Accepted Manuscript online: 2023-08-16 Article published online: 2023-09-27

TransOrbital NeuroEndoscopic Surgery for Biopsy of the Left Cavernous Sinus: A Literature Review, Case Report, and Cadaveric Proof of Concept

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J Neurol Surg Rep 2023;84:e116–e123.

Abstract

The aim of this report is to describe TransOrbital NeuroEndoscopic Surgery (TONES) as a safe alternative for obtaining a cavernous sinus (CS) biopsy. We describe this technique in a patient with a diffuse large B cell lymphoma mimicking Tolosa–Hunt's syndrome. Articles were gathered querying PubMed, Embase, and Scopus databases with terms related to a “transorbital neuroendoscopic approach.” The literature search was performed by two independent authors (N.L.F. and J.R.), with inconsistencies resolved by the senior author (M.M.D.V.). After screening abstracts for relevance, full-length articles were reviewed for pertinent variables. A comparison was conducted with the illustrative case of a 69-year-old woman who presented to the emergency department with vertigo, ophthalmoplegia, and diplopia for 2 months. A brain magnetic resonance imaging revealed an infiltrative lesion at the left CS. A presumptive diagnosis of Tolosa–Hunt syndrome was made, but a confirmatory biopsy was performed using TONES. Based on our cadaveric study, literature review, and case report, the TONES approach was safe, effective for tissue diagnosis, and associated with minor morbidity and reduced hospital stay. Additional prospective studies are required to study its viability and safety in a larger group of patients.

Keywords
- ► TransOrbital NeuroEndoscopic Surgery
- ► cavernous sinus
- ► biopsy
- ► lymphoma
- ► systematic review

Introduction

The cavernous sinus (CS) is a dural venous sinus situated within the middle cranial fossa. This anatomical compartment contains multiple neurovascular structures and is located just lateral to the sella turcica. Within the CS courses the cavernous segment of the internal carotid artery (ICA) with its ramifications, as well as the abducent nerve, sympathetic fibers, and fat, and within the space between the dura propria and the endosteal dura courses the oculomotor nerve, trochlear nerve, and the distal branches of the trigeminal nerve.[1] Surgical interventions that involve CS exploration are often tedious and complex due to the deep location and the possibility of neurovascular injury.[2,3] The subtemporal middle fossa craniotomy and the frontotemporal craniotomy with or without orbital and orbitozygomatic

received May 26, 2023
accepted after revision August 3, 2023
accepted manuscript online August 16, 2023

DOI https://doi.org/10.1055/a-2155-2419.
ISSN 2193-6358.

variations have been long considered the standard for access to the CS when complemented by the Dolenc, Hakuba, or Kawaze approaches.[4] With an increasing trend toward more minimally invasive techniques, the endoscopic endonasal approach such as transmaxillary and transpterygoid approaches have also been gaining traction. However, these approaches have the disadvantage of extensive bone loss, vidian nerve injury, and risk of vascular injury to the sphenopalatine artery or its branches.[2,5] Historically, the transorbital route has been applied in neurosurgery for at least 60 years.[6] Although it was mostly popularized for frontal lobotomies in conjunction with psychiatric care, it has evolved to a useful tool in minimally invasive neuroendoscopic surgery.[6] Some studies have proposed the TransOrbital NeuroEndoscopic Surgery (TONES) as a minimally invasive alternative approach to lesions involving the lateral CS wall. The term TONES encompasses a group of approaches that include: the precaruncular, preseptal lower eyelid, superior eyelid crease, and lateral retrocanthal approaches.[7] TONES provides ventral access to the CS with minimal brain retraction and preservation of the orbital rim and frontal bone.[3] Although the most common lesions of the CS are meningiomas and schwannomas, a small percentage is indeterminate lesions requiring a biopsy to help guide management.[8]

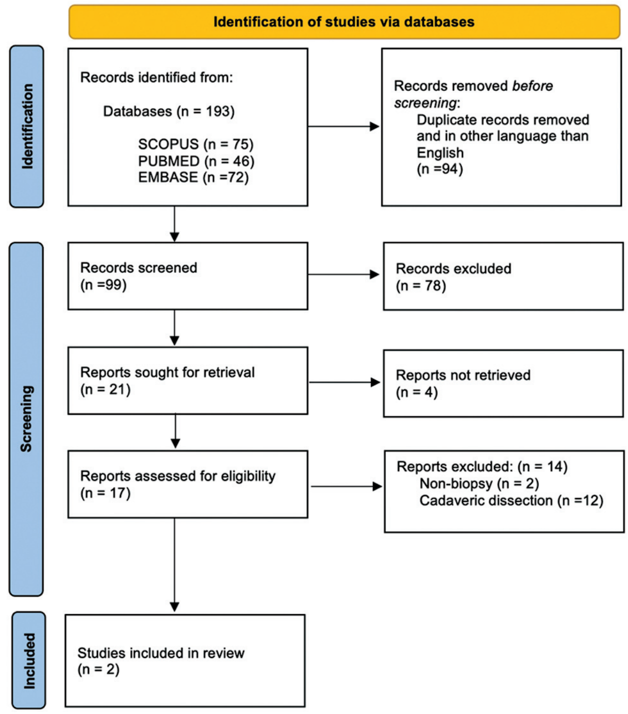

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis search strategy flow diagram.

