Repeat courses of SRS in patients initially treated with SRS alone for brain-metastatic melanoma

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Summary points

- The treatment of patients with repeat courses of stereotactic radiosurgery is both well tolerated and efficacious in patients with brain-metastatic melanoma.
- The majority of patients fail systemically prior to death; novel immunotherapeutic agents control systemic disease more effectively than previous treatments and may work synergistically with stereotactic radiosurgery to enhance intracranial control.

Aim: Stereotactic radiosurgery (SRS) is often used in the treatment of brain metastatic melanoma. Little data exist regarding outcomes of repeat course of SRS in this population. We aimed to identify treatment outcomes and toxicities in melanoma patients treated with repeat SRS after upfront SRS. **Patients & methods:** We reviewed ten consecutive patients treated with repeat SRS following upfront SRS alone for brain metastatic melanoma. **Results:** The median overall survival from initial treatment was 17.5 months. The median overall survival from repeat SRS was 6.7 months with a 6-month local control rate of 80%. The majority of patients progressed systemically before death. Four patients reported six adverse events, all grade 1. **Conclusion:** Prospective study regarding the safety and efficacy of repeat courses of SRS in patients with brain-metastatic melanoma, especially in combination with novel immunotherapies, is warranted.

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Melanoma is one of the most frequent malignancies to metastasize to the brain [1]. Prognosis following brain metastasis in patients with melanoma is extremely poor, worse than the prognosis following brain metastases from non-small-cell lung cancer, breast cancer or renal cell carcinoma, with a median overall survival (OS) of less than a year [2]. Factors associated with poor OS include worse performance status and greater number of intracranial lesions [2,3]. Stereotactic radiosurgery (SRS) can be extremely effective in the treatment of brain metastases from melanoma, with 1-year local control rates ranging from 50 to 90% [4–6]. Whole-brain radiotherapy (WBRT) is also frequently used in the treatment of brain metastatic disease although it has been linked to neurocognitive decline [7]. Recent prospective study has shown that in patients with one to three brain metastases of any tumor histology, the addition of WBRT to SRS resulted in decreased cognitive function and offered no OS benefit [8]. Current prospective studies are investigating the addition of WBRT to SRS and/or surgical resection in patients with brain-metastatic melanoma [9].

Patients with brain metastatic melanoma represent a population in whom the neurocognitive adverse effects of WBRT are particularly clinically meaningful. Patients with melanoma are often

KEYWORDS

• immunotherapy • skin (melanoma) • stereotactic radiotherapy

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younger than the average cancer patient; melanoma is the second most common malignancy in men aged 20–29 years and fourth most common among women aged 20–29 years [10]. Recent advances in the use of targeted immunotherapy, especially those targeted at the PD-1 receptor, have drastically improved survival of patients with metastatic melanoma [11–14]. This combination of young patients and recent advances in systemic therapy suggests that patients with brain-metastatic melanoma may yield a significant benefit in quality of life from avoiding the neurocognitive decline associated with WBRT.

SRS can be used as salvage therapy for brain metastases that are recurrent and/or newly developed after an initial course of SRS and/or WBRT. On retrospective analysis, upfront treatment with SRS alone does result in any decrease in OS compared with those treated with upfront WBRT and SRS. Additionally, there was a cost savings in those treated with upfront SRS alone, even when accounting for salvage therapy [15]. Retrospective analysis of 95 patients showed that repeat courses of SRS were well tolerated and efficacious; patients with melanoma ($n = 16$ patients) had a decreased OS ($p = 0.03$) relative to those with other histologies [16]. Given both the evidence of decreased OS and more rapid distant brain failure in patients with brain-metastatic melanoma relative to patients with brain metastases from other primary malignancies, we aimed to investigate a single-institution experience of repeat courses of SRS in 10 patients with brain-metastatic melanoma [2,16–17]. While this represents a relatively small cohort of patients, there is sparse literature on the use of repeat SRS. Given the significant recent advances in systemic control of melanoma with immunotherapeutic agents and the known neurocognitive effects of WBRT, further descriptions of the outcomes of patients treated with repeat courses of SRS in place of WBRT are valuable in guiding future care decisions.

