Postradiosurgery cystic degeneration in brain metastases causing delayed and potentially severe sequelae: systematic review and illustrative cases

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BACKGROUND
Cystic postradiation degeneration has previously been described in the literature as a rare but potentially severe complication after central nervous system (CNS) irradiation for vascular malformations. Limited cases have been reported in the setting of brain metastases.

OBSERVATIONS
Thirty-six total cases, including three reported here, of cystic postradiation degeneration are identified. Of 35 cases with complete clinical information, 34 (97.25%) of 35 were symptomatic from cystic changes at diagnosis. The average time between initial radiation dose and cyst development was 7.61 years (range 2–31 years). Although most patients were initially treated conservatively with medication, including steroids, 32 (88.9%) of 36 ultimately required surgical intervention. The most common interventions were craniotomy for cyst fenestration or resection (25 of 36; 69.4%) and Ommaya placement (8 of 36). After intervention, clinical improvement was seen in 10 (67%) of 15 cases, with persistent or worsening deficit or death seen in 5 (33%) of 15. Cysts were decompressed or obliterated on postoperative imaging in 20 (83.3%) of 24 cases, and recurrence was seen in 4 (16.7%) of 24.

LESSONS
Cystic degeneration is a rare and delayed sequela after radiation for brain metastases. This entity has the potential to cause significant and permanent neurological deficit if not properly recognized and addressed. Durable control can be achieved with a variety of surgical treatments, including cyst fenestration and Ommaya placement.

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KEYWORDS brain neoplasms; cysts; metastasis; radiosurgery; radiation injuries

With improvements in systemic cancer and local central nervous system (CNS) therapies, survival for patients with brain metastases is increasing, leading to an expanding population of patients who are at risk for additional long-term side effects of CNS-directed therapies.1–3 The management of brain metastases often necessitates local radiotherapy in the form of stereotactic radiosurgery (SRS) or whole-brain radiation therapy (WBRT) as primary treatment or in combination with resection. Although these modalities confer good control of CNS disease, particularly for small tumors, they also carry the well-described risk of radiation necrosis (RN) within the first 1–2 years after treatment.4,5 In large studies of SRS-treated brain metastases, RN is seen in some 20%–40% of treated lesions, of which some 10%–15% are symptomatic and necessitate intervention ranging from corticosteroid, vitamin E, pentoxifylline, and/or bevacizumab administration to palliative resection.4–6 The risk factors for RN are incompletely understood, although total radiation dose and size are known independent risk factors. More recently, a clinically distinct process of cyst formation has been described as a rare and late-developing sequela of brain radiation following arteriovenous malformation (AVM) and head and neck irradiation, but rarely in the setting of brain metastases.7,8 Here we characterize in detail additional cases of this phenomenon in the brain metastasis population, all of whom required surgical management due to marked lesions causing progressive neurological deficits, and provide a systematic review of this rare entity.

Institutional databases were searched for cases of cystic RN and yielded three cases of delayed cystic RN. We conducted a systematic search of the available literature and reported our findings...
Illustrative Cases

Case 1

A 71-year-old man with metastatic NRAS-mutant melanoma to multiple sites, including the brain, presented for neurosurgical evaluation due to identification of a large intraparenchymal brain cyst in a previously irradiated metastasis field. His initial diagnosis of cutaneous localized melanoma with negative sentinel lymph node biopsy was 12 years prior to brain metastasis diagnosis in the right parietal lobe (Fig. 1). This was treated with definitive single-fraction SRS with 10 stereotactic fields delivering 22 Gy to the 80% isodose line, with near-complete initial response observed on follow-up imaging. Remarkably, complete response of extracranial disease was achieved with combination immune checkpoint inhibitor therapy (ipilimumab plus nivolumab) 6 years thereafter. He underwent yearly surveillance imaging after SRS that showed gradually increasing heterogeneous enhancement in the right parietal lobe. Positron emission tomography scan of the brain conducted 3 years after SRS was negative for hypermetabolism without suspicion for recurrent metastasis. Given that the patient was asymptomatic and his disease was well controlled, he was monitored with imaging at least every 6–12 months until 4 years after SRS and was observed clinically thereafter.

