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Case Report

Navigated transcranial magnetic stimulation following awake craniotomy for resection of glioma: Description of two cases

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ABSTRACT

Background: Although transcranial magnetic stimulation (TMS) has been indicated as a potential therapy for several neurologic conditions, there is little known regarding its use during the postoperative rehabilitation period in patients with brain tumors. Furthermore, seizures, a common presentation in these patients, are regarded as a major contraindication for TMS therapy.

Case Description: We demonstrate that postoperative continuous theta burst stimulation (cTBS), a patterned form of repetitive TMS, was safely tolerated in addition to current neurorehabilitation techniques in two brain tumor patients, including one patient with a history of tumor-related epilepsy. We administered navigated 5 Hz cTBS to two patients within 48 h following awake craniotomy for tumor resection. Active motor thresholds were measured in both patients before TBS administration to determine stimulus intensity. We used resting-state fMRI to identify likely damaged networks based on postoperative deficits. This aided in TMS planning and allowed deficit targeted therapy contralateral to the lesioned network node. Both patients tolerated TBS therapy well and had no adverse effects, including posttreatment seizures, despite one patient having a history of tumor-related epilepsy.

Conclusion: TBS may be safe in the immediate postoperative period for patients following brain tumor resection. Additional studies are needed to quantify the efficacy of TMS in improving neurologic deficits following tumor resection.

Keywords: Brain tumor, Neurorehabilitation, Postoperative rehabilitation, Seizures, Theta burst stimulation, Transcranial magnetic stimulation

INTRODUCTION

Theta burst stimulation (TBS) is a patterned form of repetitive transcranial magnetic stimulation (rTMS) that utilizes lower frequencies and shorter pulse durations than conventional rTMS.[4,20] Within these stimulation parameters, TBS has been recognized as a safe neurorehabilitation option with few related adverse effects, as compared to more rigorous, conventional rTMS protocols.[4,17] TBS protocols are further divided into continuous TBS (cTBS), which is low-frequency rTMS applied contralateral to the affected area and intermittent TBS, which is high-frequency rTMS applied

ipsilaterally.[5,10] Despite the scarcity of TBS-induced seizures, relevant protocols typically exclude patients with a history of seizures or epilepsy out of caution from the few case reports of rTMS-associated seizures.[3,20] In addition, brain lesions are generally considered a theoretical contraindication for TMS treatment due to variability in TMS-induced current focus and magnitude, as reported in computer-based models.[14,20,24,25] However, more recent publications suggest that this variation is not significantly different between healthy controls and patients with chronic cortical stroke lesions.[14,18] In addition, Hummel *et al.* have demonstrated the utility of downregulating excitability in the intact hemisphere by utilizing cTBS to improve paresis, language, attention, memory, and somatosensory processing in stroke patients in combination with rehabilitation.[11] This approach is significant for patients with abnormal brain tissue because it allows contralateral stimulation of the normal brain to improve connectivity through this mechanism of downregulating contralateral excitement.[9,11,21]

Patients with seizures secondary to glioblastoma (GBM) may benefit from postoperative TBS treatment for rehabilitation of neurologic deficits once the tumor, and consequently, the epileptogenic focus has been resected. Of significance, recent literature has established that early neurorehabilitation in acute stroke patients results in improved outcomes, possibly due to the effects on neuroplasticity.[2,6,15] Although these results are promising, pathophysiologic differences between GBM and chronic stroke lesions mean that they should be interpreted with caution. However, these studies do suggest initiating TBS treatment immediately following tumor resection may be a worthwhile avenue of research in improving functional outcomes.[6,26]

Despite these potential benefits, there are three main concerns with initiating TBS-based neurorehabilitation in patients with brain tumors. First, these patients often present with seizures,[1,27] which have been regarded as a major contraindication to any TMS therapy.[20] Second, almost all studies of patients with brain tumors receiving any form of TMS involve presurgical or intraoperative cortical brain mapping, meaning that there is little to no literature on the short-term effects or safety of postoperative TMS. Third, there are no studies illustrating the efficacy of TBS in the postoperative period. Overall, the long- and short-term effects and safety of postoperative TBS must be evaluated for it to be considered a viable adjunct to physical therapy in the postoperative rehabilitation period.