Patients & methods

Institutional review board approval was obtained to review the records of patients treated for brain-metastatic melanoma from January 2003 to July 2013 in the Department of Radiation Oncology at University of Rochester Medical Center. Chart review was used to identify those patients who received multiple courses of SRS. All patients who received upfront WBRT were excluded. Patients who had SRS to the surgical cavity

following resection were included. Additional information was also abstracted from their chart relating to patient demographics, treatment and outcomes. The diagnosis-specific graded prognostic assessment (DS-GPA) specific for melanoma that includes Karnofsky performance status and number of intracranial metastases was used to separate patients into prognostic groupings [2,3]. Extracranial disease was defined as the presence of any evidence of disease on the most recent body imaging (CT, MR, or PET) at time of referral to radiation oncology. Of note, data for all patients treated with radiation for brain-metastatic melanoma from a similar time period at this department were published previously [18].

A LINAC-based SRS planning and delivery system was used. Patients were immobilized using a BrainLAB neurosurgical head frame. Beam shaping was accomplished with multi-leaf collimators and radiation was delivered with 6 MV photons. The gross tumor volume was defined based on MR and CT imaging. The planning target volume was equivalent to the gross tumor volume. BrainLAB planning software was used to generate a treatment plan using multiple arcs with either fixed-shape or dynamic-shaped fields. The prescribed dose to the isocenter was 15–20 Gy (median: 18 Gy). The 80% isodose line covered $\geq 99\%$ of the planning target volume. Doses to critical structures were evaluated prior to the finalization of each plan. Quality assurance was carried out as previously described [19]. The use of SRS, WBRT or the combination WBRT and SRS was determined at the discretion of the treating radiation oncologist based upon each patient's specific clinical scenario.

Local disease progression was defined via the RECIST criteria, version 1.1 in the majority of cases [20]. Post-radiation necrosis and edema were considered in several patients and investigated via serial MR scans, MR perfusion and MR spectroscopy imaging. All cases were discussed at a multidisciplinary tumor board. In the event that asymptomatic necrosis or edema were determined by clinical consensus as the most likely cause of any 'increase' in lesion size, that patient was deemed not to have failed locally unless progression was evident on serial MRI scans. Distant brain failure was defined as any new site of metastatic disease within the brain parenchyma on follow-up imaging. OS was defined as the time to death or last follow-up. Brain progression-free survival (BPFS) was defined as

time to local or distant brain recurrence, death or last follow-up. Categorical data are described with absolute frequency counts and ranges, continuous data are described via their median and range. The Kaplan–Meier method was used to determine survival statistics. The Cox proportional hazards model was used to determine relationships between patient characteristics and outcomes in both a univariate and multivariate manner. A predetermined p-value of 0.05 was used as a significant cutoff. All statistics were performed using STATA version 11 (StataCorp, TX, USA).

Results

• Patient characteristics

A total of ten patients with brain-metastatic melanoma were treated with repeat SRS as summarized in [Table 1](#). Their median age was 54.3 years (range: 47.6–78.0 years); six of the patients were under 60 years of age. Seven of the patients were male. Eight patients had a single initial intracranial metastasis, while two patients had multiple intracranial metastases, one with three and the other with eight. Seven patients had extracranial disease at the time of initial referral to radiation oncology. Seven patients had a DS-GPA score of 4, one had a score of 3, and two had a score of 2. Five patients had a total of five intracranial lesions surgically resected prior to any SRS. No patients were receiving active chemotherapy at the time of SRS.

• Outcomes

The median OS from completion of initial SRS of this cohort was 17.5 months with a range of 9.8–30.1 months as shown in [Figure 1](#). The median time to second course of SRS was 5.5 months with a range of 1.5–23.3 months. Two patients were treated with fractionated SRS to 30 Gy in three fractions, otherwise the prescribed dose in the second SRS course ranged from 17.5 to 20 Gy in 1 fraction. Four patients (40%) had the initial treated lesion(s) retreated. The number of retreated lesions ranged from one (n = 3 patients) to two (n = 1 patient). Three of the four patients who underwent SRS to a previously treated lesion also had simultaneous treatment of new intracranial lesions with SRS. Among those four patients, three received single-fraction SRS ranging from 17.5 to 20 Gy; one received fractionated SRS to a total of 30 Gy in three fractions.

