CI 14 months to undefined upper limit). For patients with symptomatic RN, median OS was 32 months (95% CI undefined lower limit to undefined upper limit) compared to 29 months (95% CI 15 months to undefined upper limit) for patients without symptomatic RN ($p = 0.16$)

All 4 patients treated for symptomatic RN initially received dexamethasone. Three of these patients experienced resolution of RN with a short course of steroids. The other patient did not experience resolution after receiving 2 weeks of dexamethasone, and was ultimately treated with bevacizumab. The decision to use bevacizumab was based

Table 3
Characteristics of patients with symptomatic RN.

Patient	Sex	Primary Tumor	Tumor location	Tumor volume (cm^3)	SRS dose (Gy)	ICI (no. doses)	Time between ICI and SRS	Time from SRS to RN (days)	OS (months)
1	M	Melanoma	Left parietal	9.25	18	Ipi (4); Durva(11)	Ipi: last 356 days prior to SRS Durva: last 71 days prior to SRS	13	6
1			Right frontal	9.6	18			13	
2	M	Renal cell	Left centrum semiovale	0.16	20	Nivo (15)	Started Nivo 26 days after SRS	211	20*
2			Right parieto-occipital	20.3	16			211	
3	M	Melanoma	Right frontal	1.3	20	Ipi (3); Pembro (28)	Started Ipi 202 days after SRS; Started Pembro 275 days after SRS	363	46*
4	M	Renal cell	Right frontal resection cavity	11.8	18	Nivo (27)	Started Nivo 25 days after SRS	89	32

Ipi = ipilimumab, Durva = durvalumab, Nivo = nivolumab, Pembro = pembrolizumab, OS = overall survival, * = still living as of last chart review.

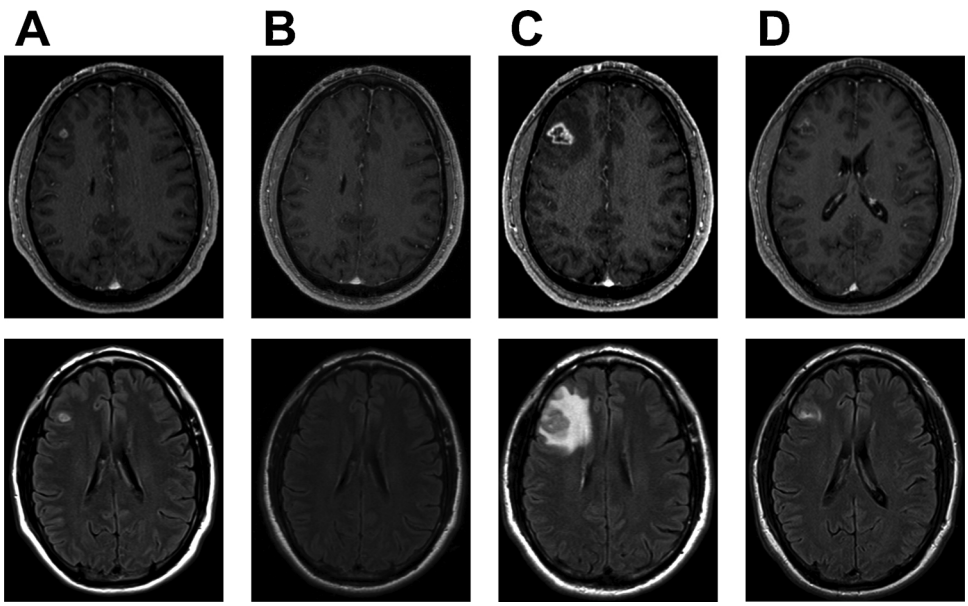

Fig. 1. Example of patient with melanoma brain metastasis treated with SRS and pembrolizumab, who developed symptomatic radiation necrosis. (A) Initial right frontal brain metastasis prior to SRS. (B) Response of lesion to 20 Gy SRS 3 months after treatment. (C) Expansion of lesion and edema consistent with radiation necrosis 18 months after SRS and after initiation of pembrolizumab. (D) Response of lesion after 2 months of bevacizumab treatment. For all images, top row demonstrates T1-weighted MRI with contrast, bottom row demonstrates FLAIR MRI.

primarily on the desire to avoid prolonged immunosuppressive steroid therapy as the patient was receiving concurrent ICI therapy. At last-follow up, 2 of 4 patients treated for symptomatic RNs were living and their three radionecrotic lesions were resolved, regressed and stable, respectively (Fig. 1).