In these two patients, we demonstrate that TBS treatment was safely tolerated immediately following awake craniotomy for tumor resection, even in a patient with a medical history of seizures. We also demonstrate that it is possible to find active motor thresholds (aMT) in patients within 48 h after surgery, despite one patient presenting with baseline motor deficits in the contralateral limb.

CASE PRESENTATIONS

This report is a descriptive series of two cases which analyzed patient outcomes in the context of a new postoperative intervention with cTBS. Informed consent was obtained from both patients to receive the cTBS as an off-label use of the MagVenture MagPro 100× machine. All risks were disclosed and oral and written consent were obtained postoperatively from both patients and their power of attorneys, respectively. Both patients received any indicated physical therapy and speech therapy as part of standard postoperative care.

We performed a retrospective review of both patients described in this manuscript with approval from our Institutional Review Board 3199. We describe all pertinent pre- and postoperative events for both patients based on data obtained from the electronic medical record. Tumor volumes were calculated using preoperative, contrast-enhanced T1-weighted MRIs as described in other studies.[28] Postoperative MRI was completed within 48 h of surgery. Extent of resection was calculated by subtracting postoperative tumor volume from preoperative tumor volume divided by preoperative tumor volume. Final pathologic diagnosis was confirmed by our institution's neuropathologist. [Table 1] for detailed patient demographics.

Table 1: Clinical parameters for patients undergoing transcranial magnetic stimulation.

Age/ gender	Tumor location	Tumor volume (cc)	EOR (%)	Pre-TMS deficits	TMS protocol	TMS treatments	Areas targeted for TMS	Post-TMS complications	LOS (days)
26/F	Left insular AA	7.7	98	Right-sided weakness and pronator drift	5 Hz/50 Hz 200 total pulses 80% aMT	1	Right M1	None	3
64/M	Left temporal GBM	89.6	95.60	Expressive aphasia	5 Hz/50 Hz 200 total pulses 80% aMT	3	Right IFG	None	9

EOR: Extent of resection, LOS: Length of hospital stay, TMS: Transcranial magnetic stimulation, AA: Anaplastic astrocytoma, GBM: Glioblastoma multiforme, cTBS: Continuous transcranial brain stimulation, M1: Motor area 1, IFG: Inferior frontal gyrus

Patient 1

A 26-year-old right-handed female with an anaplastic astrocytoma of the left insula presented with the right pronator drift [Figure 1]. A medical history was significant for prior tumor resection 6 years ago and tumor-associated epilepsy. On preoperative evaluation, she was noted to have right hemiparesis graded at 4/5, mild right pronator drift, emotional lability, and impaired attention. Following surgery, postoperative imaging was obtained [Figure 1]. Before cTBS administration, physical therapy evaluation demonstrated delayed coordination, decreased strength of the left lower extremity, right facial droop, and a postoperative change in vision from normal and midline to diminished (reported: "blurry") in the left eye. The patient's right hemiparesis and mild right pronator drift were unchanged from preoperative evaluation. Medications affecting seizure threshold that were given during a patient's hospital course are listed with dosage and time of administration when applicable in [Table 2]. Of note, patient 1 continued her home dose of levetiracetam and did not receive a loading dose or any additional antiepileptic medications with exception of a dose administered intraoperatively before direct cortical stimulation.

Patient 2

A 64-year-old right-handed male with the left temporal GBM presented to neurosurgery with expressive aphasia [Figure 2]. Patient 2 presented with expressive aphasia, generalized weakness, and gait disturbance to the ED 10 days following a very limited partial resection at an outside hospital. Outside brain CT demonstrated hemorrhage into the site of initial resection. Due to this patient's acutely worsening symptoms, the authors decided an aggressive surgical cytoreduction approach to be the most beneficial option for the patient. On preoperative evaluation, he exhibited mild right pronator drift, apraxia, expressive aphasia, and wide-based gait with decreased cadence. Following surgery, postoperative imaging was obtained [Figure 2]. Before cTBS administration, physical therapy evaluation was significant for improved gait and activity tolerance, but increased word finding difficulty, decreased left lower extremity strength graded 4/5, and right dysmetria. This ipsilateral weakness was likely due to postoperative edema leading to compression of the right corticospinal tract at the level of the tumor resection, thereby causing left lower extremity weakness. The patient's mild right pronator drift and apraxia were unchanged from preoperative evaluation. Medications affecting seizure threshold that was