The median OS following the second course of SRS was 6.7 months with a range of 1.5–23.3 months as shown in [Figure 2](#). Four patients went on to have a third course of SRS and one had a fourth course of SRS. Five patients (50%) went on to have WBRT (at the discretion of the treating physician) at some point following their second course of SRS. The median duration between completion of initial SRS and salvage WBRT was 14.6 months with a range of 7.8–17.1 months. No patients were treated with WBRT for local failure; all patients developed

Table 1. Characteristics of patients who underwent repeat stereotactic radiosurgery for brain metastatic melanoma (n = 10).

Variable	n (%)
Age >65 years	2 (20)
Male gender	7 (70)
Current smoker	0 (0)
Current alcohol consumption	6 (60)
Presence of extracranial disease	7 (70)
>1 Intracranial metastasis	2 (20)
Radiologic evidence of intratumoral hemorrhage	4 (40)
Surgery	5 (50)
Number of SRS courses:	
– 2	6 (60)
– 3	3 (30)
– 4	1 (10)
DS-GPA:	
– 2	2 (20)
– 3	1 (10)
– 4	7 (70)

DS-GPA: Diagnosis-specific graded prognostic assessment; SRS: Stereotactic radiosurgery.

distant brain failure and were subsequently treated with WBRT. The median BPFS was 2.3 months from completion of repeat SRS with a range of 1.5–12.5 months. The 6-month local control rate was 80%; the 12-month local control rate was 60%. Distant brain failure was noted in 70% of patients prior to death. Progression of extracranial disease was present in 60% of patients prior to death.

As shown in Table 2, gender, initial surgical resection, presence of extracranial disease, nor DS-GPA at initial referral had a statistically significant effect on OS. Receipt of SRS to the same site as retreatment nor a duration less than 6 months between initial and repeat SRS had a statistically significant effect on OS from time of second SRS.

• Adverse events

The frequency and severity of adverse events from the repeat course of SRS was judged at the patient's first follow-up following the second course of SRS. Adverse events were defined via the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 based on retrospective review. Four patients complained of six new adverse events, all grade one. Fatigue was the most common event, with two patients reporting this. Other complaints included

vertigo, alopecia, blurred vision and nausea. Of those receiving SRS to the same site for a second time, 25% (one of four) had any complaint. Of those receiving repeat SRS to new lesions, 50% (three of six) had any complaint.

Discussion

While our analysis includes a small number of patients, our results suggest that repeat SRS is both efficacious and safe for patients with brain-metastatic melanoma. The median OS of 6.7 months following the second SRS is slightly lower than in previous reports on heterogeneous populations reporting median OS between 7 and 11 months [16,21–22]. This is likely due to the worse prognosis that brain-metastatic melanoma carries relative to other brain-metastatic malignancies in this setting [16]. The excellent local control reported here and elsewhere suggests that while traditionally thought of as a radioresistant histology, melanoma may be particularly sensitive to the effects of hypofractionated radiotherapy. This increased response to hypofractionated radiotherapy may additionally suggest further benefit to SRS as compared with WBRT [4–6,23].

Upfront WBRT for brain metastatic disease is associated with a resultant decreased quality of life [7,24]. In patients with brain metastases from non-small-cell lung cancer, the risk of

Figure 1. Kaplan–Meier survival plot showing the overall survival from time of completion of initial stereotactic radiosurgery of patients with brain metastatic melanoma.

Figure 2. Kaplan–Meier survival plot showing the overall survival from time of completion of repeat stereotactic radiosurgery of patients with brain metastatic melanoma.

neurocognitive decline from disease progression in patients treated with upfront SRS was found to be relatively decreased compared with historical data for patients who had upfront WBRT [25]. Our cohort is notable for relatively young age; 60% of patients were under 60 years of age at time of initial referral to radiation oncology. These younger patients may particularly benefit from avoiding the neurocognitive side effects associated with WBRT. We did not analyze neurocognitive function here due to the retrospective design of this study, but given the high efficacy and safety of upfront SRS and the likely neurocognitive benefits of avoiding WBRT, we would strongly recommend the consideration of upfront use of SRS in patients with brain-metastatic melanoma where possible.