He experienced a seizure 7 years following SRS, with an electroencephalogram showing two right parietotemporal focal seizures, and brain magnetic resonance imaging (MRI) identified a complex lobulated hemorrhagic cystic lesion measuring 4 cm in maximal diameter. He was treated with lamotrigine with good seizure control. In the absence of further symptoms, this lesion was monitored radiographically, with continued slow growth. Of note, he was treated with low-dose hydrocortisone due to panhypopituitarism from immunotherapy treatment. Ten years following SRS, he developed a variant Gerstmann parietal syndrome, including progressive imbalance, spatial disorientation, and cognitive impairment with short-term memory loss, right-left-sided confusion, and dyscalculia. MRI showed cyst enlargement with peripheral enhancement, multiple loculations, and hematocrit level with associated cerebral edema and focal mass effect. MRI perfusion showed no increase in perfusion suspicious for recurrent metastasis. Given the symptomatic nature of this lesion and diagnostic uncertainty (with the differential diagnosis including metastasis recurrence, which had systemic therapeutic relevance in the absence of other disease), craniotomy with cyst fenestration and biopsy of the enhancement were performed at an outside institution. No active disease was seen on pathologic review. Postoperative MRI showed cystic decompression with improvement in midline shift. He recovered well from surgery and at last follow-up 8 months later continued on pembrolizumab with well-controlled disease burden.

FIG. 1. Case 1. Postcontrast T1-weighted MRI (A) showing a 5 × 5-mm enhancing metastasis located in the right parietal lobe. Postcontrast T1-weighted MRI (B) obtained 1 year after radiation showing a near-complete response to SRS. Four years after SRS, axial postcontrast T1-weighted MRI (C) and fluid-attenuated inversion recovery (FLAIR) MRI (D) show an irregular, heterogeneously enhancing, and partially necrotic lesion (measuring 2 cm in maximal diameter) in the right parietal lobe that has been stable on repeat imaging. Seven years after SRS, axial postcontrast T1-weighted MRI (E) and FLAIR MRI (F) show 4 × 3-cm lobulated cyst/necrotic hemorrhagic lesion with surrounding edema within the right parietal lobe. Ten years after SRS, preoperative T2-weighted MRI (G) and FLAIR MRI (H) show 5.2 × 4.2-cm complex cystic lesion with increased intralesional layering, concerning for blood products and minimal peripheral enhancement. Preoperative postcontrast T1-weighted MRI (I) shows curvilinear peripheral enhancement along the superior margin, unchanged from prior imaging. Postoperative FLAIR MRI (J) shows resection of cystic mass with improvement in midline shift.
Case 2
A 42-year-old woman with human epidermal growth factor receptor 2–positive (HER2\(^+\)) breast carcinoma presented with visual disturbance and was found to have a solitary occipital dural-based brain metastasis 2 years after her initial cancer diagnosis (Fig. 2), at which time gross total resection was performed. She underwent adjuvant hypofractionated SRS (30 Gy in five fractions) and was subsequently maintained on trastuzumab-based therapy without evidence of recurrent disease. Five years thereafter, she developed severe headaches, gait instability, and left inferior quadrantanopia, and MRI showed a large right parietal occipital cyst with internal hemorrhage without associated nodular enhancement. The cyst was evacuated for diagnostic and therapeutic purposes, and pathologic review identified histiocytic infiltrate and astrocytic proliferation without evidence of recurrent metastatic disease. The evacuated cyst fluid contained hemosiderin-laden macrophages and histiocytes. Her neurological function improved, though a partial visual field deficit persisted. She was tapered off steroids in the immediate postoperative period.

