Cureus

Open Access Case Report

DOI: 10.7759/cureus.2034

Advanced Survival in Patients with Multiple Irradiations for Brain Melanoma Metastases and Associated Abscopal Effect

Mikhail V. Galkin [1] , Andrey V. Golanov [2] , Elena Vetlova [3] , Sergey Banov, Valery V. Kostjuchenko [5]

1. Department of Radotherapy and Radiosurgery, Federal State Autonomous Institution «n.n. Burdenko National Medical Research Center of Neurosurgery» of the Ministry of Health of the I Russian Federation 2. Department of Radiation Oncology, Burdenko Neurosurgery Institute 3. Radiation Oncology Department, Burdenko Neurosurgical Institute 4. 5. Gamma Knife, Neurosurgery Business Center

Corresponding author: Mikhail V. Galkin, mgalkin@nsi.ru
Disclosures can be found in Additional Information at the end of the article

Abstract

Brain metastases are often detected in melanoma patients. Central nervous system (CNS) involvement is usually associated with poor prognosis. We describe a case of a female patient with multiple melanoma brain metastases who survived for 49 months after detection of CNS involvement and the first radiosurgery. She underwent several courses of irradiation (five radiosurgeries, stereotactic hypofractionated radiotherapy, and whole brain radiotherapy), chemotherapy (started in 12 months after the first radiosurgery), and targeted therapy (started 30 months after the first radiosurgery). The clear abscopal effect in the form of disappearance of intradermal lesions was observed after the second radiosurgery without any systemic treatment. We believe that the application of combination of different treatment modalities can significantly prolong survival in certain patients with melanoma brain metastases, and can be recommended even in case of poor prognosis.

Categories: Radiation Oncology, Neurosurgery, Oncology
Keywords: radiosurgery, abscopal effect, brain metastases, metastatic melanoma, hypofractionation

Introduction

Melanoma is characterized by high probability of brain involvement. From the stage of primary cutaneous melanoma, progression develops in about one-third of cases [1]. According to clinical and imaging data, central nervous system (CNS) metastases were found in 2-20% of patients and in 36-54% of cases according to autopsy studies [1]. The median overall survival for patients with melanoma brain metastases is 9.8 months [2]. Several treatments have been shown to significantly improve the life expectancy in these patients. They are immunotherapy and targeted BRAF- and MEK-inhibitors [3, 4]. Data about the effectiveness of conventional chemotherapy, whole brain radiotherapy, radiosurgery, and surgery are more controversial [3, 5]. Much attention is paid to the investigation of the abscopal effect which is often observed after a combination of immunotherapy with irradiation, and is associated with a higher survival in patients with melanoma metastases [6]. The irradiation alone induces the effect very rarely.

We present a case of a female patient with melanoma who was treated with several courses of irradiation (with five courses of radiosurgery (single fraction) among them, whole brain radiotherapy and stereotactic hypofractionated radiotherapy (three fractions)), which provided prolonged survival of 49 months from brain metastases detection. The interesting fact is that

Received 11/28/2017
Review began 12/01/2017
Review ended 01/02/2018
Published 01/07/2018

How to cite this article
Galkin M V, Golanov A V., Vetlova E, et al. (January 07, 2018) Advanced Survival in Patients with Multiple Irradiations for Brain Melanoma Metastases and Associated Abscopal Effect. Cureus 10(1): e2034. DOI 10.7759/cureus.2034

the radiosurgical treatment was followed by the development of abscopal effect in the form of disappearance of intradermal lesions without any systemic therapy.

Case Presentation

In May 2011, a 37-year-old woman underwent surgical resection of the melanoma in the sacrum area. Further investigation performed at the end of 2015 (when the analysis had become available) revealed malignant melanoma with V600M mutation in the BRAF gene. In May 2012, due to progression, the inguinal-femoral lymphadenectomy was performed. The patient was not recommended any systemic treatment. In June 2013, screening magnetic resonance imaging (MRI) found multiple relatively small brain metastases without edema and mass effect. The Karnofsky performance status (KPS) was 90 at that time.