One potential risk in the management of brain-metastatic disease with local therapy alone, such as SRS, is an increased risk of failure elsewhere in the brain [26]. This was especially pronounced in this cohort as 70% of patients experienced distant brain failure prior to death. Additionally, the median BPFS following second SRS was relatively short at 2.3 months. This emphasizes the role for frequent screening, even of asymptomatic patients. In a retrospective analysis of patients treated with upfront SRS for brain metastatic malignancy of any type, patients who had symptom-based follow-up

imaging had higher rates of all-cause mortality, craniotomy and prolonged hospitalizations relative to those who had routine follow-up imaging. Accounting for this, routine screening saves approximately US\$1326 per patient relative to symptom-based imaging [27]. The current National Comprehensive Cancer Network guidelines recommend 2-month interval for brain imaging for the first year following SRS alone. Prior studies support this, recommending a 2–3-month interval between brain imaging and prolonging that interval one year following the completion of SRS [28,29]. Prospective study is required to determine the ideal intervals for screening brain imaging in this high-risk population.

Our study cohort's outcomes also highlight that in patients with brain-metastatic melanoma, the vast majority progress systemically prior to death. New systemic therapies such as those targeted at PD-1 have significantly altered the course of patients with metastatic melanoma [12–14,30]. The patients in this study were treated prior to the FDA approval of either nivolumab or pembrolizumab, and as such, their effect on the rates of systemic failure in these patients could not be assessed. PD-L1 expression is also high in histologic specimens of brain metastases from melanoma, which may indicate that these novel immunotherapeutic drugs may also help

Table 2. Univariate analysis of various factors on overall survival in patients treated with repeat stereotactic radiosurgery for brain metastatic melanoma (n = 10).

Variable	OS (months)	HR	95% CI	p-value
<i>OS calculated from completion of initial therapy</i>				
Gender:				
– Male	17.5	2.72	0.54–13.5	0.22
– Female	23.7	–	–	–
Surgical resection:				
– Yes	20.4	0.55	0.14–2.08	0.37
– No	15.6	–	–	–
Extracranial disease:				
– Present	17.5	2.00	0.41–9.84	0.39
– Absent	20.4	–	–	–
DS-GPA:				
– 2	9.8	0.97	0.18–5.06	0.97
– 3	20.4	0.89	0.10–7.75	0.92
– 4	17.5	–	–	–
<i>OS calculated from completion of second course of SRS</i>				
Duration between initial and repeat SRS:				
– ≥6 months	12.5	–	–	–
– <6 months	3.8	1.61	0.41–6.27	0.50
Repeat SRS to same site as initial SRS:				
– Yes	4.7	1.61	0.40–6.54	0.51
– No	6.7	–	–	–

DS-GPA: Diagnosis-specific graded prognostic assessment; HR: Hazard ratio; OS: Overall survival; SRS: Stereotactic radiosurgery.

in intracranial control [31]. The effects of PD-1 inhibitors may also be synergistic with the effects of radiotherapy, which may further advance the prognosis of patients with brain metastatic melanoma [32,33]. This era of rapid advances in the treatment of metastatic melanoma further enhances the neurocognitive risks of WBRT and emphasizes the role of upfront SRS in patients with brain metastatic melanoma.

The limitations in this study are those inherent to any retrospective analysis. It is difficult to truly analyze toxicities of a given treatment in any retrospective manner without formalized follow-up intervals. Further, the high median OS in this patient population may represent a selection bias toward the initial management of brain metastatic disease with SRS alone in patients with a higher performance status or enhanced prognosis. The sample size of this analysis is also relatively small, limiting the strength of any conclusions that can be drawn from this analysis.

Conclusion

In this hypothesis-generating study, we analyzed the efficacy and safety of repeat course of SRS in patients with brain-metastatic

melanoma. In general, the treatment was efficacious with a 80% 6-month local control rate and no adverse events that were grade 2 or above. The median BPFS was relatively short at 2.3 months, emphasizing the role of routine screening for new brain metastases in these patients following repeat SRS. The vast majority of patients failed systemically prior to death, however recent advances in systemic treatment may alter this dynamic. We recommend further prospective study into the safety and efficacy of repeat courses of SRS in patients with brain-metastatic melanoma with an emphasis on defining the ideal interval for brain imaging and determining the effect of novel immunotherapeutic interventions on the natural history of these patients.