Review

Purpose

The aim of this report is to describe a TONES as a safe and effective alternative for obtaining a CS biopsy for indeterminate lesions. We describe this technique in a patient with an unusual presentation of a diffuse large B cell lymphoma mimicking Tolosa–Hunt's syndrome. Using the neuroanatomy dissection laboratory, we illustrate step by step the TONES approach for CS biopsy to emphasize the safety and ease of this surgical technique. We also present an extensive literature review conducted on published articles on transorbital endoscopic approach for accessing the CS.

Systematic Review

The study was conducted by adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[9] Articles were gathered by querying the PubMed, Embase, and Scopus database with the following search terms: ("Transorbital neuroendoscopic approach" OR "Transorbital neuroendoscopic surgery" OR "TONES" OR "transorbital approach" OR "endoscopic transorbital approach") AND ("cavernous sinus"). Additional articles were obtained by cross-checking references and hand searching in Medline/PubMed and Google Scholar. The initial search yielded a total of 46 articles from PubMed, 72 articles from Embase, and 75 articles from Scopus ($n = 193$). Duplicates and articles published in a language other than English were excluded ($n = 148$) Thereafter, 99 abstracts were screened for relevance and 78 were excluded because of neurovascular theme and were irrelevant to the present investigation. Four abstracts were excluded because no publication was available at this time. Seventeen full-length articles were reviewed for pertinent clinical variables. Two full length articles were excluded due to nonbiopsy and nonsuperolateral TONES. The literature search was performed by two independent authors (N.L.F. and J.R.P.), and inconsistencies were resolved by discussion with the senior authors (T.G., G. P., and M.M.D.V.) (►**Fig. 1**).

Surgical Technique

Anatomical dissections were performed at the Neurosurgical Dissection Laboratory of the University of Puerto Rico School of Medicine. One injected cadaver head preserved in 70% alcohol was provided by the University of Puerto Rico for this study. Images and videos of the dissections were obtained throughout the procedure. The specimen was thawed, positioned supine, and rigidly fixed in a Mayfield head clamp. The specimen was rotated 15 to 20 degrees to the contralateral side. Dissections started macroscopically and then proceeded endoscopically. The technique began with an incision in the left superior eyelid and was extended laterally to include the canthus (►**Fig. 2A**).[3,10,11] Although not necessary for a cadaver, a corneal protector can be used for ophthalmic preservation during this step. However, it is important to periodically remove the corneal protector to monitor pupillary dilation and symmetry, considering that force applied on the globe during this surgical approach can cause visual damage.[12] A horizontal incision in the orbicularis oculi muscle was made and a flap was raised and fixated superolaterally (►**Fig. 2B**). The superolateral orbital rim was identified and scissors were used to dissect connective tissue away from the orbital rim to expose the periosteum. The

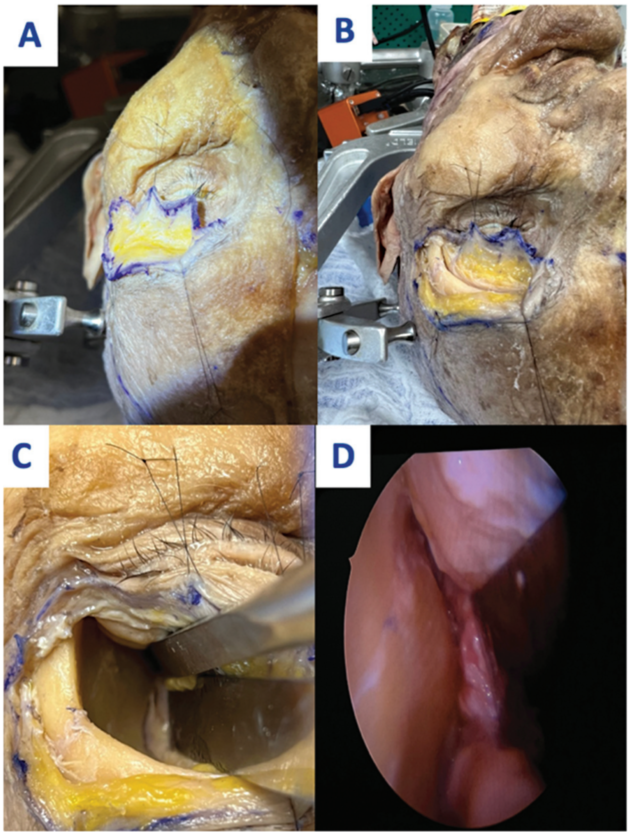

Fig. 2 (A–D) Surgical images of TransOrbital NeuroEndoscopic Surgery performed in dissection laboratory.

