Stereotactic radiosurgery as a successful method to control meningeal metastatic adenoid cystic carcinoma of the lacrimal gland: A case report

NIDAL SALIM[1], EVGENIY LIBSON[2,3], KRISTINA TUMANOVA[1] and IRINA KROTENKOVA[2]

Departments of [1]Radiation Oncology and [2]Diagnostic Imaging, European Medical Center, Moscow 129090, Russia; [3]Department of Diagnostic Imaging, Hadassah Medical Center, Jerusalem 9112001, Israel

Received March 28, 2022; Accepted June 22, 2022

DOI: 10.3892/mco.2022.2568

Abstract. Adenoid cystic carcinoma (ACC) of the lacrimal gland is a rare tumor. In addition, considering the lack of data on large groups of patients there is no standard of care to treat patients with multiple meningeal metastases of ACC. A two-year analysis of the course of the disease in a patient with synchronous oligometastatic ACC of the lacrimal gland that was treated with stereotactic radiosurgery (SRS) is presented. The aim of the present case report was to evaluate the effect of SRS in the treatment of a patient with ACC. Preliminary results confirmed that this method was highly effective in this patient. The patient is currently living with a good quality of life, normal vision and with no evidence of disease or complications. SRS exhibited reliable local tumor control and insignificant radiation-related complications, rendering it an encouraging treatment option for patients with recurrent or metastatic ACC.

Introduction

Adenoid cystic carcinoma (ACC) is a rare tumor which represents the majority of malignant neoplasms of the lacrimal gland, with a 5-year survival rate of <20%. It has a poor prognosis for long-term disease-free survival (1-3). ACC has a tendency to recur both locally and with distant metastases despite radical treatment (4). Surgery with subsequent radiotherapy is considered a standard treatment for ACC of the lacrimal gland, but complete resection in most cases is not feasible (National Comprehensive Cancer Network Head and Neck Cancers, version 3.2021) (5). There is no consensus on the recommended treatment in cases of metastatic disease, and patients are usually treated with platinum-based chemotherapy; however, this approach has recently been challenged by immunotherapy (6,7).

In the present case report, a rare clinical case of ACC of the lacrimal gland with multiple oligometastatic events that were successfully treated by radiosurgery over a 2,5-year period is presented. To the best of our knowledge, this is the first time such a case has been reported.

Case report

A 44-year-old female patient presented with facial asymmetry and pain in the left orbit, in April 2019, at the European Medical Center (Moscow, Russia). The patient was evaluated by an ophthalmologist, and the examination showed exophthalmos and lower eyelid retraction on the left side. The patient had no other complaints, normal vision, and an Eastern Cooperative Oncology Group (ECOG) score of 1. Brain magnetic resonance imaging (MRI) was recommended.

The initial brain MRI with intravenous (I/V) contrast revealed a mass in the left orbit sized 4.0x2.1x3.5 cm with sphenoid bone invasion (Fig. 1A). Upon suspicion of a malignant tumor, the patient underwent microsurgical tumor excision (R2) in April 2019, during which the eye was preserved. Pathology reports showed mix patterns of cribriform and solid types of ACC with tumor cells expressing CK7, CD117 with CK5/6 on some cells, S-100, and Ki-67 positive in 10-30% of tumor cells; a final pathology stage was pT4bN0M0, R2, LV0 (no lymphovascular invasion), Pn1 (perineural invasion). Molecular genetic testing (Caris Life Sciences) provided no evidence of microsatellite instability, low tumor mutational burden (six mutations), negative PD-L1 status, and *MYB*, *NOTCH*, and *KRAS* were not detected. Postoperative MRI images showed a residual mass in the left orbit (Fig. 1B), and body positron emission tomography-computed tomography (PET-CT) showed no evidence of metastatic disease.

Two weeks after surgery, the patient received adjuvant radiation therapy with image-guided radiation therapy (IGRT) using a volumetric modulated arc therapy (VMAT) technique to the left orbit, tumor bed, and subclinical extension with a boost to the tumor bed (total dose, 64.8 Gy) (Fig. 1C). Follow-up MRI images demonstrated complete radiological response and no evidence of active disease.

