MAYO CLINIC

MAYO CLINIC PROCEEDINGS:
INNOVATIONS, QUALITY & OUTCOMES

CASE REPORT

Minibeam Radiation Therapy for Recurrent Mucosal Melanoma: An Eye-Opening Response

Maddi A. Jacobson, MPAS, PA-C; Yasamin Sharifzadeh, MD; Arkadiusz Z. Dudek, MD, PhD; Svetomir N. Markovic, MD, PhD; Jeffrey E. Johnson, MD; Jonathan M. Morris, MD; Scott C. Lester, MD; Robert W. Mutter, MD; Michael P. Grams, PhD; and Sean S. Park, MD, PhD

Abstract

We report a case of novel radiation treatment referred to as minibeam radiation therapy (MBRT) that was used to treat recurrent mucosal melanoma. The patient's disease recurred after surgery, conventional radiation therapy, and 4 lines of systemic therapy, and then, the patient was referred to our clinic. Despite substantial disease progression after multiple prior therapies, a complete metabolic and clinical response, along with an improved quality of life and performance status, was achieved after 2 treatments of MBRT. Additionally, disease response was noted in an unirradiated abdominal metastasis. The MBRT treatments were well-tolerated, with minimal toxicity reported more than 6 months posttreatment. This case highlights the potential of MBRT as a completely novel form of radiation therapy that warrants further study.

 ■ Mayo Clin Proc Inn Qual Out 2025;9(4):100640

From the Department of Radiation Oncology (M.A.J., Y.S., R.W.M., M.P.G., S.S.P.), Division of Medical Oncology (A.Z.D., S.N.M.), Division of Breast and Melanoma Surgical Oncology, Department of Surgery (J.E.J.), Department of Radiology (J.M.M.), and Department of Molecular Pharmacology and Experimental Therapeutics (R.W.M.), Mayo Clinic, Rochester, MN.

Our institution recently translated, for the first time in humans, an innovative and potentially paradigm-shifting radiation therapy (RT) treatment called minibeam radiation therapy (MBRT).[1] This novel form of treatment uses orthovoltage radiotherapy and a tungsten collimating device to divide a uniform radiation beam into many 0.5-mm wide beamlets (Figure 1). Preclinical investigations over several decades have shown the heterogeneous dose distributions of peak (high) and valley (low) doses that are the hallmark of MBRT can result in distinct biological responses in both tumor and normal tissues.[2-6] In this case report, we describe the clinical response of a patient with recurrent mucosal melanoma who was treated with MBRT after having failed multiple lines of systemic therapy, surgery, and prior RT.

CASE

Patient Background

A 64-year-old man with recurrent metastatic sinonasal melanoma involving the right face with a vision-compromising exophytic mass surrounding the right eye was referred to our radiation oncology clinic after having failed multiple lines of systemic therapy, surgery, and prior external beam radiotherapy at an outside institution. He was originally diagnosed with mucosal melanoma of the right maxillary sinus after workup for long-term upper respiratory tract symptoms 2.5 years prior. At that time, computed tomography (CT) scan at diagnosis showed a large right maxillary sinus mass extending into the posterior inferior medial portion of the right orbit and into the right pterygopalatine fossa, with erosion of the cribriform plate. A transnasal endoscopic biopsy of the mass showed high-grade malignant neoplasm, consistent with malignant melanoma, BRAF wild type, KIT L576P mutated. A staging positron emission tomography (PET)/CT showed no evidence of distant metastatic disease at initial diagnosis.

The patient was started on ipilimumab and nivolumab, but only 2 cycles were delivered due to intolerable whole body dermatitis and COVID infection causing acute hypoxic

