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Urge-to-Cough and Cough Motor Function After Transsylvian–Transinsular Resection of Insular Gliomas: A Prospective Cohort Study

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Title

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Abstract

Purpose To characterize changes in urge-to-cough (UTC), evoked cough, and voluntary cough performance after transsylvian–transinsular resection of insular gliomas.

Methods This single-center prospective cohort included 46 adults assessed preoperatively, approximately 7 days postoperatively, and through 12 months. UTC ratings (modified Borg scale, 0 to 10) and evoked cough counts were compared at a fixed individual capsaicin concentration equal to the preoperative threshold eliciting at least two coughs (C_2). Voluntary peak cough flow (PCF) was assessed at the same visits. The primary outcome was early within-patient UTC change, analyzed using the exact sign test. Anatomical associations were exploratory.

Results Early paired UTC measurements were available in 44 patients. UTC decreased in 36/44 (81.8%), with a median paired change of −2 points (interquartile range [IQR], −2 to −1; $p < 0.001$). The median paired change in evoked cough count was −2 (IQR, −3 to −1). Among 45 patients, median paired PCF change was +3 L/min (95% confidence interval, −15 to +12). Greater resection volume within the posterior insular region correlated with a larger UTC decrease (Spearman $\rho = -0.314$; $p = 0.038$). At 12 months, median UTC change was zero among 37 assessed patients; five had lower ratings than at baseline.

Conclusion Insular glioma resection was followed by early reductions in UTC and evoked cough, with variable subsequent recovery. PCF findings do not establish preserved motor function. Anatomical associations and the clinical significance of UTC changes require further investigation.

Keywords: Insular glioma; Urge-to-cough; Capsaicin cough challenge; Peak cough flow; Transsylvian approach; Postoperative outcomes

INTRODUCTION

The surgical management of insular gliomas requires a balance between maximizing tumor resection and preserving neurological function. The deep location of the insula and its proximity to functionally important cortical and subcortical structures and a complex vascular network make this balance particularly challenging [12, 14]. Surgical outcomes are commonly assessed in terms of extent of resection, oncological control, and motor and language function. A more comprehensive assessment of postoperative function also requires consideration of the sensory and behavioral responses involved in airway protection. Reports of impaired swallowing safety and silent aspiration after insular glioma surgery underscore the clinical relevance of this issue [17].

Cough is an airway-protective response that involves stimulus perception, central regulation, and motor execution [1, 8]. The urge-to-cough (UTC) is the consciously perceived need to cough in response to airway irritation. Capsaicin challenge studies have demonstrated that this sensation can arise at concentrations below those required to elicit a cough motor response [1]. Thus, UTC, evoked cough, and voluntary cough strength are related but distinct functional measures. Combining UTC assessment with measurement of peak airflow during voluntary coughing—peak cough flow (PCF)—allows the sensory and motor components of this protective response to be characterized separately.

Functional neuroimaging studies support the involvement of the insula in cough-related sensory and behavioral processes. In healthy volunteers, capsaicin-evoked UTC has been associated with activation of a distributed network encompassing the insula, cingulate and somatosensory regions, and other cortical areas [9]. A subsequent study linked evoked cough to posterior insular activity and voluntary cough suppression to a network involving the anterior insula [8]. Neural responses associated with stimulus intensity and perceived UTC have also been shown to differ [4]. These findings provide a neurophysiological rationale for investigating UTC after insular resection. However, activation maps obtained in healthy individuals do not establish that a particular insular region is a unique cough center or that its resection necessarily causes sensory impairment. The relationship between anatomy and function therefore requires evaluation in the clinical setting.

The clinical relevance of UTC relates to responses to material entering the airway and to swallowing safety. In patients with Parkinson disease, greater dysphagia severity has been associated with lower UTC ratings and fewer capsaicin-evoked coughs [15]. Although these findings cannot be directly extrapolated to insular glioma surgery, they support considering sensory function when assessing airway protection. A prospective study of insular glioma surgery identified aspiration, including silent aspiration without a cough response, using fiberoptic endoscopic evaluation of swallowing (FEES) [17]. Such an observation on FEES does not, by itself, demonstrate reduced UTC or distinguish impaired sensation from impaired cough motor execution. Concurrent assessment of UTC, evoked cough, and voluntary cough performance may therefore help clarify the functional basis of these clinical observations.