In the same month (25 months from the disease onset), the patient was treated with Gamma-Knife radiosurgery (Figure *1*). During the session, overall 19 targets were irradiated with a marginal dose of 24 Gy prescribed for 52-91% isodose line. The mean volume of treated metastases composed 0.107 ccm (0.005-0.727 ccm). Despite the recommendation, the systemic treatment was postponed. Local oncologists evaluated her prognosis as very poor and refused to perform any systemic treatment. In six months, brain MRI demonstrated growth in four of 19 previously irradiated metastases and emergence of five new lesions. At the same period, the patient noticed the appearance of intradermal nodes on her arms and chest.

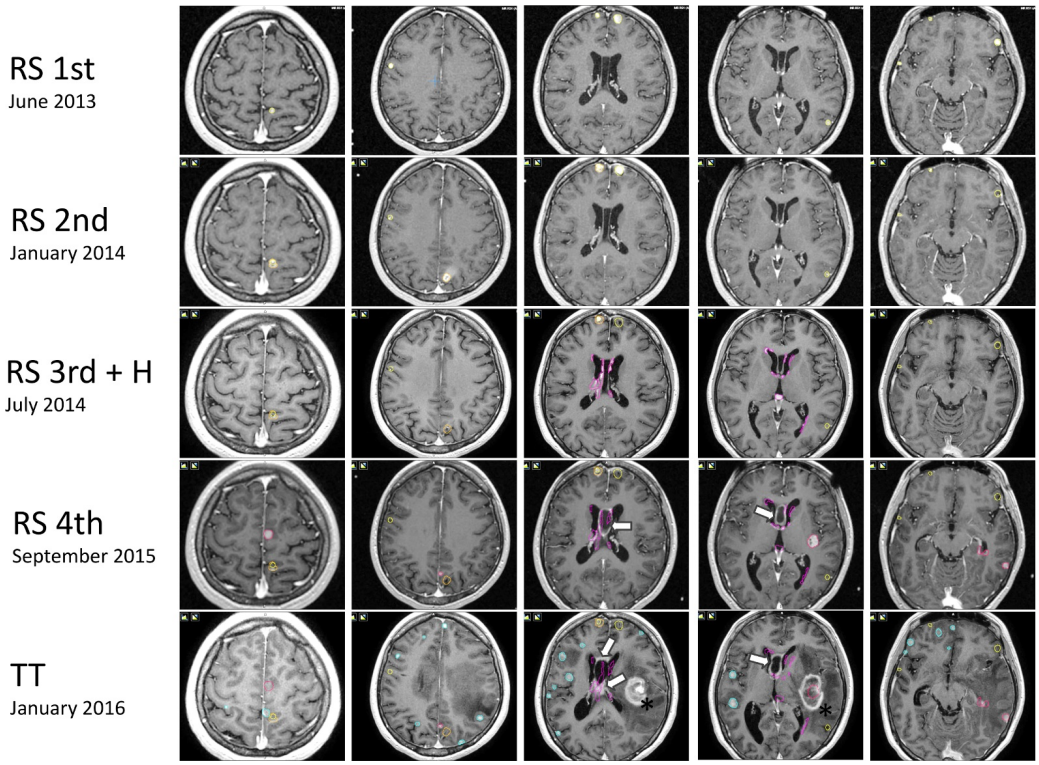

FIGURE 1: Demonstration of course of intracranial disease with serial magnetic resonance imaging (MRIs) (axial T1 with contrast enhancement) from the first radiosurgery to targeted therapy.

Abbreviations on the left represent different stages of treatment: RS 1-5 – MRIs during radiosurgeries, H – MRI before hypofractionated irradiation, TT – MRI before the initiation of targeted therapy.

The color of the contour indicates the stage when the lesion was treated: yellow – the 1st radiosurgery, orange – the 2nd radiosurgery, pink – the 3rd radiosurgery and hypofractionation, red – the 4th radiosurgery, blue – lesions before the initiation of targeted therapy.

Arrows point on posttreatment changes after the 3rd irradiation in the area of septa pellucida; asterisk indicates the hemorrhage which emerged in one of the lesion treated with the 4th radiosurgery.