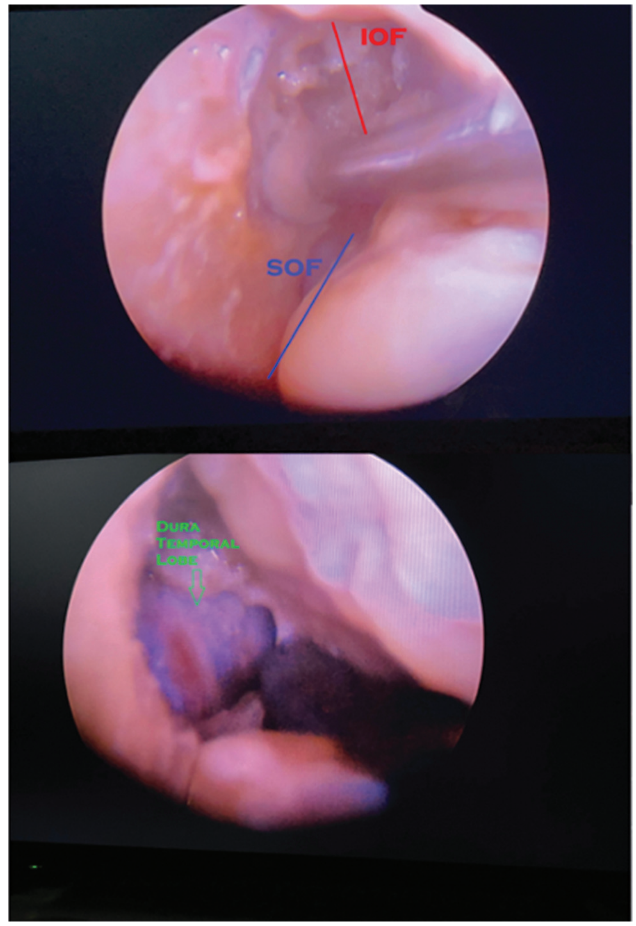

Fig. 3 Dura exposure following bone removal.

periosteum was incised and subperiosteal dissection was conducted, while concurrent gentle retraction with a malleable retractor was used to protect and displace the orbit inferomedially (►**Fig. 2C**). It is important to maintain the periorbita intact because orbital fat protrusion can affect visualization. If orbital fat herniates through the periorbital fascia, one must reduce it with bipolars instead of suctioning or pulling the tissue.[13] During the retraction, there is synergistic importance between dynamic retraction and intraocular pressure (IOP). If the IOP is instantaneously too high or low, one risks damage to the optic nerve. Therefore, continual measurement of IOP during dynamic retraction allows for safe optic nerve monitoring. In a prospective study by Kim et al, IOP was measured using a handheld tonometer, according to the degree of orbital retraction. At 10-minute intervals, the retractor would be withdrawn in 0.5 cm increments from a range of 0.0 to 2.5 cm. Maintaining the orbital retraction at less than 1.5 cm avoids critical injury. Similarly, during the operation, the orbital pressure must not be maintained for more than 60 to 100 minutes due to risk of permanent visual loss.[14] Another important aspect to consider is the oculocardiac reflex (OCR), which is a trigeminovagal bradycardia produced by tension on an extraocular muscle (EOM).[15] This could potentially occur in patients during an approach such as TONES. In a case report by Kroll et al, myocardial infarction occurred after pharmacological treatment of OCR in a patient undergoing strabismus repair.[16] According to Dunville et al, the only definitive way to prevent OCR is to remove the pressure being exerted on the eye.[17] After reaching a safe level of gentle retraction in our patient, a rigid endoscope with 0 and 30 optic lenses coupled to a high-definition camera and video monitor was used for visualization (►**Fig. 2D**). Once the superior orbital fissure (SOF) and inferior orbital fissure (IOF) were identified (►**Fig. 3**), a high-speed drill with a 3-mm coarse diamond bit was used to partially remove the anterior greater wing of the sphenoid to sufficiently expose the middle fossa dura, anterior fossa dura, and the lateral wall of the CS. Once the bone was drilled to a thin layer, it was removed with a blunt dissector. The meningo-orbital band was cauterized with bipolar and cut sharply. The lateral CS has two dural layers: the outer endosteal dura and the inner dura propria.[18] Subsequently, using microdissectors and blunt ring curettes for the peeling of the middle fossa dura off the lateral CS, the interdural plane between the temporal lobe dura and lateral CS was revealed (►**Fig. 4**).[3] To proceed further into the sinus, it is necessary to dissect the deep membranous layer of the lateral wall from the underlying cranial nerves (CNs) III, IV, and V. Following the anterior identification of the ophthalmic division of the trigeminal nerve and a careful dissection of the dural layer, complete exposure of the CS is anticipated. At this stage, entry into the sinus becomes feasible. Nonetheless, in our case report, the CS was not entered because the tumor had eroded the lateral wall.[19] Therefore, bleeding