Future perspective

In 5–10 years, the systemic control of metastatic melanoma will likely be significantly improved from where it is today as the development and deployment of novel immunotherapeutic agents hastens. Some of these agents will have efficacy against CNS disease. The risk of neurocognitive decline following WBRT is becoming more relevant, as many patients with brain-metastatic

melanoma will live long enough to experience those effects. More localized treatment (such as SRS) for brain-metastatic disease, even in the setting of multiple lesions, should be prospectively studied to report intracranial tumor control, need for salvage SRS or WBRT, neurocognitive outcomes, and quality of life outcomes.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

References

Papers of special note have been highlighted as:

• of interest; •• of considerable interest

- Gavrilovic IT, Posner JB. Brain metastases: epidemiology and pathophysiology. *J. Neurooncol.* 75(1), 5–14 (2005).
- Sperduto PW, Chao ST, Sneed PK *et al.* Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. *Int. J. Radiat. Oncol. Biol. Phys.* 77(3), 655–661 (2010).
- A simple, well-verified, widely-used prognostic criteria for survival in patients with newly-diagnosed brain metastases.
- Sperduto PW, Berkey B, Gaspar LE, Mehta M, Curran W. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. *Int. J. Radiat. Oncol. Biol. Phys.* 70(2), 510–514 (2008).
- Mori Y, Kondziolka D, Flickinger JC, Kirkwood JM, Agarwala S, Lunsford LD. Stereotactic radiosurgery for cerebral metastatic melanoma: factors affecting local disease control and survival. *Int. J. Radiat. Oncol. Biol. Phys.* 42(3), 581–589 (1998).
- Rades D, Sehmisch L, Huttenlocher S *et al.* Radiosurgery alone for 1–3 newly-diagnosed brain metastases from melanoma: impact of dose on treatment outcomes. *Anticancer Res.* 34(9), 5079–5082 (2014).
- Selek U, Chang EL, Hassenbusch SJ 3rd. Stereotactic radiosurgical treatment in 103 patients for 153 cerebral melanoma metastases. *Int. J. Radiat. Oncol. Biol. Phys.* 59(4), 1097–1106 (2004).
- A large, retrospective review showing the efficacy of stereotactic radiosurgery (SRS) in the treatment of brain metastases from melanoma, especially in those with tumors less than 2 cm³.
- Chang EL, Wefel JS, Hess KR *et al.* Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol.* 10(11), 1037–1044 (2009).
- A prospective trial showing that at 4 months, patients treated with SRS and whole brain radiotherapy for newly diagnosed brain metastases had worse declines in learning and memory function than those treated with SRS alone.
- Brown PD, Asher AL, Ballman KV *et al.* NCCTG N0574 (alliance): a Phase III randomized trial of whole brain radiation therapy (WBRT) in addition to radiosurgery (SRS) in patients with 1 to 3 brain metastases. *J. Clin. Oncol.* 33(Suppl), Abstract LBA4 (2015).
- Fogarty G, Morton RL, Vardy J *et al.* Whole brain radiotherapy after local treatment of brain metastases in melanoma patients – a randomised Phase III trial. *BMC Cancer* 11, 142 (2011).
- Desantis CE, Lin CC, Mariotto AB *et al.* Cancer treatment and survivorship statistics, 2014. *CA Cancer J. Clin.* 64(4), 252–271 (2014).
- Postow MA, Chesney J, Pavlick AC *et al.* Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N. Engl. J. Med.* 372(21), 2006–2017 (2015).
- Robert C, Long GV, Brady B *et al.* Nivolumab in previously untreated melanoma without BRAF mutation. *N. Engl. J. Med.* 372(4), 320–330 (2015).
- Robert C, Ribas A, Wolchok JD *et al.* Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a Phase 1 trial. *Lancet* 384(9948), 1109–1117 (2014).
- Robert C, Schachter J, Long GV *et al.* Pembrolizumab versus ipilimumab in advanced melanoma. *N. Engl. J. Med.* 372(26), 2521–2532 (2015).
- Hsu F, Kouhestani P, Nguyen S *et al.* Population-based outcomes of boost versus salvage radiosurgery for brain metastases after whole brain radiotherapy. *Radiother. Oncol.* 108(1), 128–131 (2013).
- Shultz DB, Modlin LA, Jayachandran P *et al.* Repeat courses of stereotactic radiosurgery (SRS), deferring whole-brain irradiation, for new brain metastases after initial SRS. *Int. J. Radiat. Oncol. Biol. Phys.* 92(5), 993–999 (2015).
- A retrospective review of patients treated at a single-institution showing the safety and efficacy of repeat courses of SRS in the management of brain metastases.
- Press RH, Prabhu RS, Nickleach DC *et al.* Novel risk stratification score for predicting early distant brain failure and salvage whole-brain radiotherapy after stereotactic radiosurgery for brain metastases. *Cancer* 121(21), 3836–3843 (2015).
- Bates JE, Youn P, Usuki KY *et al.* Brain metastasis from melanoma: the prognostic value of varying sites of extracranial disease. *J. Neurooncol.* 125(2), 411–418 (2015).
- Biswas T, Sandhu AP, Singh DP *et al.* Low-dose radiosurgery for benign intracranial lesions. *Am. J. Clin. Oncol.* 26(4), 325–331 (2003).
- Eisenhauer EA, Therasse P, Bogaerts J *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur. J. Cancer* 45(2), 228–247 (2009).
- Chen JC, Petrovich Z, Giannotta SL, Yu C, Apuzzo ML. Radiosurgical salvage therapy for patients presenting with recurrence of