The second course of radiosurgical irradiation of all new and recurring lesions was performed with Gamma-Knife in January, 2014 (Figure *1*). Nine lesions with the mean volume of 0.197 ccm (0.01-0.389 ccm) were irradiated with the marginal dose of 20 and 24 Gy prescribed to the 50-82% isodose line. The systemic treatment was not started. During three months after radiosurgery, the patient noticed complete regression of intradermal metastases without any systemic treatment. In six months, the new brain MRI showed dissemination of the disease along the ventricular system with the emergence of multiple small lesions, mainly, in the bodies of both lateral ventricles, and larger lesions in the hypothalamic area, pineal region and the lateral parts of the fourth ventricle. No new metastases in the brain parenchyma were revealed. The cerebrospinal fluid (CSF) cytology was not performed. At this moment (37 months after the disease onset and 12 months after the first radiosurgery), the systemic treatment with Cisplatin and Temozolomide was started.

In July 2014, the patient was treated with CyberKnife (Figure *1*). The choice of the apparatus was based on the shape of a conglomerate of metastases in the lateral ventricles and the decision to perform hypofractionated irradiation. At the first stage, four metastases (in the posterior horn of the left lateral ventricle) with the total volume of 0.215 ccm were irradiated radiosurgically with the mean dose of 20.3 Gy, and the prescription dose of 18.5 Gy for 77% isodose line. In two days, the second stage of hypofractionated treatment with CyberKnife was launched (Figure *2*). The irradiation was performed in three fractions with 48 hours interfraction interval. The first target composed by 11 lesions (in the body of the left lateral ventricle) with the total volume of 1.5 ccm, the second target composed by 11 lesions (in the body of the right lateral ventricle) with the total volume of 3.2 ccm, and the third target (in the pineal region) with the volume of 0.4 ccm were irradiated up to mean dose of 24 Gy (22.6 Gy prescribed for 85% isodose line). Systemic treatment with Cisplatin and Temozolomide was continued up to 10 courses. MRI in two months after the irradiation revealed partial response of several irradiated lesions, and stabilization of others. MRI in 12 months demonstrated complete response of the ventricular lesions. At the same time, the posttreatment changes in the corpus callosum and septa pellucida were found. In 14 months, again, progression was detected, which manifested by the emergence of new metastases.