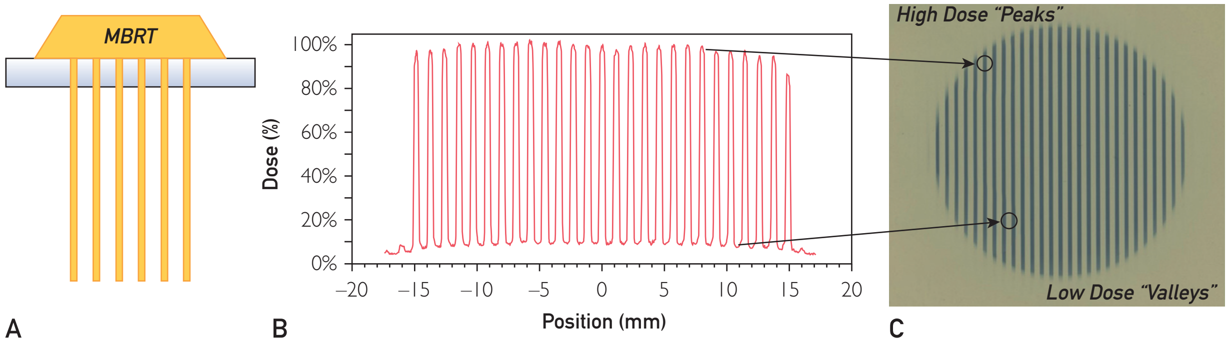

FIGURE 1. Schematic representation of minibeam radiation therapy (MBRT). (A) MBRT uses a tungsten collimator with narrow slits to divide an initially uniform beam of orthovoltage x-rays into distinct planar minibeams that are 0.5 mm wide and spaced 1.1 mm on center. (B) The resulting heterogeneous dose distribution consists of high-dose "peaks" and low-dose "valleys". (C) Radiation-sensitive film shows a cross-sectional view of a circular MBRT field. Peak regions correspond to the open slits in the collimator and are seen as dark lines, whereas the adjacent valley regions are blocked by the collimator and remain unexposed.

respiratory failure. Five months after initiation of dual checkpoint inhibitors, restaging magnetic resonance imaging (MRI) showed no response, and his therapy was switched to carboplatin and paclitaxel. After 4 cycles of chemotherapy, a follow-up MRI still showed no response. The patient then underwent a right maxillary sinus tumor percutaneous embolization, intra-arterial tumor embolization of the right sphenopalatine branch, followed by resection of sinonasal and anterior skull-base mucosal melanoma. Postoperative MRI revealed nodular abnormal contrast enhancement in the deep tissues of the right buccal region worrisome for residual tumor. Therefore, the patient underwent a right lateral rhinotomy with an upper lip split to excise the residual right maxillary tumor 1 month later. Final pathology showed mucosal melanoma involving skeletal muscle and bone in the right maxillary sinus with positive lateral and superior bone margins. He then underwent a revision right lateral rhinotomy to clear the margins. MRI 1 month after this final surgery revealed an aggressive regrowth of a large enhancing mass, approximately 4.1 cm in the greatest extent, involving the right orbit with involvement of the lacrimal gland and displacement of the lateral and inferior recuts with possible invasion into the lateral rectus insertion of the globe. The patient was experiencing pressure symptoms from the extrusion of the regrowth and ecchymosis of the eye at this time.

In an attempt to palliate his symptoms, 45 Gy in 15 fractions of conventional RT was delivered to the right orbit, optic nerve, and maxillary sinus tumor bed at an outside institution and occurred approximately 1 year after his initial diagnosis. After RT, he was started on imatinib 400 mg twice daily, followed by nivolumab a month later.

After 4 months of imatinib and nivolumab, the patient was evaluated by ophthalmology for right lower lid ectropion. A right orbital mass resection was performed, which pathologically confirmed recurrent malignant melanoma. He continued imatinib and nivolumab postoperatively. A few months later, MRI of the brain and orbits showed new enhancing nodular lesions along the inferior aspect of the right orbit anterior to the frontal process of the zygoma. A restaging CT chest/abdomen/pelvis also revealed increased size of a right lower quadrant nodule and new left adrenal nodule, all concerning for metastatic disease. A biopsy of the right lower quadrant abdominal soft tissue mass showed metastatic melanoma.

At 20 months after his initial diagnosis and 10 months after completion of palliative RT, the patient was started on nilotinib, which was his fourth line of therapy. A restaging CT abdomen and pelvis revealed high-grade

Mayo Clin Proc Inn Qual Out ■ August 2025;9(4):100640 ■ https://doi.org/10.1016/j.mayocpiqo.2025.100640
www.mcpiqojournal.org

FIGURE 2. Patient response and setup photographs. (A) Photograph of the tumor on the first day of minibeam radiation therapy (MBRT) to the right inferior orbit. (B) MBRT treatment setup photograph, showing a patient-specific 3-dimensional—printed collimator holder affixed to the patient's face, which secures the tungsten collimator directly over the target. The tungsten collimator slides into the holder, and an 8-cm diameter cone is brought in contact with the tungsten and defined the MBRT field size. Photographs of treatment response taken (C) 1 week, (D) 2 weeks, (E) 5 weeks, and (F) 11 weeks after the initial MBRT treatment to the right inferior orbit.