Correspondence to: Dr Kristina Tumanova, Department of Radiation Oncology, European Medical Center, 35 Schepkina Street, Moscow 129090, Russia
E-mail: ktumanova@emcmos.ru

Key words: metastatic adenoid cystic carcinoma, stereotactic radiosurgery, multiple meningeal metastases

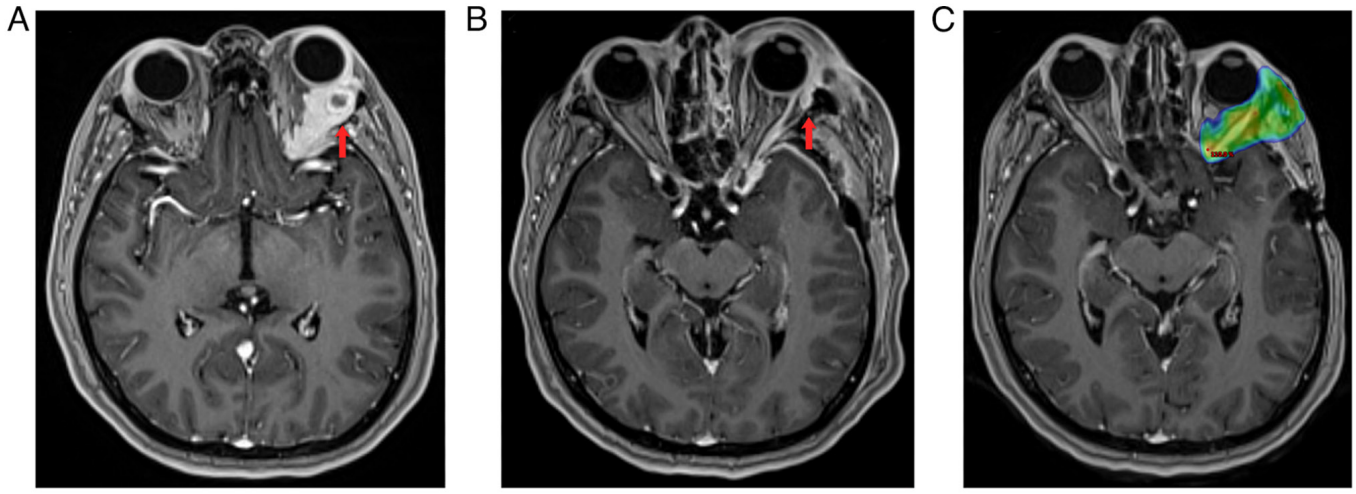


Figure 1. (A) Brain MRI with I/V contrast before surgery. The red arrow indicates a mass in the left orbit sized 4.0x2.1x3.5 cm with sphenoid bone invasion. (B) Brain MRI with I/V contrast after surgery. The red arrow indicates a residual mass in the left orbit. (C) Mapping of the treated lesion of the patient, based on the pre-irradiation therapy brain CT scan fused with the brain MRI. The patient was simulated in the supine position with the arms down, using a customized thermoplastic facemask for immobilization. PTV was defined as PTV_45 (the left orbit), 1.8 Gy per fraction; PTV_54 (tumor bed), 1.8 Gy per fraction (total dose, 54 Gy); and PTV_64.8 (residual contrast-enhancing tumor on post-surgical MRI), 1.8 Gy per fraction (total dose, 64.8). Organs at risk were delineated using the Eclipse™ treatment planning system (version 15.6; Varian Medical Systems). Heterogeneity correction was used for planning. The prescribed radiation treatment was completed. MRI, magnetic resonance imaging; I/V, intravenous; CT, computed tomography; PTV, planning target volume.