On follow-up imaging 6 months after evacuation, the parietal cyst reaccumulated to approximately the same dimensions as prior to surgical evacuation. This was initially treated conservatively with continued observation without use of steroids or bevacizumab. However, she developed headaches and worsening left-sided visual deficit and was treated with low-dose dexamethasone for palliation, and MRI showed progressive enlargement of the parenchymal cyst to 6 cm in maximal diameter. The cyst was again evacuated 13 months after prior evacuation with wide lysis of cortical adhesions, biopsy of enhancing margins, and placement of intracavitary catheter and subcutaneous Ommaya reservoir to allow future percutaneous biopsy of enhancing margins, and placement of intracavitary cyst decompression. Pathology was consistent with reactive changes, including gliosis, hemosiderin deposition, and neovascularization, again without evidence of metastatic disease. Postoperatively, she experienced resolution of her headaches and improvement in her vision. On follow-up imaging, partial though lesser reaccumulation as compared with prior cyst dimensions was identified, without need for aspiration through 2 years of observation.

Case 3
A 43-year-old woman with metastatic breast cancer (estrogen receptor–positive/progesterone receptor–negative/HER2\(+\)) underwent WBRT (30 Gy/10 fractions) due to multiple subcentimeter brain lesions (Fig. 3). On surveillance imaging, she was found to have a 9-mm left parietal-occipital (PO) lesion and a 4-mm right frontal lesion, for which she underwent SRS 3 and 4 years after WBRT, respectively. Subsequently, she developed a right-sided visual field cut and was found to have cystic changes within the left PO area. Cyst fenestration (and resection of any identified viable tumor) was planned but canceled in the setting of cyst shrinkage. She was not started on bevacizumab or steroids prior to cyst contraction. Six years after WBRT, the right frontal lesion became significantly enlarged, and the patient underwent cyst fenestration. Histological analysis showed gliosis, hemosiderin deposition, and focal chronic inflammation, consistent with postradiation reactive changes. There was no viable tumor identified. On follow-up imaging 1 year postoperatively, there was no recurrence of the cystic radiation degeneration but slight increase in the size of the left PO cystic lesion, which stabilized on subsequent imaging.

Literature Review
The initial search returned 338 articles, of which 190 were non-duplicates. Eighteen were determined to be relevant, of which four were in a non-English language (one Russian, one Japanese, and two French). Three papers were excluded due to incomplete information to allow definitive determination of cystic RN and not cystic tumor recurrence or solid RN. Including the three cases reported in this series, there are a total of 36 reported cases from 11 articles.\(^8,10–19\) A limitation of this review is the single-center nature of most case reports. Of 35 cases with complete clinical information, 34 (97%) were symptomatic from the cystic changes at diagnosis. The average time between initial radiation treatment and cystic RN appearance was 7.61 years (range 2–31 years). Although many patients were initially managed with conservative therapy, 32 (89%) of 36 underwent surgical intervention. Most patients (25 of 36; 69%) ultimately underwent craniotomy for cyst fenestration or resection. In 8 (22%) of 36 cases, placement of an intracystic catheter and Ommaya reservoir was performed. Of the reports describing clinical status after intervention, 10 (67%) of 15 had clinical improvement, 4 (27%) of 15 had persistent deficit, and 1 (6%) of 15 died. Of the reports describing radiographic outcome after intervention, 20 (83%) of 24 cases had cystic decompression or no recurrence, whereas 4 (17%) of 24 cases experienced recurrence.

Discussion
Observations
RN is a common complication of SRS after brain metastasis treatment and is most commonly described to occur approximately 1–2 years after radiation.\(^4\) Typical RN fluctuates in size, in some cases resolves spontaneously, and often is treated with medical intervention such as corticosteroids. This report illustrates an uncommon subtype of delayed radiation injury that is an entity separate from the typical course of classical RN. This delayed process has a different radiographic appearance, without the associated edema, nondiscrete contrast-enhancing borders, and central necrosis that are pathognomonic for RN. The highlighted cases occurred many years after SRS with cystic changes with partially hemorrhagic fluid expansion, without enhancing borders or reactive edema but with resultant neurological compromise requiring surgical intervention. A similar entity has been reported in the literature as a late complication of SRS for vascular malformations, which have different biarchitectures from brain metastases.\(^7\) In a systematic review looking at cyst formation after SRS for brain AVMs, a cystic degeneration rate of 3% was estimated, with an average formation time of 6.5 years. Among 64 patients with available clinical information, 33% were symptomatic (21 of 64), and 33% (21 of 64) required surgical intervention. One hypothesis for the development of cystic degeneration is that it is due to the breakdown of the blood–brain barrier with simultaneous increase in permeability of damaged vessel walls after radiation; however, the pathophysiology of this process may vary by underlying brain lesion (AVM, brain metastasis, or collateral brain injury by radiation targeted extracranially).\(^14\)