obstruction at the level of the second portion of the duodenum secondary to 5.9-cm mass arising from the duodenum or pancreatic head. He underwent palliative gastrojejunostomy for relief of obstruction. He subsequently developed biliary obstruction requiring transduodenal biliary stent placement. At this point, the large periorbital mass with concern for skin ulceration was obstructing vision in his right eye (Figure 2A). Unfortunately, the patient's melanoma was unresponsive to nilotinib, and tumor-infiltrating lymphocyte (TIL) therapy was planned, which requires up to 6 weeks of ex vivo stimulation and expansion of lymphocytes. There was concern that the mass would develop ulceration or other local complications that would prevent lymphodepleting chemotherapy or interleukin 2 infusion. As a bridge to TIL therapy with lifileucel, palliative reirradiation to the inferior orbital disease using MBRT was discussed with the goal of providing local control to reduce symptoms and improve quality of life. Patient consent was thorough, and included the rationale for MBRT, the paucity of human clinical data, and alternatives including no anticancer therapy.

MBRT Treatment

Full details of the MBRT treatment process have been published elsewhere.[1] Briefly, MBRT treatment planning consisted of a pretreatment CT scan and delineation of the gross tumor volume (GTV). A patient-specific 3-dimensional—printed plastic collimator holder, which conformed to the patient's face, was fabricated. This device holds the tungsten collimator in place directly above the GTV. For MBRT treatment delivery, the plastic collimator holder with the collimator in place was secured to the patient. A total peak dose of 60 Gy to the skin surface was prescribed to be delivered in 2 daily fractions to the right inferior orbit and maxillary sinus treatment. The 180-kV output from an Xstrahl 300 (Xstrahl Inc) orthovoltage unit was used for treatment. An 8-cm diameter circular cone defined the overall field size and was positioned such that the end of the cone was flush with the surface of the tungsten collimator (Figure 2B). Between the first and second fractions, the tungsten collimator was rotated by 90°. Therefore, the peak dose prescription corresponds to the overlapping regions of the slits between the 2 fractions. The valley dose was 4 Gy per fraction and the irradiation time 11 minutes. Six weeks later, the process was repeated to treat the right upper medial orbit with a prescription peak dose of 50 Gy to the skin surface in 2 daily fractions. Due to the smaller size and shallow depth of the target, a 5-cm diameter circular cone and 100-kV x-ray energy was used. The valley dose per fraction was 2.7 Gy and the irradiation time 8 minutes. The patient remained on nilotinib during both MBRT treatments. Photographs of the tumor on the first day of MBRT, the treatment setup, and the response over time are shown in Figure 2. All photographs are used with patient consent.

Response and Adverse Effects

Within days following the first fraction of MBRT, the patient reported improvements in his ability to open his eye. Over the next several weeks, he reported significant and rapid shrinkage of the mass surrounding his right eye with improved vision. In the first 2 weeks after MBRT, he went through a period of keratoconjunctivitis that was treated with eye drops. He reported an initial "sunburn like" sensation over the skin in the treatment field that resolved around one month after treatment. Grade 1 erythema was noted in the MBRT field without dry or moist desquamation. He denied eye pain during or after treatment, besides some muscular pain with eye movement at the end of the day.

PET/CT imaging before and after MBRT to the right inferior orbit and face showed a complete metabolic response of metastatic melanoma at 13 weeks post-MBRT consistent with clinical response (Figures 2 [photographs] and 3A, B). PET/CT imaging before and 7 weeks after MBRT to the right upper medial orbit also showed a complete metabolic response (Figure 3C, D). Additionally, an abscopal response of the right intra-abdominal lesion was noted with complete metabolic response and corresponding clinical improvement in his abdominal pain and early satiety (Figure 4). The patient's appetite and performance status improved drastically with weight gain, and he went on to receive TIL therapy 15 and 9 weeks after MBRT to the right inferior orbit and right upper medial orbit, respectively. Therefore, the images in Figures 2-4 were all acquired before TIL therapy. The most recent PET/CT imaging 6 months after MBRT showed persistent complete metabolic response to all sites of disease. Additionally, results of circulating tumor DNA assays (Natera Inc) showed continually decreasing levels of circulating tumor DNA after the first MBRT treatment. These levels were undetectable starting 4 months after MBRT and continue to be undetectable at the most recent time point of 6 months.