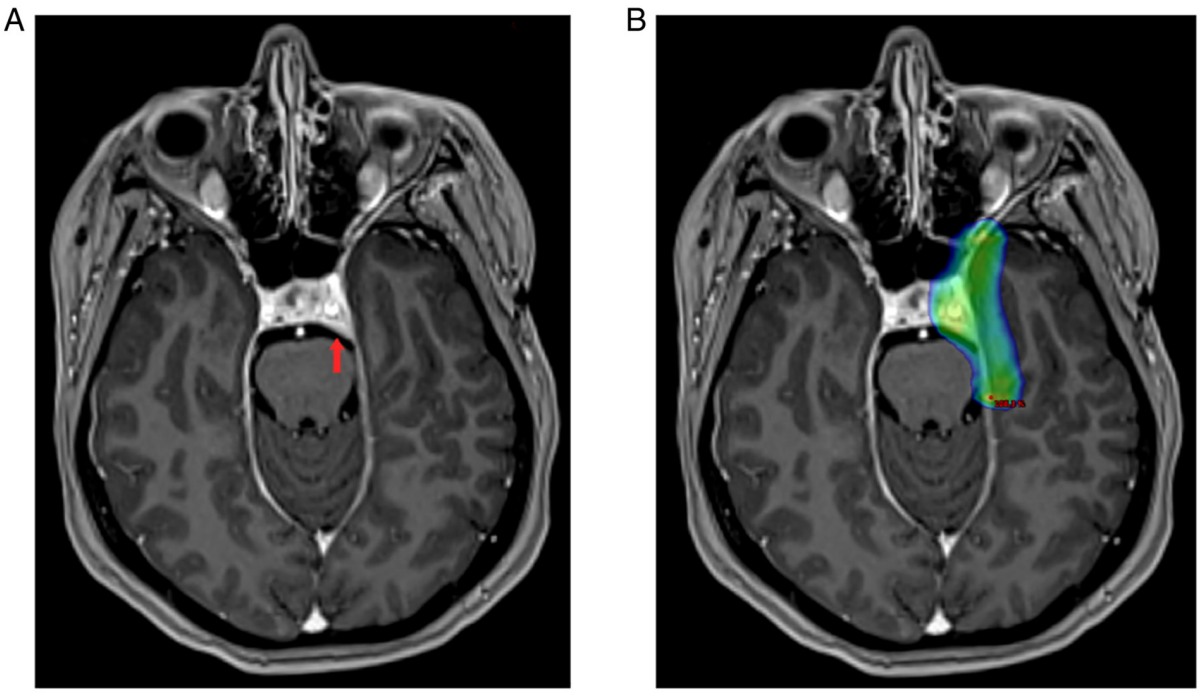


Figure 2. (A) Brain MRI with I/V contrast. The red arrow indicates homogeneous contrast uptake in the near left posterior cavernous sinus (1.4x0.9 cm). (B) Mapping of the treated lesion of the patient, based on the pre-irradiation therapy brain CT scan fused with the brain MRI. The patient was simulated in the supine position with arms down, using a customized thermoplastic facemask for immobilization. PTV included 4.0 Gy per fraction (total dose, 40.0 Gy) for the residual tumor in the left cavernous sinus with subclinical extension, and 4.0 Gy per fraction (total dose, 48.0 Gy) along the lateral part or tentorium. Heterogeneity correction was used for planning. The prescribed radiation treatment was completed. MRI, magnetic resonance imaging; I/V, intravenous; CT, computed tomography; PTV, planning target volume.

In December 2019, the MRI with I/V contrast revealed a homogeneous contrast uptake near the left posterior cavernous sinus (1.4x0.9 cm), outside of the radiation therapy fields (Fig. 2A). The patient received stereotactic fractionated radiation therapy (SFRT) to the left posterior cavernous sinus with a total dose of 48 Gy (Fig. 2B). A follow-up MRI provided no evidence of the disease.

In April 2020, a brain MRI with I/V contrast showed a new contrast-enhancing lesion on the surface of the left gyrus rectus (Fig. 3A). A multidisciplinary meeting recommended