4. Discussion

Having demonstrated overwhelming clinical benefit in numerous phase III trials, ICIs have now become the standard first or second line therapy for cancers that most commonly metastasize to the brain, including melanoma, lung cancer, and renal cell carcinoma [14–16]. It is, therefore, expected that most of the patients treated with SRS for brain metastases from these primary malignancies will receive an ICI at some point in their treatment course. Significant interest has arisen in understanding the interactions of SRS and ICI use, particularly with regard to development of RN and inflammatory pseudoprogression. Previous retrospective studies have suggested an increased incidence of RN in patients treated with SRS and an ICI compared to SRS alone. In a study of 310 melanoma brain metastases receiving SRS with or without ipilimumab, Diao et al. found that patients treated with ipilimumab had a higher incidence of RN (6% and 8% for two groups treated with ipilimumab versus 0% for those treated without ipilimumab, $p = 0.005$) [12]. A study by Colaco et al. investigating 180 patients treated with SRS plus an ICI and/or chemotherapy found that 12 (37.5%) of 32 patients treated with SRS and an ICI alone developed RN, while only 7 (4.7%) of the remaining 148 patients did [13]. On multivariate analysis the association between RN and ICI use trended toward significance (OR = 2.71, $p = 0.06$).

Previously published studies on the risk of RN in patients treated with ICIs have defined RN on the basis of radiographic findings with/without histopathologic confirmation. It is unclear from these reports how many patients were truly symptomatic from the changes identified on surveillance imaging. Our study is the first to establish the incidence of symptomatic RN requiring intervention in patients with brain metastases treated with both SRS and an ICI. We found that 7% of patients who received SRS and an ICI developed symptomatic RN. Primary pathology of renal cell carcinoma and metastases in the cerebral cortex were found to be risk factors for the development of symptomatic RN. Overall, the incidence of symptomatic RN was similar to the 7–10% rate of RN commonly reported in patients whose brain metastases are treated with SRS in the absence of an ICI [17,18]. Our findings suggest a limited, if any, additional risk to treating patients with SRS while receiving ICIs, as compared to treatment of brain metastases with SRS alone.

The results of this study offer important insight to clinicians treating patients with ICI-responsive cancers and brain metastases. Two recent phase II trials of ICI for patients with melanoma and brain metastases demonstrated a limited response of metastases less than 3 cm to medical therapy alone. These trials found an overall response rate of 46–57% with most of the patients having a partial or complete response, and less than 5% stable disease [19,20]. Despite a response rate much lower than the > 90% PR/CR typically seen with SRS, the authors of these studies have suggested in the discussion that medical therapy with ICI alone should replace the use of SRS for asymptomatic disease. One of their arguments for this assertion is that SRS carries a significant risk of RN. On the basis of anecdotal evidence and a small number of studies demonstrating increased radiographic RN with the combination of SRS and ICI, a general concern about the risks of RN has arisen in this patient population. Our study reveals that the true risk of a clinically significant adverse outcome from combined SRS and ICI treatment is small and should not be used as justification to forego proven effective treatment with SRS in patients who are receiving or will receive ICI treatment. Similar to other reports, our study found that patients who developed symptomatic RN had improved survival, with a median OS of 32 months in patients with symptomatic RN versus 29 months in the remaining patients. Therefore, the small risk of RN can be tolerated.

In our study, patients who developed symptomatic RN were initially treated with dexamethasone to reduce associated edema and symptoms. Three of four patients experienced sufficient resolution of symptoms with less than 2 weeks of dexamethasone, after which they were able to continue systemic therapy without further steroids. One patient required treatment with bevacizumab due to prolonged steroid dependence beyond 2 weeks. As these patients depend on a functional immune response for control of their entire tumor burden, prolonged immunosuppression with steroids should be avoided. Bevacizumab offers an excellent alternative to address edema and related symptoms without the associated immunosuppression of dexamethasone.

Admittedly, this study is limited by its retrospective design. Patient inclusion was biased by treatment at a single center and availability of records. Our study is also limited by its modest sample size. Given that only 4 of 57 patients developed symptomatic RN, our study lacks power to identify potential significant differences in risk factors for the development of symptomatic RN. Due to the limited sample size, a

multivariate logistic regression lacked power to identify risk factors despite differences in tumor type and location that were significant in univariate analysis. Additionally, our study may have underestimated the rate of symptomatic RN presenting with neurocognitive deficits. Although all patients received routine evaluation including a basic neurologic examination, rigorous neuropsychological testing was not performed. Such testing may reveal more cognitive deficits than are apparent in a short follow-up clinic visit. The ability to identify RN on MRI, as well as the decision to treat symptomatic RN, may have differed by provider adding another source of bias. Ultimately, a prospective, multi-centered database of SRS outcomes in patients treated with ICI is needed to clearly define the risks and predictive factors for development of RN in this patient population.

5. Conclusions

The incidence of symptomatic radiation necrosis in patients with brain metastases treated with both SRS and an ICI is as low as 7%, similar to the previously published risks of RN with SRS treatment alone. We recommend the use of combined SRS and ICIs to treat brain metastases, when indicated, on the basis of low symptomatic radiation necrosis rates and effectiveness.