DISCUSSION

We report safe and effective use of MBRT in a highly challenging clinical scenario involving recurrent mucosal melanoma. Prior to MBRT, the patient reported in this case report experienced disease progression despite maximal extent of surgery, prior RT, and 4 lines of systemic therapy. However, a dramatic treatment response and corresponding improvement in quality of life was noted after 2 novel MBRT treatments to the right inferior orbit and face and right upper medial orbit. Furthermore, the MBRT treatments were well-tolerated with the patient reporting minimal toxicity more than 6 months after treatment with no decline in visual acuity or any eye-related symptoms including scleritis or

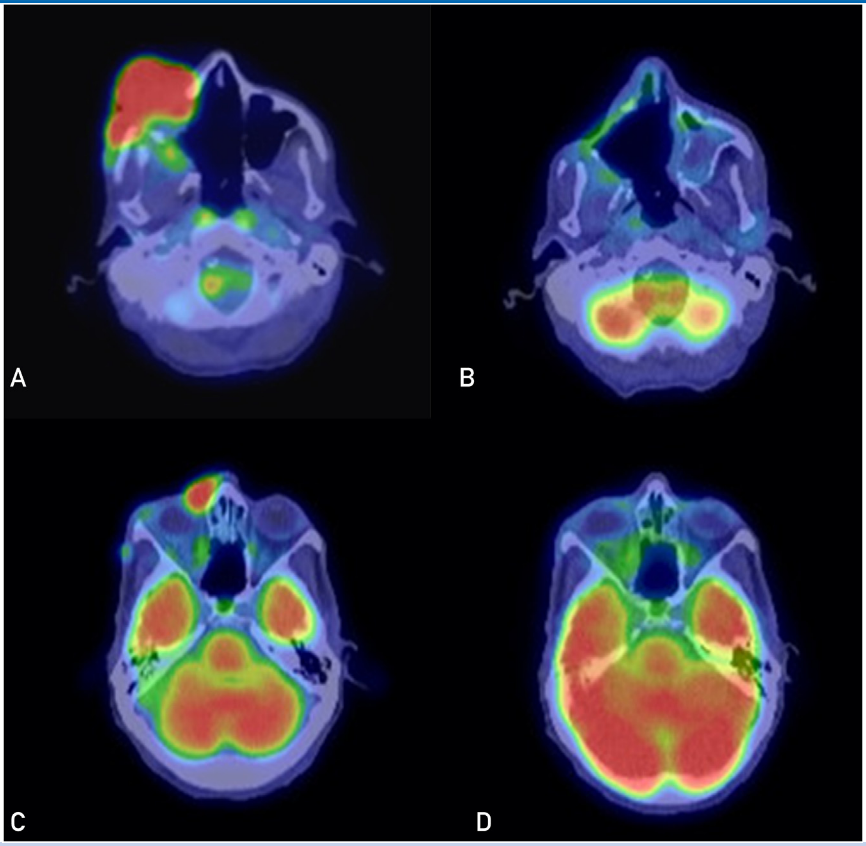

FIGURE 3. Positron emission tomography/computed tomography (PET/CT) images show complete metabolic response of recurrent mucosal melanoma after minibeam radiation therapy (MBRT). (A) Initial PET/CT 1 week before first MBRT treatment shows a large enhancing mass in the right inferior orbit. (B) Subsequent tumor response 13 weeks after MBRT. (C) Initial PET/CT showing enhancing mass in the right upper medial orbit 10 days before the second course of MBRT. (D) Subsequent tumor response 7 weeks after the second MBRT treatment to the right upper medial orbit.

retinitis. Surprisingly, an abscopal response was noted in his unirradiated abdominal metastasis, which led to a significant improvement in patient's oral intake and performance status. Although long-term follow-up and clinical trials are required to further determine the safety of MBRT, the lack of acute toxicity is promising and

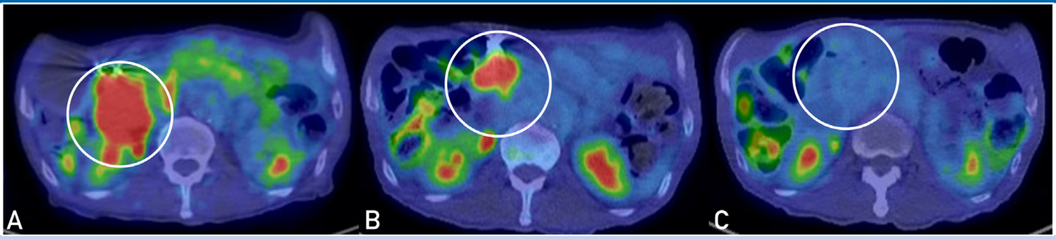

FIGURE 4. Despite not being treated with radiation therapy, Positron emission tomography/computed tomography (PET/CT) imaging reported response of the right lower quadrant soft tissue mass (indicated by white circle). (A) One week before the first course of minibeam radiation therapy (MBRT) to the right inferior orbit. Tumor response at (B) 4.5 and (C) 13 weeks after the first course of MBRT.

mirrors several preclinical MBRT studies.[7-11] Accordingly, the normal tissue sparing capacity of MBRT may prove useful in patients requiring reirradiation since they are at substantial risk for toxicity. A phase 1 dose escalation trial to determine the maximum tolerated dose of MBRT is planned at our institution with tissue and blood collection to study response mechanisms. As a case report, our findings have limitations. Careful interpretation is warranted as results for the single patient reported in this report may not be generalizable to a broader population and cannot establish causality due to the observational nature.