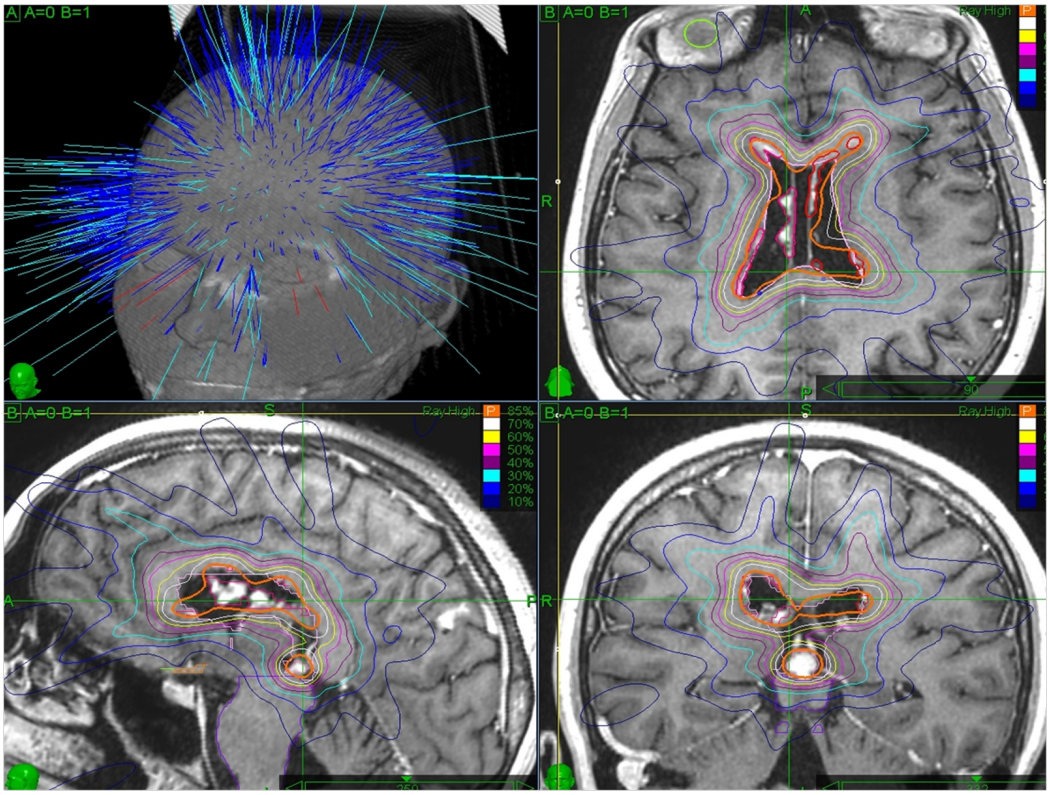

FIGURE 2: Dose distribution during the hypofractionated irradiation of ventricular lesions.

Targets in the lateral ventricles are contoured with red and purple lines. Orange contour is the prescription isodose line.

Another radiosurgical treatment was performed with Gamma-Knife unit in September, 2015 (52 months from the disease onset, 27 months from the first intracranial progression) (Figure *1*). Sixteen targets with the mean volume 0.165 ccm (0.006-1.011 ccm) were irradiated with the marginal dose of 24 Gy prescribed to 51-92% isodose line. In two months, the patient experienced rapid development of right-sided hemiparesis and aphasia. MRI demonstrated the emergence of 10 new metastases and hemorrhage in the place of metastasis in the left parietal lobe. The BRAF mutation was found at this time, and targeted therapy (Vemurafenib) was recommended. Again, due to some problems, the recommended treatment was not started, and the previous regimen with Cisplatin and Temozolomide was continued with grade 3-4 treatment toxicity detected. In two months, MRI demonstrated more than 20 new metastases and enlargement of 10 lesions found with previous MRI. Also, seven intradermal metastases were found in the skin of forearm, shoulder, and chest.

The targeted therapy with Dabrafenib and Trametinib was started in January, 2016 (30 months after the first radiosurgery) (Figure *1*). The treatment led to clinical and radiographic improvement. During several months regression of aphasia and hemiparesis, improvement of cognitive function and diminishing of intradermal lesions were detected. In four months, MRI revealed partial regression of 10 metastases emerged after last radiosurgery. No new lesions were detected. The posttreatment changes in corpus callosum and septa pellucida were still visible. In six months (11 months from the initiation of targeted therapy), the growth of intradermal lesions was found. MRI showed the increase of size (of non-irradiated lesions) and quantity of metastases along with regression of posttreatment changes in corpus callosum and

septa pellucida (Figure 3). The intensity of targeted therapy was increased. The next MRI (13 months after targeted therapy initiation) revealed further enlargement of nine largest lesions (with MR characteristics different from other lesions) with minor growth of other metastases (>20). Her KPS was graded at 70. Her cognitive function was assessed, according to the Mini-Mental State Examination (score of 22) and Montreal Cognitive Assessment (MoCA) on which she scored 19.