Although experimental and clinical evidence supports a role for the insula in cough control, the magnitude and recovery trajectory of UTC changes after insular glioma resection, and their relationship to motor measures, remain insufficiently characterized. Because stimulus intensity influences perceived sensation [4], comparing preoperative and postoperative UTC at the same

individualized capsaicin concentration is methodologically important. Interpretation also requires consideration of both resection anatomy and potential postoperative ischemic injury [12]. This approach can inform hypotheses about anatomical associations, although an association between resection volume and UTC alone cannot establish causality.

The primary objective of this prospective cohort study was to evaluate early changes in UTC after transsylvian–transinsular resection of insular gliomas. UTC approximately 7 days after surgery was compared with baseline at an individualized capsaicin concentration equal to each patient's preoperative C_2 threshold—the lowest concentration eliciting at least two coughs—and held constant at subsequent assessments. Parallel assessment of UTC and motor measures characterized changes in these functions separately. Secondary objectives were to describe their trajectories over 12 months, assess swallowing safety using documented FEES findings, and explore the association between resection volume within the posterior insular region and changes in UTC.

MATERIALS AND METHODS

Study design and participants

This single-center prospective cohort study evaluated urge-to-cough (UTC), evoked cough, and voluntary cough motor function in 46 patients who underwent transsylvian–transinsular resection of insular gliomas at the Republican Specialized Scientific and Practical Medical Center of Neurosurgery, Tashkent, Uzbekistan. Patients were enrolled from February 2022 through July 2025, and follow-up data collection ended in August 2026. The cohort included 22 patients from the center's previously published FEES study [17] and 24 additional eligible patients who were not included in that report. Postoperative changes were assessed relative to each participant's baseline measurements. The present study extended the assessment of postoperative airway protection by directly measuring cough sensation and motor function.

Adults scheduled for resection who could understand the test instructions, use the UTC scale, and provide informed consent were eligible. Exclusion criteria comprised neurological disease independently affecting cough, active respiratory infection, uncontrolled airway obstruction, clinically significant laryngeal disease, and contraindications to cough provocation. In patients with aphasia, comprehension of instructions and the ability to indicate a rating nonverbally were assessed individually. Inability to complete postoperative testing was recorded as a missing assessment and did not, by itself, justify exclusion from the cohort. Glioma diagnoses were confirmed histologically; molecular classification was not reported in this dataset.

The study was approved by the local ethics committee of the Republican Specialized Scientific and Practical Medical Center of Neurosurgery, Tashkent, Uzbekistan (Protocol No. 10-2022). All methods were performed in accordance with the relevant guidelines and regulations. Written informed consent was obtained from all participants. Personal identifiers in study records were replaced with codes. Surgical decisions were based on clinical indications and the principle of maximal safe resection.

Assessment schedule

Assessments were scheduled 3 days before surgery, within a window of days −5 to −1 (T_0); on postoperative day 7, within days 5–9 (T_1); at 4 weeks, within days 21–35 (T_2); at 3 months, within days 76–104 (T_3); at 6 months, within days 150–210 (T_4); and at 12 months, within days 335–395

(T_5). The assessment battery at each visit comprised UTC, evoked cough, peak cough flow (PCF), Karnofsky Performance Status (KPS), and neurological findings. Actual assessment dates and reasons for missed visits were recorded.

Testing was performed with the participant seated upright in the following sequence: 10 minutes of rest, PCF measurement, at least 10 minutes of recovery, capsaicin challenge, and at least 30 minutes of observation. When FEES was performed on the same day, it followed the recovery period. Intubation duration, extubation timing, recent opioid and sedative use, respiratory symptoms, food intake, smoking, subsequent oncological treatment, and disease progression were recorded. Essential medications were not withheld.

Surgery and MRI assessment

The surgical approach, insular entry site, anatomical relationships to vessels, monitoring findings, and limits of resection were obtained from operative reports. Preoperative and early postoperative magnetic resonance imaging (MRI) was assessed using the available T_1-weighted, contrast-enhanced T_1-weighted, T_2-weighted, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) maps, and susceptibility-sensitive sequences. Postoperative computed tomography (CT) was scheduled within 24 hours. MRI was scheduled within 24–48 hours, consistent with recommendations for early postoperative imaging [16]. Actual imaging intervals were obtained from Digital Imaging and Communications in Medicine (DICOM) timestamps.