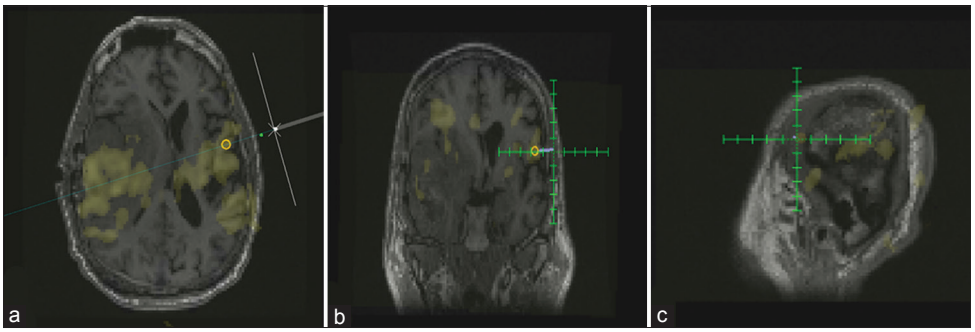

Figure 1: Pre- and postoperative magnetic resonance imaging of the first patient's recurrent left insular glioma, glioma resection, and temporal lobectomy. (a) Noncontrast, T1-weighted sagittal image highlights the patient's previous resection cavity. (b) Sagittal and (c) coronal MR images demonstrate the patient's postoperative resection cavity as well as resection of the left anterior temporal lobe. *Indicates the postoperative resection cavity in all panels.

Table 2: Patient 1 – 26/F.

Event	Day 0	Day 1	Day 2	Day 3
Keppra/1000 mg	7:44*			
Keppra/500 mg	14:50, 21:14	8:53, 15:38, 21:20	8:07, 15:13, 21:09	8:31, 15:29
Acetaminophen 500 mg	22:06		15:15	
Hydrocodone 7.5 mg		7:31	0:06	6:38
Trazodone HCL 50 mg	21:00	21:20	21:09	
Craniotomy for tumor resection	7:00 to 12:30			
TMS		17:00		
Physical therapy	7:00, 9:30	14:00	13:00	9:00
Speech therapy	7:00, 10:00	9:00		

*Intravenously administrated

given during a patient's hospital course are listed with dosage and time of administration when applicable in [Table 3].

Independent component analysis (ICA) and identification of cortical networks

Postoperative rfMRI was obtained in both patients to identify networks through ICA and to target cTBS therapy contralateral to the network nodes associated with the most significant postoperative deficit. The resting-state functional data were preprocessed using the Multivariate Exploratory Linear Decomposition into Independent Components application of the FSL toolbox v. 5.0 (www.fmrib.ox.ac.uk/fsl).[23] The images were smoothed with a Gaussian kernel of full width at half maximum of 8 mm. A slice timing correction was used to correct for the different acquisition times. The data were then preprocessed with high-pass temporal filtering (cutoff of 100 s) and with the removal of nonbrain structures from the echo planar imaging volumes (brain extraction tool). A threshold of 0.66 was used to eliminate extraneous noise within brain networks. All independent components were reviewed to identify distinct brain networks. The resulting ICA threshold maps were displayed on the patient's postoperative anatomical MRI using the Multi-image Analysis GUI (Mango) 4.0.1 (ric.uthscsa.edu/mango). We identified brain networks pertinent to postoperative deficits specific to each patient, based on previous literature regarding anatomic location and published functional activation maps.[8,21,22]

Treatment rationale

For patient 1, we targeted the motor network through right primary motor cortex (M1) with one session of cTBS.[5,8,22] Due to her most recent seizure being 2 weeks before presentation for surgery, lack in severity of deficits, and length of stay, the patient received only one treatment. Our goal with initiation of this intervention was to safely restore motor network function and improve her right hemiparesis by decreasing the contralateral inhibitory