There have been isolated reports in the literature of cystic degeneration, often labeled as a form of RN, after SRS to treat brain metastasis. Through comprehensive literature review, we identified 11 articles reporting cases of postradiation cystic RN for brain metastases or head and neck cancer (Table 1).\(^8,10–19\) As discussed in the literature review section, the majority of cases were symptomatic from cyst development (97%) and underwent surgical intervention (89%). A key finding
of the results was the average time to development of cystic RN of 7.61 years (range 2–31 years) after radiation. This is significantly longer than the average time to development of classical RN, which is estimated to occur 1–2 years after radiation.

As shown, this disease has the potential to be highly morbid and difficult to treat even surgically. Of the 36 cases presented, 25 underwent cyst fenestration. Intracystic catheter and Ommaya reservoir placement was used in eight cases; in five cases, this was the sole treatment, one in conjunction with stereotactic cyst aspiration and two with placement in the cyst resection cavity after resection. Although two-thirds of patients had clinical improvement after intervention, one-third had persistent neurological deficit, and one died. The majority of patients (20 of 24 cases) had radiographic evidence of cystic decompression or no recurrence on postoperative imaging. One patient who presented with seizures was successfully treated with anticonvulsant medication and did not require surgical intervention. There is an isolated case report of the use of multiple cystoperitoneal shunts that failed to achieve adequate control of cyst growth. In a large series of patients who survived more than 3 years without recurrence of brain metastasis following radiotherapy, eight patients were found to have delayed cyst formation ranging from 37 to 121 months after first radiation treatment. The median time to cyst formation was 53 months. Of the seven symptomatic individuals, five underwent catheter and Ommaya reservoir placement and two refused surgical intervention. Of these, two required aspiration via their reservoirs, with one patient requiring multiple aspirations.

As demonstrated through our three cases with an average maximal dimension of 5.35 cm prior to intervention, the size of the cystic lesion
can be significantly larger and more morbid than the initial treated lesion. This is similar to the average maximal dimension of 5.6 cm (range 3–8 cm) of cyst size prior to intervention in the literature.11,12,16 Symptoms are a result of mass effect, edema, and brain compression, leading to diffuse neurological symptoms with or without focal neurological deficit. These cases, along with the existing literature, highlight the complexity of this complication, which can require multimodal treatment approaches. Although two cases were successfully managed with craniotomy and cyst fenestration, the other required a second, salvage operation with cyst wall resection, adhesion lysis, and Ommaya placement for definitive management, with subsequent partial fluid reaccumulation. Of note, in our present series, patients were not treated with bevacizumab prior to surgery. Although the high rates of symptomatic presentation (97%) and need for surgical intervention (89%) seen in this series and other reports are subject to selection bias, consideration for intervention in this setting may be appropriate in large or expanding cysts at first development of symptoms or potentially with impending symptoms. However, given the apparently very indolent presentation and unclear natural history of this process, we would generally reserve surgical intervention for palliation or for cases with diagnostic need and/or high suspicion of recurrence needing local control given the difficulty of salvage.13