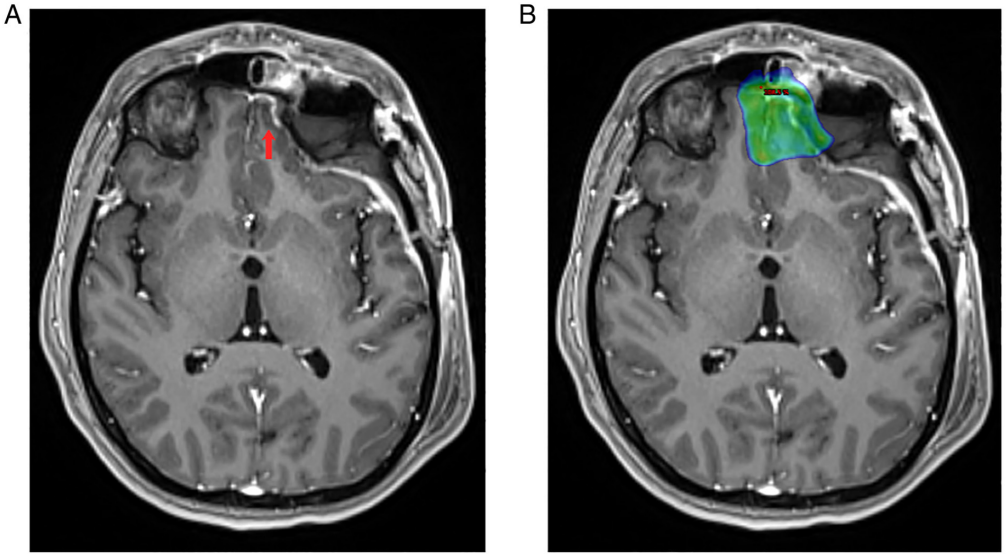


Figure 3. (A) Brain MRI with I/V contrast. The red arrow indicates a new contrast-enhancing lesion on the surface of the left gyrus rectus. (B) Mapping of the treated lesion of the patient, based on the pre-irradiation therapy brain CT scan fused with the brain MRI. The patient was simulated in the supine position with arms down, using a customized thermoplastic facemask for immobilization. PTV was defined as a postoperative area in the left frontal lobe with subclinical extension using 3.0 Gy per fraction with a boost to the tumor bed in the left frontal lobe, 4.0 Gy per fraction (total dose, 33.0 Gy). Heterogeneity correction was used for planning. The prescribed radiation treatment was completed. MRI, magnetic resonance imaging; I/V, intravenous; CT, computed tomography; PTV, planning target volume.

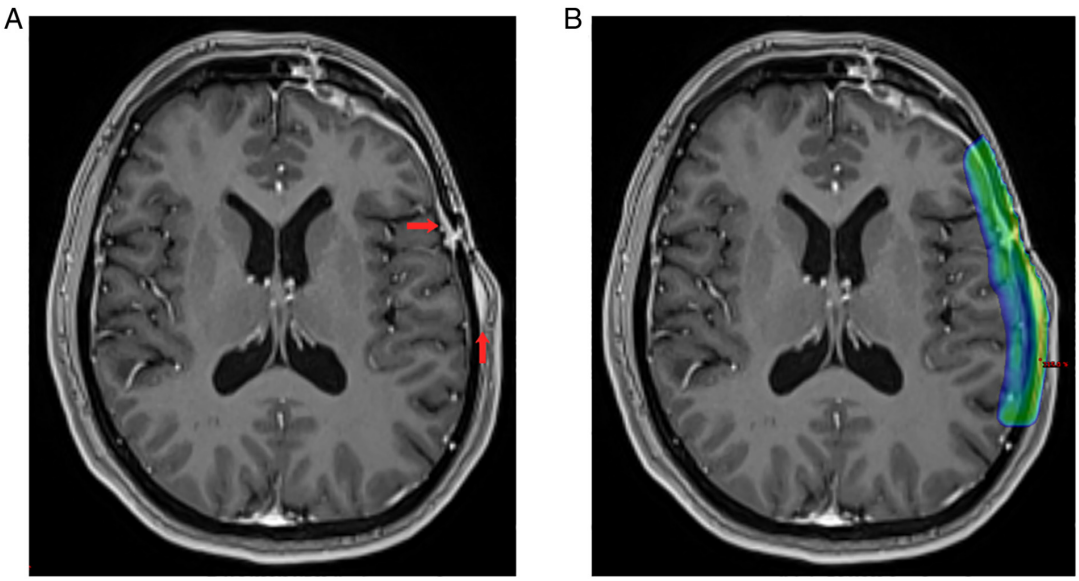


Figure 4. (A) Brain MRI with I/V contrast. The red arrows indicate local thickening of the dura mater in the region of postoperative burr holes in the temporal bone that appears to be pachymeningeal recurrence, and similar solid contrast-enhancing lesions in the soft tissue of the temporal region that appears to be tumor progression. (B) Mapping of the treated lesion of the patient, based on the pre-irradiation therapy brain CT scan fused with the brain MRI. The patient was simulated in the supine position with arms down, using a customized thermoplastic facemask for immobilization. PTV was defined as two lesions of local dura mater thickening in the region of postoperative burr holes with subclinical extension, 3.5 Gy per fraction (total dose, 28.0 Gy) with sequential boost, 3.0 Gy per fraction (total dose, 46.0 Gy). Heterogeneity correction was used for planning. The prescribed radiation treatment was completed. MRI, magnetic resonance imaging; I/V, intravenous; CT, computed tomography; PTV, planning target volume.