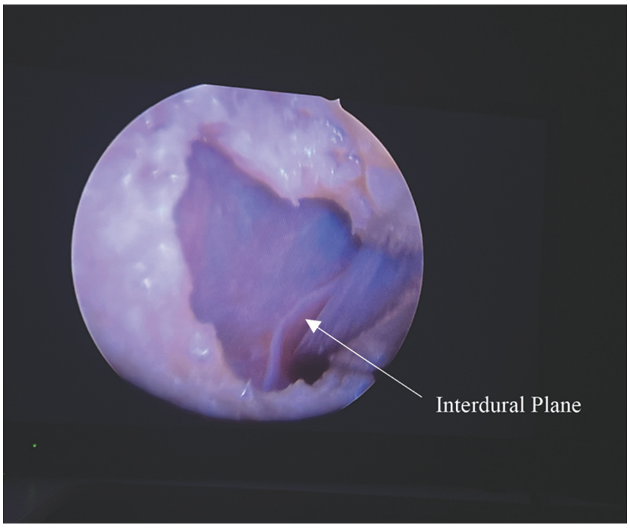

Fig. 4 Interdural plane.

from the area surrounding the CS was minimal. During the clinical procedure, tumor samples were taken with micro-pituitary forceps and sent for frozen and permanent section, and biopsy was diagnostic of a lymphoid process. At the end of the biopsy, there was no evidence of intraoperative cerebrospinal fluid (CSF) leak, and the area was packaged with a hemostatic agent for a period of 5 minutes. This was irrigated away with antibiotic containing saline and clear effluence documented hemostasis. The temporal dura was covered with an onlay of collagen dura substitute and secured in place with a fibrin sealant. The oculoplastic surgeon then entered the field, returned the globe to its original position, and performed the final closure for a cosmetically appealing result. The periosteum was repositioned and sutured at the superolateral orbital margin utilizing a 5–0 absorbable suture. The skin incision was then closed with a 6–0 fast absorbing plain gut.[20] The patient tolerated the procedure well, was extubated in the operating room, and transferred to the recovery room in stable condition.

Results

Case Report

A 69-year-old woman with medical history of hypertension, hyperlipidemia, peripheral arterial disease, and diabetes mellitus was referred to the emergency department due to left ptosis and diplopia. Symptoms started 2 months prior to our initial evaluation with left nasal pain, left-sided headaches, and blurred vision. She denied any other systemic symptoms such as nausea, vomiting, recent weight changes, jaw claudication, joint pain, flashes, or floaters. Initial ophthalmological evaluation showed a visual acuity of 20/20 bilaterally and IOP at 11 mm Hg on the right and 10 mm Hg on the left. Extraocular movements were full on the right eye, with limitation on all gazes with negative forced duction testing on the left eye (►**Fig. 5**).[21] Ishihara color plates were complete on both eyes, no afferent pupillary defect was observed, and no evidence of proptosis was seen. External evaluation was remarkable for left-sided ptosis with margin to pupillary rim distance of 5 and −2 in her left eye. Levator function was 14 and 10 mm on right and left eyes, respectively. Slit lamp evaluation was found within normal limits and dilated fundus examination had no evidence of optic nerve swelling, pallor, or any other acute pathologies.

Differential diagnosis upon presentation was broad as the patient had a painful ophthalmoplegia that resulted in almost complete extraocular limitation of her left eye. Initial inflammatory parameters were within normal limit for the patient's age and reactive plasma regain testing was negative. Brain magnetic resonance imaging (MRI) with and without contrast showed an enhancing lesion along the dura of the left CS extending anteriorly via the SOF and apex (►**Fig. 6**).