Tumor and residual tumor volumes were segmented using 3D Slicer 5.8.1. Extent of resection (EOR) was calculated as follows:

$$EOR = 100 \times \frac{V_{pre} - V_{res}}{V_{pre}}$$

Here, Vpre and Vres denote preoperative and residual tumor volumes in cm^3, respectively. Enhancing and nonenhancing components were delineated on contrast-enhanced T_1-weighted and T_2/FLAIR images, respectively, with postoperative edema and ischemia considered during interpretation. The central insular sulcus served as the boundary between anterior and posterior insular regions. Resection overlap volumes quantified the volume of intersection between the resection and each of these anatomical regions; they did not represent the volume of resected insular cortex alone.

New restricted diffusion was defined as increased DWI signal with a corresponding reduction in ADC relative to baseline images. An exploratory subgroup comprised patients whose resections were confined to the insular region and who had no new restricted diffusion; even a thin rim of restricted diffusion around the resection cavity excluded a patient from this subgroup. Nondiagnostic DWI examinations were not classified as showing absence of restricted diffusion. Anatomical laterality and handedness were recorded separately from language dominance, which was assigned only on the basis of documented language-specific assessments.

Capsaicin cough challenge

A dosimeter-controlled, single-breath capsaicin challenge followed European Respiratory Society (ERS) methodological principles [10]. A nominal 10 mmol/L stock solution was prepared from 30.5 mg capsaicin, 1 mL ethanol, and 1 mL polysorbate 80, made up to a total volume of 10 mL with 0.9% sodium chloride. A tenfold dilution yielded 1000 µmol/L, followed by serial twofold dilutions.

Solutions were prepared under pharmacy supervision on the day of testing, stored at 4 °C protected from light, brought to room temperature before use, and discarded after testing [7].

The delivery system comprised a DeVilbiss 646 nebulizer and a KoKo DigiDoser, with inspiratory flow limited to 0.5 L/s. At a calibrated output of 1.007 mL/min, a 1.2-second pulse aerosolized approximately 20 µL of solution; this represents nebulizer output rather than pulmonary deposition [2]. Concentrations were 0.49, 0.98, 1.95, 3.91, 7.81, 15.63, 31.25, 62.5, 125, 250, 500, and 1000 µmol/L. One inhalation was administered at each concentration, with intervals of at least 60 seconds and a maximum of 12 active inhalations.

Two capsaicin-free vehicle controls matched to the subsequent active solution were randomly interspersed in a coded sequence maintained across visits. Participants were instructed to cough naturally, without deliberately suppressing or amplifying their response. Individual explosive cough events were counted from audio recordings during the first 15 seconds after inhalation. C_2 and C_5 were defined as the lowest concentrations eliciting at least two and five coughs, respectively. Testing ended when C_5, the maximum concentration, or a clinical stopping criterion was reached. Thresholds not reached after the maximum exposure were recorded as >1000 µmol/L; prematurely terminated tests were coded separately.

UTC and voluntary cough

UTC was rated on a modified Borg scale from 0 to 10, where 0 indicates no urge to cough and 10 indicates the maximum urge; the 0.5 category and intermediate integer ratings were retained [6]. Standardized instructions in Uzbek and a practice rating to familiarize participants with the scale preceded testing. During the 15–30-second interval after inhalation, participants rated the strongest urge experienced during the first 15 seconds. Inability to provide a rating was recorded as missing data.

The reference concentration C* was defined as each participant's C_2 measured at T_0 and remained unchanged at subsequent visits. UTC(C*) was obtained from the routine ascending concentration sequence. A measurement was considered unavailable if baseline C_2 could not be established or subsequent testing ended before C* was reached. Exposure was not extended solely to obtain this measurement.

PCF was measured using an airtight mask, an MLT1000L/FE141 system, PowerLab 8/35, and LabChart 8, with a sampling rate of 1000 Hz and a 100 Hz filter. The assembled system underwent checks for zero offset and volume and flow measurement accuracy. After one familiarization attempt, participants inhaled deeply and coughed as forcefully as possible. Three technically valid attempts were obtained at least 60 seconds apart; the highest flow was retained in L/min. Air leakage, an incorrect maneuver, or signal saturation invalidated an attempt; low flow alone did not.