References

[1] L. Nayak, E.Q. Lee, P.Y. Wen, Epidemiology of brain metastases, Curr. Oncol. Rep. 14 (1) (2012) 48–54.
[2] H. Takei, E. Rouah, Y. Ishida, Brain metastasis: clinical characteristics, pathological findings and molecular subtyping for therapeutic implications, Brain Tumor Pathol. 33 (1) (2016) 1–12.
[3] A.V. Tallet, F. Dhermain, E. Le Rhun, G. Noël, Y.M. Kirova, Combined irradiation and targeted therapy or immune checkpoint blockade in brain metastases: toxicities and efficacy, Ann. Oncol. 28 (12) (2017) 2962–2976.
[4] A.P. Kiess, J.D. Wolchok, C.A. Barker, M.A. Postow, V. Tabar, J.T. Huse, et al., Stereotactic radiosurgery for melanoma brain metastases in patients receiving ipilimumab: safety profile and efficacy of combined treatment, Int. J. Radiat. Oncol. Biol. Phys. 92 (2) (2015) 368–375.
[5] K. Tazi, A. Hathaway, C. Chiuzan, K. Shirai, Survival of melanoma patients with brain metastases treated with ipilimumab and stereotactic radiosurgery, Cancer Med. 4 (1) (2015) 1–6.
[6] A.W. Silk, M.F. Bassetti, B.T. West, C.I. Tsien, C.D. Lao, Ipilimumab and radiation therapy for melanoma brain metastases, Cancer Med. 2 (6) (2013) 899–906.
[7] J.P. Knisely, J.B. Yu, J. Flanigan, M. Sznol, H.M. Kluger, V.L. Chiang, Radiosurgery for melanoma brain metastases in the ipilimumab era and the possibility of longer survival, J. Neurosurg. 117 (2) (2012) 227–233.
[8] A.S. Berghoff, V.A. Venur, M. Preusser, M.S. Ahluwalia, Immune checkpoint inhibitors in brain metastases: from biology to treatment, American Society of Clinical Oncology Educational Book. American Society of Clinical Oncology. Meeting 35 (2016) e116–e122.
[9] A.A. Tarhini, J. Cherian, S.J. Moschos, H.A. Tawbi, Y. Shuai, W.E. Gooding, et al., Safety and efficacy of combination immunotherapy with interferon alfa-2b and tremelimumab in patients with stage IV melanoma, J. Clin. Oncol. 30 (3) (2012) 322.
[10] E.S. Anderson, M.A. Postow, J.D. Wolchok, R.J. Young, Å. Ballangrud, T.A. Chan, et al., Melanoma brain metastases treated with stereotactic radiosurgery and concurrent pembrolizumab display marked regression; efficacy and safety of combined treatment, J. Immunother. Cancer 5 (1) (2017) 76.
[11] K.A. Ahmed, S. Kim, J. Arrington, A.O. Naghavi, T.J. Dilling, B.C. Creelan, et al., Outcomes targeting the PD-1/PD-L1 axis in conjunction with stereotactic radiation for patients with non-small cell lung cancer brain metastases, J. Neurooncol. 133 (2) (2017) 331–338.
[12] K. Diao, S.X. Bian, D.M. Routman, C. Yu, P.E. Kim, N.A. Wagle, et al., Combination ipilimumab and radiosurgery for brain metastases: tumor, edema, and adverse radiation effects, J. Neurosurg. (2018) 1–10.
[13] R.J. Colaco, P. Martin, H.M. Kluger, J.B. Yu, V.L. Chiang, Does immunotherapy increase the rate of radiation necrosis after radiosurgical treatment of brain metastases? J. Neurosurg. 125 (1) (2016) 17–23.
[14] J.D. Wolchok, V. Chiarion-Sileni, R. Gonzalez, P. Rutkowski, J.J. Grob, C.L. Cowey, et al., Overall survival with combined nivolumab and ipilimumab in advanced melanoma, N. Engl. J. Med. 377 (14) (2017) 1345–1356.
[15] R.J. Motzer, N.M. Tannir, D.F. McDermott, O. Arén Frontera, B. Melichar, T.K. Choueiri, et al., Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma, N. Engl. J. Med. 378 (14) (2018) 1277–1290.
[16] L. Gandhi, D. Rodríguez-Abreu, S. Gadgeel, E. Esteban, E. Felip, F. De Angelis, et al., Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer, N. Engl. J. Med. (2018).
[17] G. Minniti, E. Clarke, G. Lanzetta, M.F. Osti, G. Trasimeni, A. Bozzao, et al., Stereotactic radiosurgery for brain metastases: analysis of outcome and risk of brain radionecrosis, Radiat. Oncol. 6 (1) (2011) 48.
[18] L.S. Chin, L. Ma, S. DiBiase, Radiation necrosis following gamma knife surgery: a case-controlled comparison of treatment parameters and long-term clinical follow up, J. Neurosurg. 94 (6) (2001) 899–904.
[19] G.V. Long, V. Atkinson, S. Lo, S. Sandhu, A.D. Guminski, M.P. Brown, et al., Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study, Lancet Oncol. 19 (5) (2018) 672–681.
[20] H.A. Tawbi, P.A. Forsyth, A. Algazi, O. Hamid, F.S. Hodi, S.J. Moschos, et al., Combined nivolumab and ipilimumab in melanoma metastatic to the brain, N. Engl. J. Med. 379 (8) (2018) 722–730.