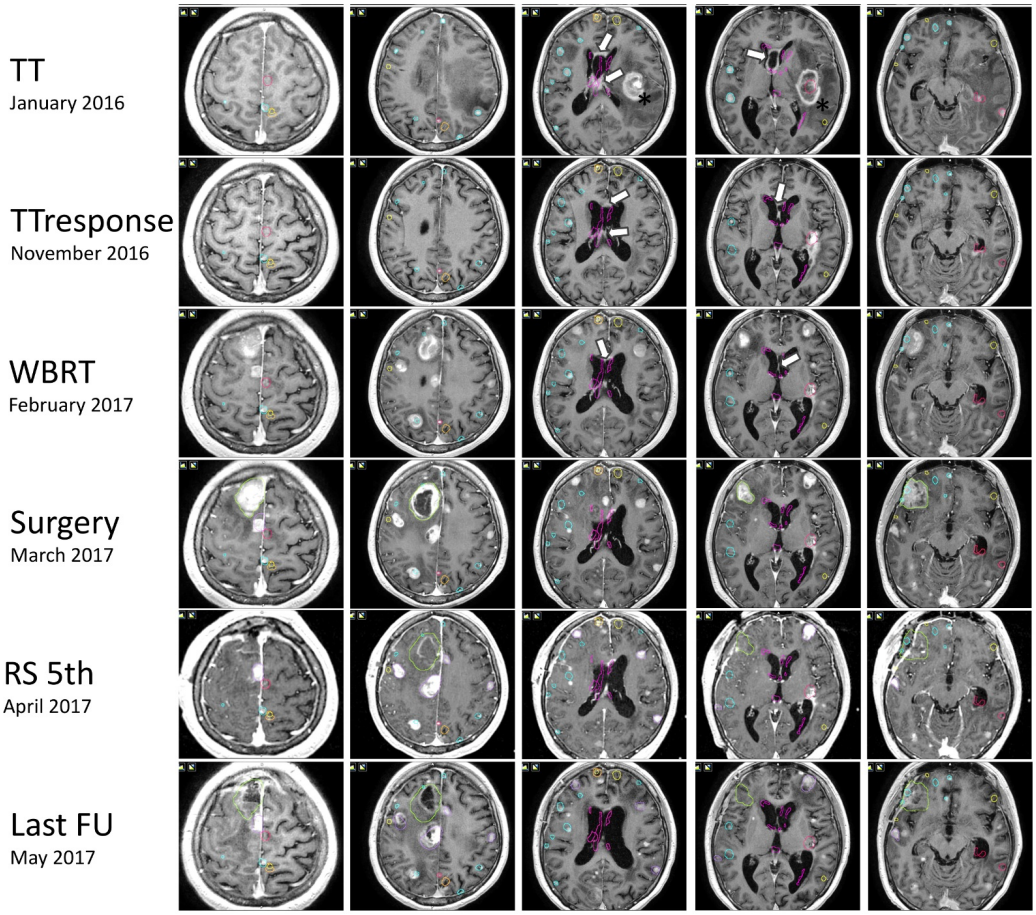

FIGURE 3: Demonstration of course of intracranial disease with serial magnetic resonance imaging (MRIs) (axial T1 with contrast enhancement) from the targeted therapy to the last follow-up.

Abbreviations on the left represent different stages of treatment: RS 1-5 – MRIs during radiosurgeries, TT – MRI before the initiation of targeted therapy, TTresponse – MRI demonstrating maximum response to targeted therapy, WBRT – MRI before the whole brain radiotherapy, Last FU – the last MRI.

The color of the contour indicates the stage when the lesion was treated: yellow – the 1st radiosurgery, orange – the 2nd radiosurgery, pink – the 3rd radiosurgery and hypofractionation, red – the 4th radiosurgery, blue – lesions before the initiation of targeted therapy, green – lesions removed with surgical intervention, purple – the 5th radiosurgery.

Arrows point on posttreatment changes after the 3rd irradiation in the area of septa pellucida; asterisk indicates the hemorrhage which emerged in one of the lesion treated with the 4th radiosurgery.

In February 2017, the whole brain radiotherapy was performed with 10 fractions of 3 Gy (Figure 3). The irradiation was performed along with targeted therapy and dexamethasone (4 mg daily). The irradiation was combined with targeted therapy in an attempt to increase the treatment effectiveness with respect to severe progression. No skin toxicity was noted. The MRI in one month demonstrated cystic transformation and enlargement of two lesions in the right frontal lobe with mass effect, minor decrease of several lesions, and stabilization of others. No distinct new metastases were detected.

In March 2017, the surgical resection of two lesions in the right frontal lobe was performed (Figure 3). After the intervention, epileptic seizures and left-sided hemiparesis (grade 2 muscle strength) developed. In April 2017, 17 growing lesions were treated with Gamma-Knife radiosurgery up to marginal dose of 18 Gy prescribed to 53-89% isodose line (Figure 3). The mean target volume was 0.891 ccm (0.182-5.292 ccm). In two months after radiosurgery, MRI revealed regression of postsurgical changes, minor enlargement of several non-irradiated lesions (Figure 3). The irradiated lesions were stable. No new lesion emerged.

The patient died in three months after the last radiosurgery (49 months after the first radiosurgery), due to intracranial and extracranial progression. The disease course is demonstrated in Figure 4.