surgical excision to further verify the histology of this lesion. On April 8 2020, the lesion was removed and a pathology report confirmed metastasis of ACC. Adjuvant radiation therapy to the postoperative area (a total dose, 33.0 Gy) was administered (Fig. 3B) with a complete radiological response.

In July 2020, an MRI scan revealed two meningeal metastases in the temporal region along the postoperative tract (Fig. 4A). In August 2020, the patient underwent SFRT for the above mentioned lesions (a total dose, 46.0 Gy), (Fig. 4B). Follow-up MRI images showed complete radiological response.

In January 2021, a brain MRI with I/V contrast revealed a new contrast-enhancing lesion in the anterior part of the falx cerebri (Fig. 5A). SFRT was performed on this region (a total dose, 46.0 Gy) (Fig. 5B) in the same month. As of June 2021, the patient exhibited no evidence of residual disease.

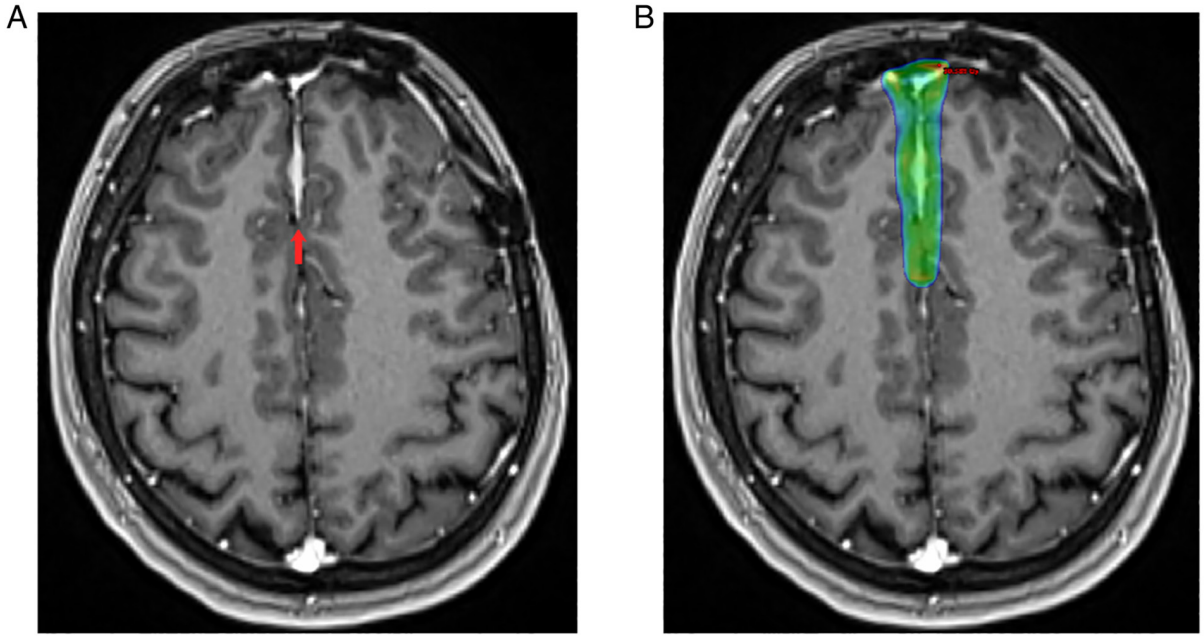


Figure 5. (A) Brain MRI with I/V contrast. The red arrow indicates a new contrast-enhancing lesion in the anterior part of the falx cerebri. (B) Mapping of the treated lesion of the patient, based on the pre-irradiation therapy brain CT scan fused with the brain MRI. The patient was simulated in the supine position with arms down, using a customized thermoplastic facemask for immobilization. PTV was defined as a region of contrast-enhancing lesion in the anterior part of falx cerebri with subclinical extension, using 3.5 Gy per fraction with sequential boost, 3.0 Gy per fraction (total dose, 46.0 Gy). Heterogeneity correction was used for planning. The prescribed radiation treatment was completed. MRI, magnetic resonance imaging; I/V, intravenous; CT, computed tomography; PTV, planning target volume.