We, along with others, hypothesize that this process may be one of induced abnormal neovascularization, microvascular malformation, or increased permeability through the blood–brain barrier due to injured vessel walls that results in cystic formation, along with sporadic peripheral enhancement and intralobar hematocrit levels often identified.14,15 One could hypothesize that cystic degeneration is the natural history for long-term survivors of brain metastases after radiation therapy and is likely highly underreported, given that this often is only identified with symptoms after patients are in remission from their cancer. Although obtaining sufficient tissue poses a challenge to deeper study, given the current rarity of this disease and a paucity of identified solid/nodularity for sampling in these cases, further research is needed to understand the pathogenesis of this potentially morbid process to help prevent or identify patients at elevated risk, such as lifetime dosing of brain-directed irradiation. This is particularly important because this patient population’s prognosis is broadly improving, making complications from treatment an increasingly relevant concern. We anticipate that this entity will therefore be increasingly encountered, and we advocate for symptomatic and potentially radiographic monitoring for long-term survivors of brain metastasis radiation treatment.16

A major limitation of this report is the inability to determine a true incidence of this complication. The two major factors that contribute to inability to determine the incidence are (1) the long-delayed presentation and patient death caused by their metastatic cancer or loss to follow-up many years after treatment at a tertiary cancer center and (2) the frequent prevalence of cystic components of treated metastases that do not evolve. Although our series highlights three cases that came to neurosurgical attention due to their expansile and symptomatic nature, there are likely many more indolent cases in patients treated with SRS. Although this systematic review summarizes the clinical and interventional aspects of this rare condition, future work should be dedicated to determining the true incidence and risk factors for this disease and the natural history of its precursors, particularly because outcomes are improving in the brain metastatic cancer