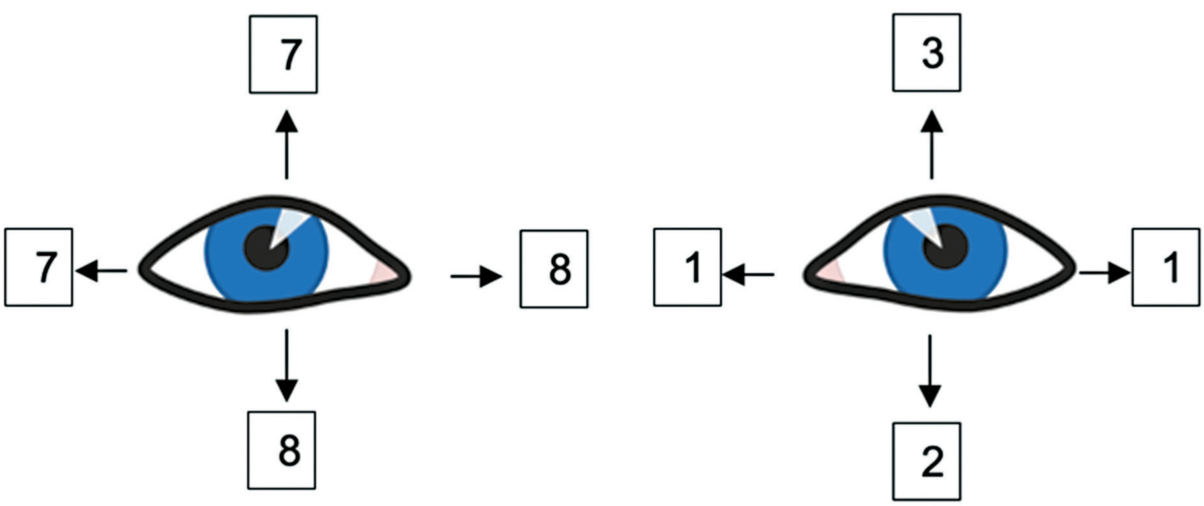

Fig. 5 Initial measurement of the four cardinal ocular movement.