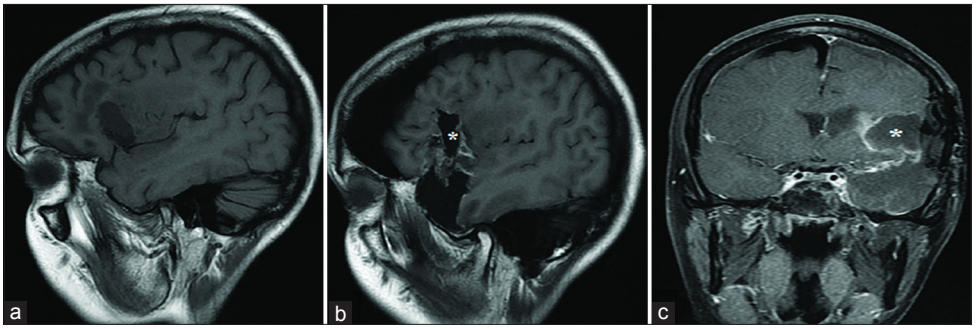

Figure 2: Pre- and post-operative magnetic resonance imaging of the first patient's recurrent left insular glioma, glioma resection, and temporal lobectomy. (a) Non-contrast, T1-weighted sagittal image highlights the patient's previous resection cavity. (b) Sagittal and (c) coronal MR images demonstrate the patient's post-operative resection cavity as well as resection of the left anterior temporal lobe. ((*) indicates the post-operative resection cavity in all panels.)

Table 3: Patient 2 – 64/M.

Event	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
Phenytoin/300 mg	19:25	9:36	8:25		9:15	8:29	8:17	9:57	8:15	9:21
Keppra/500 mg				7:11*						
Gabapentin/600 mg		20:54	22:05	21:07	20:41	20:55	21:26	21:37	21:09	
Fentanyl citrate/50 MCG				16:40, 21:06	03:56, 10:32, 17:13	21:08				
Hydrocodone/325 mg				21:07	21:59	19:19	06:33, 17:08, 21:26	03:52, 16:44, 21:38	05:46, 21:10, 19:36	00:27, 05:49
Craniotomy for tumor resection				8:00 to 13:00						
TMS						14:00	15:30		14:40	
Physical therapy				7:15, 10:00	9:10	10:15	15:00	11:30		8:30
Occupational therapy					9:10	10:40	10:40	14:40		
Speech therapy				7:15, 10:00	14:00		11:00			

*Intravenously administrated

effect of M1.[4,7] Studies examining cTBS for poststroke rehabilitation have revealed the utility of downregulating excitability in the intact hemisphere to improve paresis.[11] The basis of this mechanism has been explored in studies with healthy volunteers, which demonstrate cTBS decreases the excitability of the stimulated motor cortex and increases excitability of the contralateral motor cortex.[4,7] This altered excitability results in the potential for improved motor function of the impaired appendage.[11]

Patient 2 demonstrated worsening expressive aphasia postoperatively. Therefore, we attempted to target the language network by stimulating the right inferior frontal gyrus (IFG). The overall goal of this approach was to restore language network function by reducing cortical excitability of the contralesional IFG, thereby reducing severity of the expressive aphasia deficit.[9,21] Despite initial theories of speech and language production being lateralized to the left hemisphere, it has been shown to have similarities to the motor network requiring input and execution from both hemispheres.[21] Our aim was to improve patient 2's language function by inhibiting the intact hemisphere to allow improved or more equal coupling of reception and production of information due to the requirement of bilateral transformation.[9,21]

Stimulation protocol

Independent components were loaded into the TMS platform (Magventure MagPro 100×). Each patient's anatomic image was uploaded as a NIFTI file and then the ICA map at threshold was overlaid to facilitate navigation of the TMS coil to the targeted network node. TMS planning on Localite TMS Navigator Version 3.0.48 (Localite TMS Navigator, Localite, Sankt Augustin, Germany) was initiated, and both the target and entry point were selected to allow guidance of the TMS coil and direction of the current [Figure 3]. aMT was found by stimulating the right M1 and causing a visible twitch in flexor digitorum interossei and abductor pollicis brevis. Notably, both patients had left-sided lesions; therefore, right M1, contralateral to the lesion, was stimulated to find aMT.

Navigated cTBS was administered with a MagVenture MagPro device using a Figure 8 coil at bedside in the ICU for both patients. Patient 1 received one session of 5 Hz cTBS targeted to right M1 at 80% of aMT for a total of 200 pulses. This intervention was administered about 28 h following surgery. Patient 2 received three sessions of 5 Hz cTBS to right IFG at 80% of aMT for a total of 600 pulses, 48 h postoperatively.