Swallowing assessment and safety

FEES findings were analyzed only when an endoscopic assessment was documented, using the clinical framework described in the center's previous FEES study [17]. The present analysis included available baseline and T_1 examinations and selective follow-up assessments at T_2, T_3, and T_4; no FEES data were available at T_5. Aspiration was defined as a Penetration–Aspiration Scale (PAS) score of 6–8 and silent aspiration as a PAS score of 8 [13]. Unperformed assessments remained missing, and later FEES findings were interpreted only within the examined subgroups. Absence of cough during aspiration was not treated as a direct measure of UTC.

Early postoperative PCF measurement and cough provocation required documented clinical clearance from the treating neurosurgeon and responsible physician. Testing was deferred in the presence of bronchospasm or respiratory, hemodynamic, or neurological instability. Peripheral oxygen saturation (SpO_2) and pulse were monitored continuously, and blood pressure periodically. Criteria for immediate test cessation and clinical reassessment comprised respiratory compromise, clinically significant desaturation or hemodynamic deterioration, sudden severe headache, a new neurological sign, or a participant's request. Trained personnel and emergency treatment resources were available. Observation continued for at least 30 minutes and until the baseline clinical condition was restored. Adverse events, treatment provided, and reasons for delaying or terminating tests were documented.

Outcomes and statistical analysis

The primary outcome was defined as follows:

$$\Delta UTC = UTC(T_1, C*) - UTC(T_0, C*)$$

Secondary outcomes included PCF, cough count at C*, C_2/C_5, aspiration, and subsequent recovery. Associations with resection overlap volume within the posterior insular region were exploratory.

Paired UTC changes were summarized using the median, interquartile range, and numbers of participants with decreased, unchanged, and increased ratings. The primary comparison used a two-sided exact sign test at $\alpha = 0.05$. Pairs with zero differences were excluded from the test but retained in descriptive reporting. An exact binomial 95% confidence interval was calculated for the proportion of participants with decreased UTC among pairs with nonzero differences. Holm adjustment was applied to the four subsequent comparisons with baseline.

The T_1–T_0 change in PCF was summarized as the median of the individual paired differences, with a 95% percentile bootstrap confidence interval based on 10,000 patient-level resamples. Spearman correlations were used to assess associations between resection overlap volume within the posterior insular region and ΔUTC, and between ΔUTC and ΔPCF. C_2/C_5 thresholds above the maximum concentration were retained as right-censored values. The numbers of evaluable participants and missing assessments were reported for each outcome. A confidence interval for PCF change that included zero was not interpreted as evidence of equivalence or preservation of motor function.

Missing measurements were not replaced with zero or imputed by carrying the previous observation forward. In the sensitivity analysis, N denoted the number of participants with an evaluable baseline measurement who were alive at T_1; D, the number with an observed decrease in UTC; and M+, the number with baseline UTC >0 and a missing T_1 measurement. The bounds for the proportion with decreased UTC were D/N and (D + M+)/N. Participants with baseline UTC = 0 were not assigned a decrease under either scenario. This denominator was reported separately from the sign-test denominator. UTC values after death were not imputed.

RESULTS

Patient characteristics and completeness of assessments

The cohort comprised 46 patients. Median age was 37 [27; 53] years, and 20 patients (43.5%) were female. Tumors were left-sided in 28 patients (60.9%). Histological grade 2, 3, and 4 tumors were recorded in 15 (32.6%), 19 (41.3%), and 12 (26.1%) patients, respectively. Molecular classification was not reported in this dataset.

The preoperative median Karnofsky Performance Status (KPS) score was 90 [80; 90]. Mild aphasia was present in 6 patients (13.0%) and hemiparesis in 8 patients (17.4%). Intubation duration was 6.7 [5.5; 7.5] hours, and the interval from completion of surgery to extubation was 2.2 [1.4; 2.9] hours. At the early postoperative assessment (T_1), the median KPS score was 80 [70; 90]. New hemiparesis was recorded in two patients, worsening of pre-existing hemiparesis in two patients, and new mild aphasia in three patients. Patients with aphasia retained the ability to understand the test instructions.