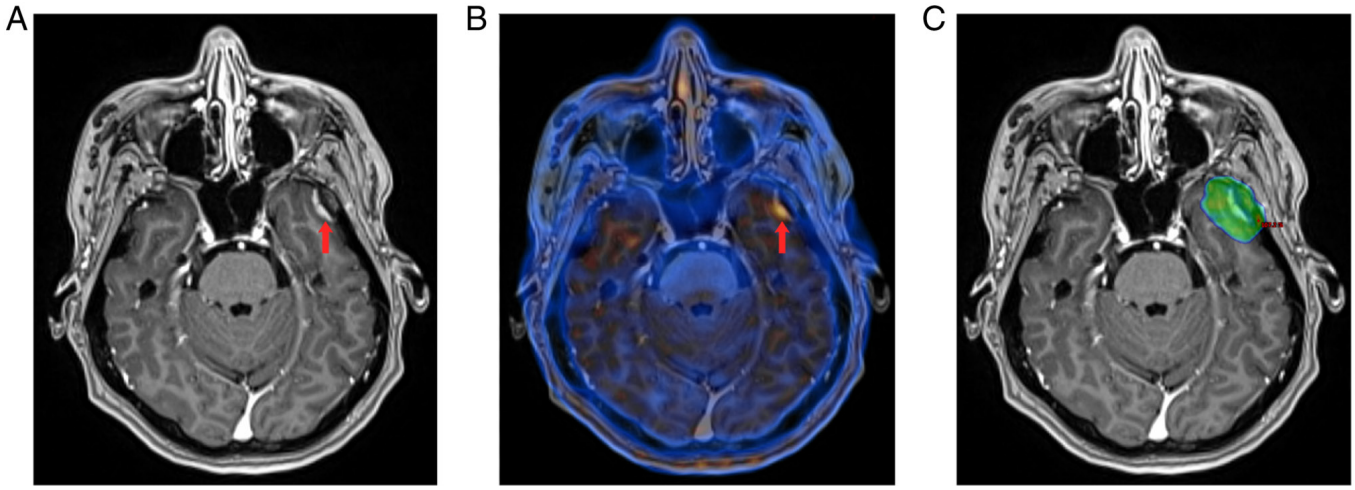


Figure 6. (A) Brain MRI with I/V contrast. The red arrow indicates a new contrast-enhancing pachymeningeal lesion in the basal region of the left temporal lobe. (B) Head PET-CT. The red arrow indicates solid dural metastasis in the left temporal lobe (SUVmax 2.95). (C) Mapping of the treated lesion of the patient, based on the pre-irradiation therapy brain CT scan fused with the brain MRI. The patient was simulated in the supine position with arms down, using a customized thermoplastic facemask for immobilization. PTV was defined as a pachymeningeal lesion in the basal region of the left temporal lobe with subclinical extension, 3.5 Gy per fraction with sequential boost, 3.0 Gy per fraction (total dose, 46.0 Gy). Heterogeneity correction was used for planning. The prescribed radiation treatment was completed. CT, computed tomography; I/V, intravenous; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-CT; PTV, planning target volume.

In June 2021, an MRI with I/V contrast revealed a new contrast-enhancing meningeal lesion of the left temporal lobe (Fig. 6A). Head PET-CT demonstrated solid dural metastasis in the region of the left temporal lobe (SUVmax 2.95) (Fig. 6B). The planning target volume (PTV) of SFRT in the recurrence area (a total dose, 46.0 Gy) in June-July 2021, is revealed in Fig. 6C.

The final MRI and PET-CT scans from July 2021 showed complete radiological response. The patient is currently living with no evidence of disease and with a good quality of life.