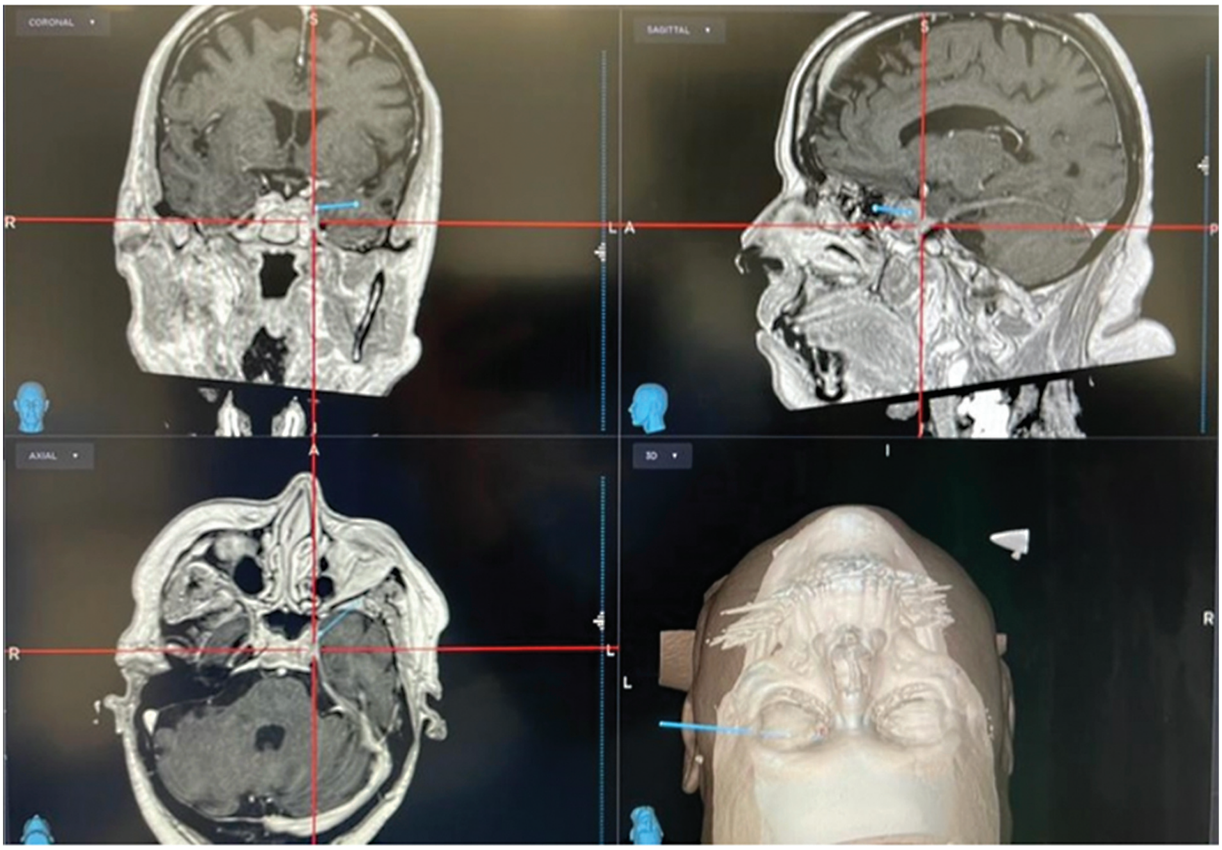

Fig. 6 Preoperative imaging of 69-year-old woman.

At that time, differential diagnosis included Tolosa–Hunt's syndrome/idiopathic inflammatory pseudo-tumor, neurosarcoidosis, or lymphoma. Yet, considering that the patient had no previous symptoms or concerns the most likely diagnosis was Tolosa–Hunt's syndrome. However, further work-up was required as this is a diagnosis of exclusion. The patient was admitted for malignancy and infectious work-ups which came back negative, and neurology was consulted. Lumbar puncture was performed and found normal CSF analysis, including negative CSF cytology. Hence, the patient was started on 250 mg intravenous (IV) solumedrol for 3 days with symptomatic improvement. After 3 days, the patient was discharged home with 60 mg daily of oral prednisone and outpatient ophthalmology follow-up. Patient remained stable after discharge with regular follow-up, excellent vision, and continuing standard prednisone taper. Yet, at 1 month, she was found with significant decrease in vision at counting fingers, loss of color vision with Ishihara color plates at 0/12, left afferent pupillary defect, and worsening ophthalmoplegia (►**Fig. 7**).[21] At that time, the patient was taking 20 mg of oral prednisone daily, yet due to the new findings, she was readmitted for a new brain MRI and possible biopsy.

Repeat brain MRI with and without IV contrast showed an interval increase in the size of the enhancing lesion along the CS. The patient was restarted on solumedrol 250 mg IV daily, and biopsy was recommended. From an ophthalmology standpoint, biopsy options included a left optic nerve sheath biopsy which had a risk of permanent vision loss and chance of false negatives as only the most anterior portion of the sheath can be accessed through the orbit. Thus, neurosurgery was consulted to discuss other biopsy alternatives. Open transcranial microscopic biopsy via traditional skull base approaches, endoscopic endonasal transsphenoidal transpterygoid/transmaxillary approaches, endoscopic transorbital approaches, and combined approaches were discussed, and the TONES biopsy of the left CS was ultimately recommended due to minimal risk of left temporal lobe morbidity and an already compromised eye mobility and visual acuity.

Preoperative examination revealed left palpebral ptosis and blurred vision. Pathology revealed a diffuse large B cell lymphoma. Immunohistochemistry was positive for Bcl-2, Bcl-6 (20%), CD3, CD5, CD20, CD79A, Ki67 (90%), MUM1, and c-Myc (50%). Postoperative brain computed tomography revealed minimal pneumocephalus at the left CS and tortuosity of the left optic nerve. No intracranial hemorrhage or extra-axial fluid collection was noted. Postoperative day (POD) 1, visual acuity was 20/400, EOM limited in all quadrants, CNs III, IV, VI affected, left pupil no reaction, and + afferent pupillary defect by reserve. Eyes were anisocoric, right with 3 mm and left pupil dilated and nonreactive (6 mm). On bedside examination, left eye had complete ptosis with upper eyelid sutures in place, periorbital edema with ecchymosis but ability to open eyelid, and inferior chemosis with diffuse injection. On POD 5, the patient was