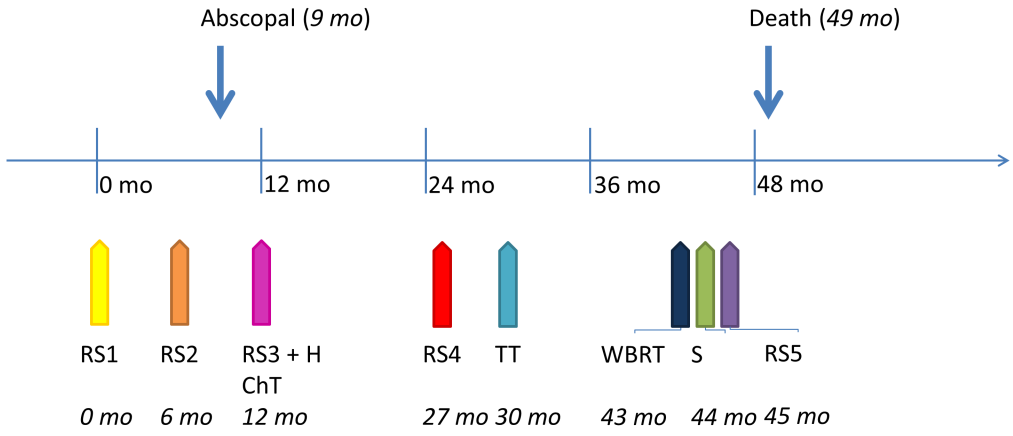

FIGURE 4: The disease course.

Abbreviations for treatments are the following: RS 1-5 – radiosurgeries, H – hypofractionated irradiation, ChT – chemotherapy, TT – targeted therapy, WBRT – whole brain radiotherapy, S – surgery.

Discussion

We have presented a case of a patient with multiple melanoma brain metastases. The case can

be interesting for specialists because of the patient's lifetime which was much longer than could be expected, and abscopal effect noticed.

It is known that the progression of the melanoma can often emerge with a significant time gap after the treatment of a primary cutaneous lesion. Regional lymph nodes metastases develop in a median of 16–19 months, and direct distant metastases occur in a median of 24–25 months [1]. The same was seen in the case discussed. The regional metastases appeared in 12 months after excision of the cutaneous lesion, and the brain metastases occurred in 25 months. After the development of distant metastases, the disease course becomes more vigorous that significantly affects lifetime expectation [3].

According to graded prognostic assessment (GPA) index, the estimated median survival time for the patient should be 8.3 months (age < 70 years, KPS 90-100, extracranial metastases are presented, brain metastases > 4, BRAF positive) with the interval of 3.9-18.2 months for 25th-75th percentile range. The patient presented survived for 49 months after detection of brain metastases. Due to organizational problems, the patient did not receive systemic treatment for a long time. Chemotherapy with Cisplatin and Temozolomide was started in 12 months after the first radiosurgery. Although, according to published data, this treatment, as well as other chemotherapy regimens, is characterized by low response rates and short progression-free survival in patients with metastatic melanoma [4]. The targeted therapy with Dabrafenib and Trametinib was launched only in 30 months after the first radiosurgery, and the patient survived for 19 months after its onset.

It is difficult to establish, what was the reason for such prolonged survival – the treatment itself, tumor properties or both.

Melanoma is considered to be radioresistant tumor [6]. That is the reason for low effectiveness of whole brain irradiation [5]. Higher doses delivered with radiosurgery appear to be more effective. Radiosurgery provides pretty good local control about 49-97% [4]. The median overall survival in patients with brain metastases treated with radiosurgery is 5.3-10.4 months [4]. Multiple radiosurgeries are associated with better survival [7]. Solitary lesion or oligometastases are associated with better survival than multiple lesions [4]. In our observation, radiosurgery provided rather high local growth control, and the rate of emergence of new brain metastases enabled to perform repeated irradiations. Although large studies are needed to identify if the multiple radiosurgeries lead to extended survival or prolonged survival allows to perform multiple radiosurgeries.