FIG. 3. Case 3. Postcontrast axial T1-weighted MRI (A) showing multiple subcentimeter lesions prior to WBRT. Postcontrast axial T1-weighted MRI (B) showing a 9-mm left PO lesion 1 month after SRS, 3 years after WBRT. Postcontrast axial T1-weighted MRI (C) showing a 4-mm right frontal lesion prior to SRS and the treatment-related changes to radiation for the left PO lesion. Axial fluid-attenuated inversion recovery (FLAIR) MRI (D) showing a left occipital cystic lesion measuring 3.9 × 3.6 × 3.9 cm approximately 1 year after radiation to the lesion. Axial FLAIR MRI (E) 2 months later shows a decrease in the size of the cystic lesion in the left occipital lobe. The right inferior frontal gyrus lesion with associated surrounding edema has increased. One and one-half years later, postcontrast T1-weighted MRI (F) and FLAIR MRI (G) show a nonenhancing cystic right frontal lobe lesion with layering hemorrhage, measuring 5.4 × 4.8 cm with 0.9 cm of leftward midline shift. Postoperative T1-weighted postcontrast MRI (H) shows resection of the right frontal cystic lesion. Follow-up imaging at 2 years shows near resolution of the right frontal cystic lesion on T1-weighted postcontrast (I) and FLAIR (J) MRI but an increase in the size of the previously decreased left occipital cystic lesion.
<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Pathology</th>
<th>No. of Pts</th>
<th>Symptoms (mass effect vs focal deficit)</th>
<th>Type of Radiation, Total Dose (fraction no.)</th>
<th>No. of Yrs After Radiation Until cRN</th>
<th>Intervention</th>
<th>Clinical &amp; Radiographic Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial pathologies: primary CNS tumor and brain metastases</td>
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<tr>
<td>Kawano et al., 1996</td>
<td>Glioma, unknown classification</td>
<td>1</td>
<td>Focal deficit (hemiparesis)</td>
<td>NOS</td>
<td>8–10</td>
<td>Resection (×4)</td>
<td>Recurrence</td>
</tr>
<tr>
<td>Hoshi et al., 2003</td>
<td>Pituitary adenoma</td>
<td>1</td>
<td>Mass effect (dementia), focal deficit</td>
<td>Conventional, 80 Gy</td>
<td>24 (rt), 31 (lt) temporal lobe cystic lesions</td>
<td>Resection</td>
<td>Clinical improvement</td>
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<tr>
<td>Ishikawa et al., 2009</td>
<td>Brain metastases: lung (4), breast (1), ovarian (1), kidney (1), esophagus (1)</td>
<td>8</td>
<td>7/8 symptomatic</td>
<td>SRS, 29–50 Gy</td>
<td>3.1–10.1</td>
<td>5/8 intracystic catheter/Ommaya reservoir</td>
<td>4/5 w/ clinical improvement; 1 death (POD)</td>
</tr>
<tr>
<td>Aizawa et al., 2018</td>
<td>Brain metastasis: mucoepidermoid carcinoma</td>
<td>1</td>
<td>Focal deficit (partial paralysis)</td>
<td>WBRT (40 Gy in 16 fractions) + SRS, 22.5 Gy (1 fraction at isocenter)</td>
<td>10</td>
<td>Conservative treatment failed, resection, intracystic catheter/Ommaya reservoir</td>
<td>Persistent deficit, no recurrence</td>
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<td>Present series</td>
<td>Brain metastasis: melanoma</td>
<td>1</td>
<td>Focal deficit (parietal syndrome)</td>
<td>SRS (22 Gy in 1 fraction)</td>
<td>10</td>
<td>Cyst fenestration</td>
<td>Persistent deficit, cystic decompression</td>
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<td>Present series</td>
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<td>1</td>
<td>Mass effect (headache, gait instability), focal deficit (visual field cut)</td>
<td>SRS (30 Gy in 5 fractions)</td>
<td>5</td>
<td>Resection, intracystic catheter/Ommaya reservoir</td>
<td>Improvement in focal deficit, partial recurrence</td>
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<tr>
<td>Present series</td>
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<td>Focal deficit (visual field cut)</td>
<td>WBRT, SRS</td>
<td>2</td>
<td>Cyst fenestration</td>
<td>Persistent deficit, no recurrence</td>
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<td>Extracranial pathologies</td>
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<td>Bederson et al., 1990</td>
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<td>1</td>
<td>Mass effect (memory deficit)</td>
<td>NOS, 70 Gy</td>
<td>10</td>
<td>Fenestration, internal shunting of bilat cysts</td>
<td>Clinical improvement, resolution of lesions</td>
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<td>Persistent deficit, cystic decompression</td>
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<td>Mass effect (headache, memory loss)</td>
<td>NOS</td>
<td>9</td>
<td>Stereotactic aspiration of cyst, intracystic catheter/Ommaya reservoir</td>
<td>Clinical improvement</td>
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<td>Resection</td>
<td>Clinical improvement</td>
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<td>Recurrence</td>
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<tr>
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<td>Mass effect (Sz), focal deficit (cranial nerve VII palsy)</td>
<td>NOS</td>
<td>4</td>
<td>Conservative</td>
<td>Clinical improvement</td>
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CONTINUED ON PAGE 7 *
cRN = cystic radiation necrosis; NPC = nasopharyngeal cancer; NOS = not otherwise specified; POD = progression of disease; RT = radiation therapy; SCC = squamous cell carcinoma; Sz = seizure.

population. Although Ishikawa et al.14 identified cyst formation at a significantly higher rate among patients with more SRS treatments, precise radiation parameters were not reported. Determining any significant risk factors for cystic degeneration will require large-scale prospective data collection and long-term follow-up and will be crucial to monitoring individuals for this condition. In addition, further investigation should be performed into the molecular mechanisms underlying the development of this disease process in the brain metastasis and nonmalignant populations.

Lessons
Delayed cystic RN can occur after radiation for brain metastases with the potential to cause severe brain compression with neurological deficit and requiring multimodality treatment approaches. Further understanding of this entity is required as survival increases for patients with previously irradiated brain metastases, and clinicians should have an index of suspicion for this process and other forms of radiation injury or malignant progression, even in the setting of long-controlled disease.

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References


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Conception and design: Moss, Giantini-Larsen, El Ahmadieh, Beal. Acquisition of data: Giantini-Larsen, Abou-Mrad, Beal, Young. Analysis and interpretation of data: Moss, Giantini-Larsen, El Ahmadieh, Beal, Young, Rosenblum. Drafting the article: Giantini-Larsen, Abou-Mrad, Goldberg, El Ahmadieh, Young, Rosenblum. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Moss. Study supervision: Moss.

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