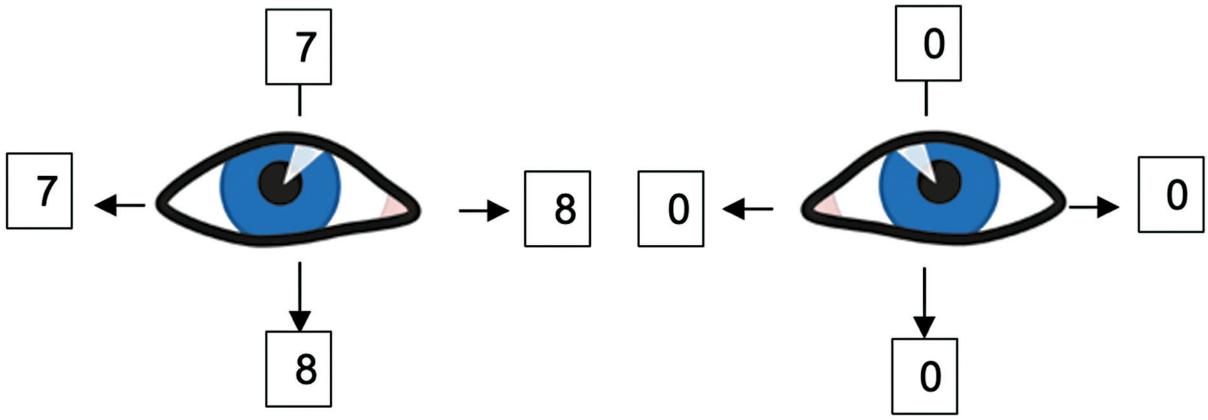

Fig. 7 Follow-up measurements after the patient was found with worsening ophthalmoplegia, now presenting with a frozen globe, which is complete limitation in extraocular muscle.

doing well. The only finding on physical examination was mild swelling of the left eye and hemifacial sensory loss on pinprick (V1, V2, V3 distribution due to trigeminal nerve infiltration of lymphoma). At discharge on POD 5, her only lasting deficit was left vision loss. Approximately 1 month postoperative, the patient underwent her first course of chemotherapy. The patient has been followed up for 3 months postoperation; she reported being satisfied with the outcome of the procedure. Her hemifacial sensory loss has been gradually resolving, as she reports sensation in the mentum. Blindness of the left eye persists.

Literature Case Reports

The present study aimed to evaluate the safety and effectiveness of the TONES approach as an alternative to biopsy the anterolateral CS, based on a cadaveric study, literature review, and case report. Our findings suggest that the TONES approach is a viable option, as it is associated with minimal morbidity, rapid recovery, and short hospital stay as evidenced by previous case reports (►**Table 1**).[6,8,22,23]

The first illustrative case report included in our study involves a 57-year-old man with painful ophthalmoplegia of the left eye, in which a lateral orbitotomy approach was used to diagnose a lymphoma, due to the minimal supportive studies of a purely transorbital approach.[24] This patient had minimal to absent morbidity and near resolution of his symptoms during the postoperative period. In comparison, our study demonstrates that a similar lesion can be biopsied using a less invasive technique with favorable outcome. Moreover, Son et al (2022) documented a case of a 55-year-old woman who presented with persistent right facial droop, pain, blurriness, vertigo, and imbalance. Brain MRI revealed an enhancing lesion in Meckel's cave (MC) without CS involvement, which was biopsied via a lateral transorbital approach, resulting in an amyloidoma diagnosis with minimal to absent morbidity with stable postoperative conditions and mild symptomatic improvement. Based on our results, we suggest that if CS involvement is present, a minimally invasive superolateral transorbital approach could be employed to reach the lesion directly.

Discussion

Many studies have evaluated the newly emerging TONES technique as an alternative approach to accessing the CS.[25] However, only some of these works consider the procedure for performing CS biopsies. In 2014, Bly et al noted that "the greatest utility of this approach may be for biopsies of lesions within the MC and lateral CS."

The classic subtemporal craniotomy (STC) and variations of the fronto-orbito-temporal-zygomatic approach have been long considered the standard approach to reach the CS. The STC classic approach begins with a 5-cm lazy S skin incision at the inferior rim of the zygomatic arch extending along the hairline incision. Interfascial and temporalis muscle dissection are performed to reveal the squamous bone and posterior greater wing of sphenoid. A low-set temporal keyhole craniotomy is made over the middle portion of the zygomatic arch. Extradural drilling middle fossa floor flattening allows for blunt dissection of dura off the middle fossa floor. The dura mater of the temporal lobe is peeled starting with V3 until CS is exposed.[4] This approach may result in considerable morbidity if not performed properly by experienced teams as cases in the literature have showed

Table 1 Studies using TransOrbital NeuroEndoscopic Surgery for procedural biopsy

Study	Age (y)	Sex	Pathology	Diagnostic modality	Postoperative outcome
Chabot et al (2017)	57	M	Lymphoma	Biopsy	Near resolution of cranial nerve palsies
Son et al (2022)	55	F	Amyloidoma	Biopsy	Stable unilateral facial pain and weakness
Frontera et al (2023)	69	F	Lymphoma	Biopsy	Transient hemifacial sensory loss on pinprick

oculomotor palsy, trochlear palsy, contralateral hemiparesis, homonymous hemianopsia, and aphasia. In contrast, the pretemporal frontotemporal craniotomy begins at the upper border of the zygomatic arch, anterior to the superficial temporal artery; the incision continues superiorly toward the upper tip of the external ear and curves anteriorly to end behind the hairline in the frontal region. The cutaneous and temporalis flaps are reflected anteriorly from the underlying bone. A basal frontotemporosphenoidal craniotomy is performed utilizing five burr holes. In this approach, additional drilling is done at the greater and lesser wing of the sphenoid as to permit retraction of the temporal lobe inferiorly and posteriorly.[26] Similarly, this approach, if not executed properly, has shown injury to the frontal and temporal lobes causing transient or permanent aphasia and contralateral weakness. Furthermore, manipulation of the major vessels at the sylvian fissure may also lead to direct or indirect injury resulting in critical stroke.