The second reason for good survival of the patient could be the abscopal effect observed. It was manifested by the complete regression of intradermal metastases after the second radiosurgery of brain lesions without any systemic treatment. The abscopal effect is defined as a regression of metastases situated at a distance from the irradiated tumor of the same origin. More often the abscopal effect was detected in patients who had received both irradiation and immune therapy (Ipilimumab in most published cases) [6]. The patients with abscopal effect demonstrated significantly higher survival comparing the patients without such event [6]. There are only few cases described where irradiation only induced this effect in melanoma patients [6]. The similar mechanism may lead to vitiligo emergence after radiotherapy for melanoma [8]. There are also cases described where surgical intervention induced reduction of distant melanoma metastases [9]. Discussing the abscopal effect, we should mention the opportunity of spontaneous regression of the primary melanoma and/or metastases. Kalialis, et al. presented the review of 76 cases of spontaneous regression of melanoma metastases [10]. The spontaneous regression was much more common in primary melanoma than in metastases. The authors identified factors (operative trauma, infection, immunologic factors, etc.) which could have stimulated the immune response in the main part of cases. So, it seems that the

significant part of spontaneous regressions is presented by some kind of abscopal effect.

The launch of targeted therapy also seems to be an important factor affecting survival. In the case, it was started in 30 months after the first radiosurgery and was administered during 19 months until the patient's death. The implementation of this treatment has influenced the prognosis of the patients with melanoma dramatically. Compared to standard chemotherapy, both BRAF- and MEK-inhibitors separately significantly improve the survival of patients with metastatic melanoma, and the combination of both appears to be even more effective [3, 5].

Conclusions

In the case, we have presented a rare case of the patient with melanoma brain metastases which stands out due to significantly long survival period. The patient died in 49 months after the first radiosurgery for multiple brain metastases, whilst the median survival time had been estimated as only 8.3 months, according to GPA index. The prolonged survival in the case can be connected with multiple irradiations (five courses of radiosurgery, whole brain radiotherapy, and stereotactic hypofractionation), the abscopal effect emerged (clearly manifested by regression of intradermal lesions after the second radiosurgery), and conduction of targeted therapy (launched 30 months after the first radiosurgery and lasted for 19 months). So, consistent timely application of different stereotactic irradiation techniques and targeted therapy can lead to "chronization" of the disease, and, thus, improve the survival even in such unfavorable diagnosis as melanoma with multiple brain metastases.

Additional Information

Disclosures

Human subjects: Consent was obtained by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Leiter U, Meier F, Schittek B, et al.: The natural course of cutaneous melanoma . J Surg Oncol. 2004, 86:172–178. 10.1002/jso.20079
2. Sperduto PW, Jiang W, Brown PD, et al.: Estimating survival in melanoma patients with brain metastases: an update of the graded prognostic assessment for melanoma using molecular markers (melanoma-molGPA). Int J Radiat Oncol Biol Phys. 2017, 99:812-816. 10.1016/j.ijrobp.2017.06.2454
3. Frinton E, Tong D, Tan J, et al.: Metastatic melanoma: prognostic factors and survival in patients with brain metastases. J Neurooncol. 2017, 135:507–512. 10.1007/s11060-017-2591-9
4. McWilliams RR, Rao RD, Buckner JC, et al.: Melanoma-induced brain metastases. Expert Rev Anticancer Ther. 2008, 8:743–755. 10.1586/14737140.8.5.743
5. Chukwueke U, Batchelor T, Brastianos P: Management of brain metastases in patients with melanoma. J Oncol Pract. 2016, 12:536–542. 10.1200/JOP.2016.011882
6. Espenel S, Vallard A, Rancoule C, et al.: Melanoma: last call for radiotherapy. Crit Rev Oncol Hematol. 2017, 110:13–19. 10.1016/j.critrevonc.2016.12.003
7. Samlowski WE, Watson GA, Wang M, et al.: Multimodality treatment of melanoma brain metastases incorporating stereotactic radiosurgery (SRS). Cancer. 2007, 109:1855–1862. 10.1002/cncr.22605

8. Abood A, Saleh DB, Watt DAL: Malignant melanoma and vitiligo: can radiotherapy shed light on the subject?. J Plast Reconstr Aesthet Surg. 2009, 62:119–120. 10.1016/j.bjps.2008.06.063
9. Bramhall RJ, Mahady K, Peach AHS: Spontaneous regression of metastatic melanoma - clinical evidence of the abscopal effect. Eur J Surg Oncol. 2014, 40:34–41. 10.1016/j.ejso.2013.09.026
10. Kalialis LV, Drzewiecki KT, Klyver H: Spontaneous regression of metastases from melanoma: review of the literature. Melanoma Res. 2009, 19:275-282. 10.1097/CMR.0b013e32832eabd5