- metastatic disease to the brain. *Neurosurgery* 46(4), 860–866; discussion 866–867 (2000).
- 22 Kwon KY, Kong DS, Lee JI, Nam DH, Park K, Kim JH. Outcome of repeated radiosurgery for recurrent metastatic brain tumors. *Clin. Neurol. Neurosurg.* 109(2), 132–137 (2007).
- 23 Powell JW, Chung CT, Shah HR *et al.* Gamma Knife surgery in the management of radioresistant brain metastases in high-risk patients with melanoma, renal cell carcinoma, and sarcoma. *J. Neurosurg.* 109(Suppl), 122–128 (2008).
- 24 Li J, Bentzen SM, Li J, Renschler M, Mehta MP. Relationship between neurocognitive function and quality of life after whole-brain radiotherapy in patients with brain metastasis. *Int. J. Radiat. Oncol. Biol. Phys.* 71(1), 64–70 (2008).
- A retrospective review of data from a prospective trial showing that the declines in neurocognitive function associated with whole brain radiotherapy are also associated with a subsequent decline in quality of life.
- 25 Mariya Y, Sekizawa G, Matsuoka Y, Seki H, Sugawara T, Sasaki Y. Repeat stereotactic radiosurgery in the management of brain metastases from non-small cell lung cancer. *Tohoku J. Exp. Med.* 223(2), 125–131 (2011).
- 26 Soon YY, Tham IW, Lim KH, Koh WY, Lu JJ. Surgery or radiosurgery plus whole brain radiotherapy versus surgery or radiosurgery alone for brain metastases. *Cochrane Database Syst. Rev.* 3, CD009454 (2014).
- 27 Lester SC, Taksler GB, Kuremsky JG *et al.* Clinical and economic outcomes of patients with brain metastases based on symptoms: an argument for routine brain screening of those treated with upfront radiosurgery. *Cancer* 120(3), 433–441 (2014).
- 28 Lutterbach J, Cyron D, Henne K, Ostertag CB. Radiosurgery followed by planned observation in patients with one to three brain metastases. *Neurosurgery* 62(Suppl. 2), 776–784 (2008).
- 29 Sheehan JP, Yen CP, Nguyen J, Rainey JA, Dassoulas K, Schlesinger DJ. Timing and risk factors for new brain metastasis formation in patients initially treated only with gamma knife surgery. Clinical article. *J. Neurosurg.* 114(3), 763–768 (2011).
- 30 Ribas A, Puzanov I, Dummer R *et al.* Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, Phase 2 trial. *Lancet Oncol.* 16(8), 908–918 (2015).
- 31 Berghoff AS, Ricken G, Widhalm G *et al.* Tumour-infiltrating lymphocytes and expression of programmed death ligand 1 (PD-L1) in melanoma brain metastases. *Histopathology* 66(2), 289–299 (2015).
- An immunohistochemical review of brain metastases from melanoma finding a large proportion of lymphocytic infiltrates and high PD-L1 expression, suggesting anti-PD1 therapies may be beneficial in the control of melanoma brain metastases.
- 32 Postow MA, Callahan MK, Barker CA *et al.* Immunologic correlates of the abscopal effect in a patient with melanoma. *N. Engl. J. Med.* 366(10), 925–931 (2012).
- 33 Twyman-Saint Victor C, Rech AJ, Maity A *et al.* Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. *Nature* 520(7547), 373–377 (2015).