There are multiple reasons why the TONES approach is useful for minimally invasive procedures. First, the complex geometric relations in the deep skull base pose challenges regarding which angles of attack are optimal for adequate visualization. Practitioners can obtain ample visualization via this approach since the entire lateral CS wall, including the oculomotor, trochlear, and trigeminal nerves, corresponding branches, and the middle meningeal artery, is exposed.[3,5] On the other hand, an endonasal approach is more limited by the trajectory of the ICA.[5] This corridor allows a unique perspective on the anteromedial and anterolateral triangles of the middle cerebral fossa to conduct a biopsy of the CS.[5,18] Moreover, lateral transorbital approach provides a direct route to MC, which lies directly adjacent to the CS. Although our study focuses primarily on the CS, it is important to note that lesions involving MC and extending into the CS can also be approached via TONES for biopsy procedures. In a case report documented by Son et al, they describe a lateral canthal transorbital approach to the CS for a unique case of MC amyloidoma. Further, if we consider endoscope-assisted approaches toward lesions located between V2 and V3, lateral transorbital approach allows access to MC/CS without collateral manipulation of the trigeminal nerve or branching. Other techniques to reach MC/CS, such as the retrosigmoid approach and the traditional preauricular subtemporal extradural approach, require more invasive surgery.[8]

Another theoretical advantage of TONES is the favorable tissue preservation due to its minimal collateral damage. From a cosmetic point of view, the smaller skin incision can be easily hidden in the natural skin crease. As opposed to transcranially or endonasal, endoscopic transorbital approach is a more conservative approach regarding the preservation of the anatomy. For example, the endoscopic endonasal technique requires the removal of tissue in the middle turbinate, superior turbinate, uncinate process, posterior aspect of nasal septum, sphenoid rostrum, posterior ethmoid, and sellar floor bone. A transcranial approach removes the zygomatic arch and lesser wing of the sphenoid,[5] whereas with TONES approach, one would only remove the bone between the SOF and IOF, sparing the orbital rim and frontal bone. Moreover, the bone may be reconstructed, limiting the possibility of orbital herniation through craniotomy, which is another advantage, as it is a relatively simple and fast procedure due to the thinness of the orbital bone. Furthermore, the temporalis muscle is preserved, reducing the risk of atrophy.[3] This technique can be employed without manipulating deep CNs or entering venous spaces because the angle of attack is direct and short. In fact, a study by Bly et al utilized a three-dimensional computer model with virtual endoscopy to demonstrate the superiority of the transorbital approach because it provides the most direct pathway to the sellar compartment. The model further suggests that this approach can significantly decrease the distance to the target lesion.[27,28] The average working distance to the CS is shorter through a transorbital (6 cm) rather than a transnasal (>9.5 cm) approach, which allows for less tissue damage.[2] Furthermore, this technique minimized temporal lobe and dura retraction while sufficiently exposing the skull base.[18] A study by Lima et al showed that once the intradural corridor has been created, a biopsy of the CS wall does not require temporal lobe retraction for two specific targets. Overall that study supported the use of the LTOA for biopsies in the lateral CS wall because of the smallest horizontal angles of attack and decreased surgical freedom, contributing to tissue preservation.

Limitations

There are several limitations in this study. First, the study is based on a single case report, which limits the generalizability of the findings. The conclusions drawn from a single patient's experience may not apply to other individuals with different conditions or presentations.

Second, cadaveric studies usually involve a limited number of specimens, often due to the scarcity and availability of cadavers. Similarly, the variability among cadavers, and lack of physiologic functioning may impact the study's results. The study relies on a literature review and a cadaveric study, in addition to the case report. While these sources contribute valuable information, they may not provide a comprehensive understanding of the safety and effectiveness of the TONES approach. Further studies, particularly prospective studies with larger sample sizes, are necessary to build a stronger evidence base.

Conclusion

The TONES approach appears to be a safe and effective option for biopsy of lesions in the anterolateral compartment of the CS. The available literature is emerging and larger prospective studies comparing TONES with more traditional approaches are needed to establish superiority and better define patient selection criteria.

Conflict of Interest
None declared.

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