RESULTS

Safety of cTBS intervention

During treatment, there were no adverse effects such as itching, tingling, burning, headache, or dizziness, and no serious adverse effects such as seizure. There were no significant changes in vitals following TMS administration.

Clinical assessment – Patient 1

The total length of stay for the first patient was 3 days. Postoperative deficits included continued right hemiparesis graded at 4/5, mild right pronator drift, delayed coordination, and impaired attention, with new deficits including decreased strength of the left lower extremity graded at 4/5 with break-away weakness to resistance, right facial droop, and blurred vision in the left eye. Before discharge, the patient was able to ambulate independently, with lower extremity strength improved to 4+/5 bilaterally. All other postoperative deficits were unchanged at discharge and there were no differences in neurologic examination before and after cTBS administration. At the 4-week follow-up, the left lower extremity strength improved to 5/5 and right upper extremity strength improved to 4+/5. The patient denied any seizures and all postoperative deficits were unchanged. After the 4-week follow-up, patient 1 transferred care to an oncologist closer to her home, though clinic and

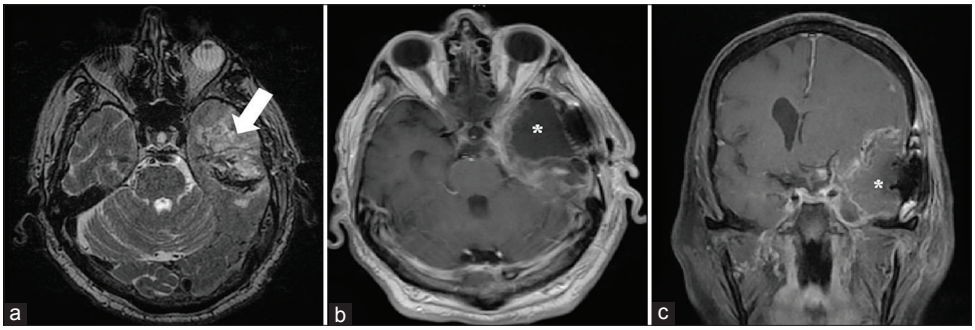

Figure 3: Pre- and post-operative magnetic resonance imaging of the second patient's left temporal glioblastoma and its resection cavity. (a) T2-weighted axial image demonstrates the patient's tumor (white arrow). (b) Axial and (c) coronal MR images demonstrate the patient's post-operative resection cavity consistent with a left anterior temporal lobectomy. ((*) indicates the post-operative resection cavity in all panels).

radiation treatment notes were followed through fax for 4 months postoperatively. Two months postoperatively, this patient continued to have right facial weakness right upper extremity weakness graded at 3/5. Unfortunately, radiation was not initiated for more than 3 months following tumor resection and no chemotherapy was reported. As part of an effort to account for patients lost to follow up, obituaries were reviewed to determine if a patient had died. Through examining obituaries in this patient's home town, we learned that she died abruptly at 4 months and 2 weeks following surgery, despite having no complications to her postoperative treatment regimen. It is unclear what led to the delay in adjunct treatment for this patient, but partial brain radiation was completed 9 days before death. Although no immediate postradiation complications were reported, the authors believe that the effect of postradiation edema in addition to the treatment delay may have contributed to this patient's unexpected deterioration.

Clinical assessment – Patient 2

The total length of stay for the second patient was 9 days, however, surgical resection was not performed until hospital day 4. Postoperative deficits included continued mild right pronator drift and apraxia, worsening of expressive aphasia, a change from subjective left lower extremity weakness to 4/5 strength, and new postoperative right dysmetria. At discharge, coordination of the upper extremities had improved with resolution of the postoperative right dysmetria. All other postoperative deficits were unchanged at discharge and there were no differences in neurologic examination before and after cTBS administration. At the 2-week follow-up, the patient was reported to have continued difficulty with word finding, though this was improved from discharge. No other deficits were noted at this follow-up. This patient's follow-up was limited past 2 weeks, and chemotherapy and radiation were not completed postoperatively. Through examining obituaries in this patient's home town, we learned that he died 4 months after his surgery. The authors believe that the combination of this patient's complex presentation with the lack of adjuvant treatment following the second surgical resection likely led to this patient's rapid deterioration.