Discussion

ACC of the lacrimal gland is a rare type of tumor (8). Despite the lack of data on large groups of patients, some authors recommend surgery followed by radiation or proton therapy (9-11). Others maintain that radical surgery should be incorporated into the treatment and can improve control of the local disease, and possibly, long-term survival (12,13). Woo *et al* reviewed the published literature on management strategies for lacrimal gland carcinomas from over the past 40 years and concluded that treatment strategies for ACC of the lacrimal gland varied and local control did not necessarily prevent future relapse. Improved radiation therapy techniques may offer opportunities for the management of lacrimal gland carcinomas in patients with unresectable disease (6). In the present case, radical surgery was not possible due to bone invasion and due to the desire of the patient, who, after receiving the histological report and a long discussion with regard to the diagnosis and possible treatment options, refused a radical surgical operation. In such cases, radiotherapy remains the only viable treatment option.

Due to the impermeability of the blood-brain barrier to numerous chemotherapeutic agents, there are no evidence-based recommendations and there are no accepted standard chemotherapy regimens for ACC. Additionally, the National Comprehensive Cancer Network provides no recommendations regarding chemotherapy in this context (http://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf).

The effects of intra-arterial cytoreductive chemotherapy with cisplatin + 5-FU or cisplatin, doxorubicin, and cyclophosphamide (CAP) are currently being investigated, and preliminary findings show poor results either as single agents or as combination therapy (14,15). Licitra *et al* described the cases of treatment with CAP, and 67% of patients achieved partial response or stable disease, but no cases of complete response were reported (16). Previous research has revealed the possibility of other treatment options, such as chemotherapy and targeted therapy, based on genomic profiling (7,17).

In the present case, molecular genetic testing (Caris Life Sciences) did not provide a sufficient basis for alternative chemotherapy regimens.

Radiosurgery is a well-known and effective method for the treatment of brain metastases. Results from a randomized, controlled phase 3 trial presented at the American Society for Radiation Oncology Annual Meeting in October 2020 suggested that SRS should be the standard of care for patients with multiple brain metastases (18). In addition, the Radiation Therapy Oncology Group (RTOG) 9508 randomized trial demonstrated that SRS improved survival in patients with single brain metastases (19). Thus, SRS was attempted as this was deemed as the only possible and safe method for this patient.

In conclusion, a number of the rare defined disease data on specific treatments and outcomes are not yet available. Preliminary results confirmed that in the present case SRS achieved excellent control of the six events of recurrence of the ACC disease over 2,2 years, while other treatment options were not possible. To date, the patient is still living with a good quality of life, normal vision, no complications, and no evidence of disease.

Unfortunately, this case was not presented to the local Multidisciplinary Head and Neck Tumor Board (European Medical Center, Moscow, Russia) before the first surgery. The surgery was supposed to be diagnostic in order to obtain histological material. The fact that the tumor was not radically removed and may have affected the further course of the disease, is acknowledged.

Despite the efficiency, SRS has a number of limitations such as limited availability, high price and additionally, there is a paucity of professionals to commission, utilize, and maintain safe and effective SRS practices in developing countries. Furthermore, certain side effects such as tiredness and swelling in the brain may occur in the first few weeks after stereotactic radiosurgery. Swelling in the brain at or near the treatment site can cause signs and symptoms such as headaches, nausea and vomiting, which were not observed in the present patient. Further clinical observation based on large groups of patients is needed to evaluate this approach.

The present case is unique in our practice. Due to the aggressive nature of the ACC and poor prognosis of this tumor in the short/medium term the condition of the patient is continually being monitored. The patient is also continuing to undergo routine brain MRI with contrast every 3 months and PET-CT every 6 months.

Acknowledgements

Not applicable.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Availability of data and materials

Available from the corresponding author upon reasonable request.

Authors' contributions

All authors (NS, EL, KT and IK) contributed to the study conception and design. Material preparation, data collection and analysis were performed by NS, KT and EL. The first draft of the manuscript was written by KT and all authors commented on previous versions of the manuscript. Images and description of MRI results were prepared by IK. NS and KT confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethics approval for the study was obtained from the Local Research Ethics Committee (European Medical Center, Moscow, Russia) dated April 16, 2019. Informed consent was obtained from the patient.

Patient consent for publication

Written consent for publication of this case report including all images, was obtained from the patient.

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

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