POTENTIAL COMPETING INTERESTS

Dr Park reports NIH grants from R01CA 274985, R01CA278908, R01CA294704, and R01AG82681. The other authors report no competing interests.

ETHICS STATEMENT

All photographs are used with patient consent.

ACKNOWLEDGMENTS

Drs Jacobson and Sharifzadeh contributed equally to this work.

Abbreviations and Acronyms: **CT,** computed tomography; **MBRT,** minibeam radiation therapy; **MRI,** magnetic resonance imaging; **PET,** positron emission tomography

Publication dates: Received for publication March 20, 2025; revisions received May 21, 2025; accepted for publication May 28, 2025.

Correspondence: Address to Michael P. Grams, PhD, Mayo Clinic Department of Radiation Oncology, 200 1st St SW, Rochester, MN 55905 (grams.michael@mayo.edu).

REFERENCES

1. Grams MP, Mateus CQ, Mashayekhi M, et al. Minibeam radiation therapy treatment (MBRT): commissioning and first clinical implementation. *Int J Radiat Oncol Biol Phys*. 2024;120(5):1423-1424. https://doi.org/10.1016/j.ijrobp.2024.06.035.
2. Dilmanian FA, Zhong Z, Bacarian T, et al. Interlaced x-ray microplanar beams: a radiosurgery approach with clinical potential. *Proc Natl Acad Sci U S A*. 2006;103(25):9709-9714. https://doi.org/10.1073/pnas.0603567103.
3. Deman P, Vautrin M, Edouard M, et al. Monochromatic minibeams radiotherapy: from healthy tissue-sparing effect studies toward first experimental glioma bearing rats therapy. *Int J Radiat Oncol Biol Phys*. 2012;82(4):e693-e700. https://doi.org/10.1016/j.ijrobp.2011.09.013.
4. Price LSL, Rivera JN, Madden AJ, et al. Minibeam radiation therapy enhanced tumor delivery of PEGylated liposomal doxorubicin in a triple-negative breast cancer mouse model. *Ther Adv Med Oncol*. 2021;13:17588359211053700. https://doi.org/10.1177/17588359211053700.
5. Bertho A, Iturri L, Brisebard E, et al. Evaluation of the role of the immune system response after minibeam radiation therapy. *Int J Radiat Oncol Biol Phys*. 2023;115(2):426-439. https://doi.org/10.1016/j.ijrobp.2022.08.011.
6. Fazzari J, Fernandez-Palomo C, Pellicioli P, et al. Spatially fractionated minibeam radiation delivered at clinically feasible dose rates induces transient vascular permeability. *Sci Rep*. 2025;15(1):8210. https://doi.org/10.1038/s41598-025-87395-9.
7. Yuan H, Rivera JN, Frank JE, Nagel J, Shen C, Chang SX. Minibeam spatially fractionated radiation therapy for whole-brain re-irradiation—a pilot toxicity study in a healthy mouse model. *Radiation*. 2024;4(2):125-141.
8. Prezado Y, Deman P, Varlet P, et al. Tolerance to dose escalation in minibeam radiation therapy applied to normal rat brain: long-term clinical, radiological and histopathological analysis. *Radiat Res*. 2015;184(3):314-321. https://doi.org/10.1667/RR14018.1.
9. Sammer M, Teiluf K, Girst S, et al. Beam size limit for pencil minibeam radiotherapy determined from side effects in an in-vivo mouse ear model. *Plos One*. 2019;14(9):e0221454. https://doi.org/10.1371/journal.pone.0221454.
10. Rivera JN, Kierski TM, Kasoji SK, Abrantes AS, Dayton PA, Chang SX. Conventional dose rate spatially-fractionated radiation therapy (SFRT) treatment response and its association with dosimetric parameters—a preclinical study in a Fischer 344 rat model. *Plos One*. 2020;15(6):e0229053. https://doi.org/10.1371/journal.pone.0229053.
11. Garcia DA, Fazzari JM, Hlushchuk R, et al. Minibeam radiotherapy valley dose determines tolerance to acute and late effects in the mouse oral cavity. *Int J Radiat Oncol Biol Phys*. 2025. https://doi.org/10.1016/j.ijrobp.2025.03.016. Published online March 15.