Postoperative motor threshold

The aMT for patient 1 was found at 45% maximum stimulator output (MSO), 28 h following awake craniotomy for anaplastic astrocytoma resection of the left insula. The aMT for patient 2 was found at 48% MSO, 48 h following awake craniotomy for residual GBM of the left temporal lobe. Two more sessions of cTBS were administered, one on postoperative day 3 and one on postoperative day 5. The aMT for patient 2 on postoperative day 3 was found at 40% MSO and 38% MSO on postoperative day 5.

DISCUSSION

At present, there is little to no literature on the short-term effects or safety, let alone efficacy, of postoperative TMS as an adjunct to neurorehabilitation in brain tumor patients. We demonstrate two cases of cTBS administered within 48 h of awake craniotomy for tumor resection, with no immediate postoperative complications or adverse effects to TBS or at the 2-week follow-up. These preliminary results suggest that postoperative TBS is potentially safe and well-tolerated during the postoperative recovery period.

While this case series adds to the existing literature on TBS as a tool for motor rehabilitation, to the author's knowledge, it is the first description of postoperative TBS for aphasia in glioma patients. The TBS protocol for patient 2 was similar to protocols utilized in poststroke patients with residual aphasia.[9,21] Further studies of postoperative cTBS are needed to determine the efficacy of the described TMS protocols in glioma patients with motor and speech deficits.

Although this study is limited by a number of factors including very short-term follow-up in only two patients, it demonstrates that postoperative cTBS was administered safely in the two patients presented, as well as possibly aiding in transient improvement of neurological deficits. In one study, TBS has been linked to treatment-induced seizures in patients without a prior history of seizures, while other rTMS stimulation protocols have been associated with a limited incidence of seizures.[12,13,16,17,20] However, patients with a medical history of seizures are generally excluded from receiving TMS due to the risk of therapy-induced epileptic complications.[3,12,16,17,19,20] In addition, a recent systematic review examined rTMS studies involving patients with a history of epilepsy and found that out of 410 patients, 12 reported seizures, with only one reporting an abnormal seizure for that patient.[19] It is significant to note that in both incidences of abnormal rTMS-induced seizure, standard parameters for stimulation were not followed.[19,20] For instance, the epilepsy rTMS protocol utilized a frequency of 16 Hz and 100% of the potential machine output, a much higher intensity than the standard 80% of motor threshold.[19] Other contraindications, such as discontinuing antiepileptic medications and sleep deprivation, may have played additional roles in these cases.[17,19,20]

While we demonstrate that postoperative TBS was safely administered to two immediate postoperative awake craniotomy patients, further examination of safety concerns in brain tumor patients following tumor resection is warranted. However, this study is not without its limitations. The accuracy of the fMRI postoperatively may have been compromised due to surgically induced signal changes. In attempt to minimize these changes, both scans were acquired within 24 h of surgery. Both patients had a limited survival

following their tumor resection, with patient 1 having an overall survival of 6 years and patient 2 having an overall survival of 4 months. The lack of follow-up with prompt adjuvant therapies in both patients, in addition to the recurrent nature of patient 1's tumor and patient 2's complex presentation with tumor hemorrhage, likely complicated the disease course for patients. While we believe combined TBS and neurorehabilitation following craniotomy for tumor resection shows promise for improving postsurgical patient outcomes, further examination of the efficacy in brain tumor patients is necessary. Randomized controlled trials comparing postoperative outcomes of patients receiving TBS and neurorehabilitation, as opposed to neurorehabilitation alone, will be critical in understanding the lasting effects of TBS in brain tumor patients. Future research should be aimed at determining the efficacy and long-term effects of TBS as an adjunct to traditional postoperative neurorehabilitation.

CONCLUSION

We present two cases of patients receiving a postoperative TBS and neurorehabilitation intervention with no adverse effects. Although one patient had a history of tumor associated seizures, both patients tolerated TBS treatment well and experienced no adverse effects. We show that TBS was safely undertaken, though the efficacy and long-term effects of TBS as a postoperative rehabilitative measure need to be investigated with future research.

Statement of ethics

This study was conducted in accordance with the Helsinki Declaration as revised in 2013. This study was reviewed and approved by University of Oklahoma Health Sciences Center Institutional Review Board. Both patients provided their written informed consent to participate in this study.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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