The baseline C_2 threshold and the corresponding individual reference concentration, C*, were established in all 46 patients. The T_1 capsaicin challenge was performed in 45 patients at a median of 7 [5; 8] days after surgery. Paired baseline and early postoperative measurements of UTC(C*) and cough count at C* were available for 44 patients, while paired measurements of peak voluntary cough flow (PCF) were available for 45 patients. The challenge was deferred for clinical reasons in one patient. In another patient, testing ended because C_5 was reached before C*, so UTC(C*) and cough count at C* were unavailable. Both patients remained in the overall cohort.

Early postoperative urge-to-cough and cough responses

At the same individual C* concentration, the median urge-to-cough (UTC) rating was 4 [4; 5] points preoperatively and 3 [2; 4] points at T_1. The median within-patient difference was −2 [−2; −1] points. UTC decreased in 36/44 patients (81.8%), remained unchanged in 7/44 (15.9%), and increased in 1/44 (2.3%). The two-sided exact sign test indicated a decrease in UTC ($p < 0.001$). The corresponding results are summarized in Table 1.

UTC decreased in 36 of the 37 non-tied paired observations, giving a decrease proportion of 97.3% in this group, with an exact binomial 95% confidence interval (CI) of 85.84–99.93%. This interval pertains to the proportion with a decrease among non-tied pairs.

Table 1. Paired baseline and early postoperative measurements

Measure	Paired observations, n	T_0	T_1	Within-patient change, Δ
UTC(C*), points	44	4 [4; 5]	3 [2; 4]	−2 [−2; −1]
Cough count at C*	44	3 [2; 4]	1 [0; 1]	−2 [−3; −1]
PCF, L/min	45	455 [404; 506]	448 [396; 513]	+3 [−26; 22]

Values are presented as median [first quartile; third quartile]. Δ denotes the median of the individual differences, calculated as $T_1 - T_0$ for each patient.

The median evoked cough count at C* decreased from 3 [2; 4] to 1 [0; 1], with a median within-patient change of −2 [−3; −1] coughs. The median within-patient change in PCF was +3 L/min, with a percentile bootstrap 95% CI of −15 to +12 L/min based on 10,000 paired resamples. No statistically significant monotonic association was detected between ΔUTC and ΔPCF (Spearman $\rho = 0.030$; $p = 0.848$; $n = 44$).

Capsaicin-evoked cough thresholds

C_2 was established in all 46 baseline tests and all 45 tests performed at T_1. Median C_2 was 31.25 [15.63; 62.5] μmol/L at T_0 and 62.5 [15.63; 125] μmol/L at T_1. Among paired observations, the median within-patient shift in C_2 was +1 [+1; +1] step in the doubling concentration series.

C_5 was established in 44/46 tests at T_0 and 42/45 tests at T_1. In the remaining two and three tests, respectively, C_5 was not reached despite exposure through the maximum concentration; these values were recorded as >1000 μmol/L. The corresponding results are summarized in Table 2.

Table 2. Distribution of C_2 and C_5 thresholds by concentration

Concentration, μmol/L	C_2 T_0, n	C_2 T_1, n	C_5 T_0, n	C_5 T_1, n
7.81	8	0	0	0
15.63	9	12	0	0
31.25	12	7	3	0
62.5	10	9	9	5
125	7	7	13	10
250	0	10	8	8
500	0	0	9	8
1000	0	0	2	11
>1000	0	0	2	3
Test not performed	0	1	0	1

No C_2 or C_5 threshold was identified within the 0.49–3.91 μmol/L concentration range. A value of >1000 μmol/L denotes a threshold that was not reached despite completion of the maximum exposure.

MRI findings and association with resection topography

Median preoperative tumor volume was 46.74 [34.62; 75.05] cm^3, residual tumor volume was 3.36 [1.30; 6.26] cm^3, and extent of resection was 92.7 [87.5; 96.7]%. Postoperative MRI was assessed at a median of 33.5 [30; 41.3] hours after completion of surgery. Resection overlap volumes with the anterior and posterior insular regions, delineated according to the central insular sulcus, were 26.84 [15.47; 37.74] and 14.39 [7.75; 24.79] cm^3, respectively. Two illustrative cases demonstrating preoperative and postoperative imaging findings and intraoperative views of the transsylvian–transinsular approach are presented in Figs. 1 and 2.

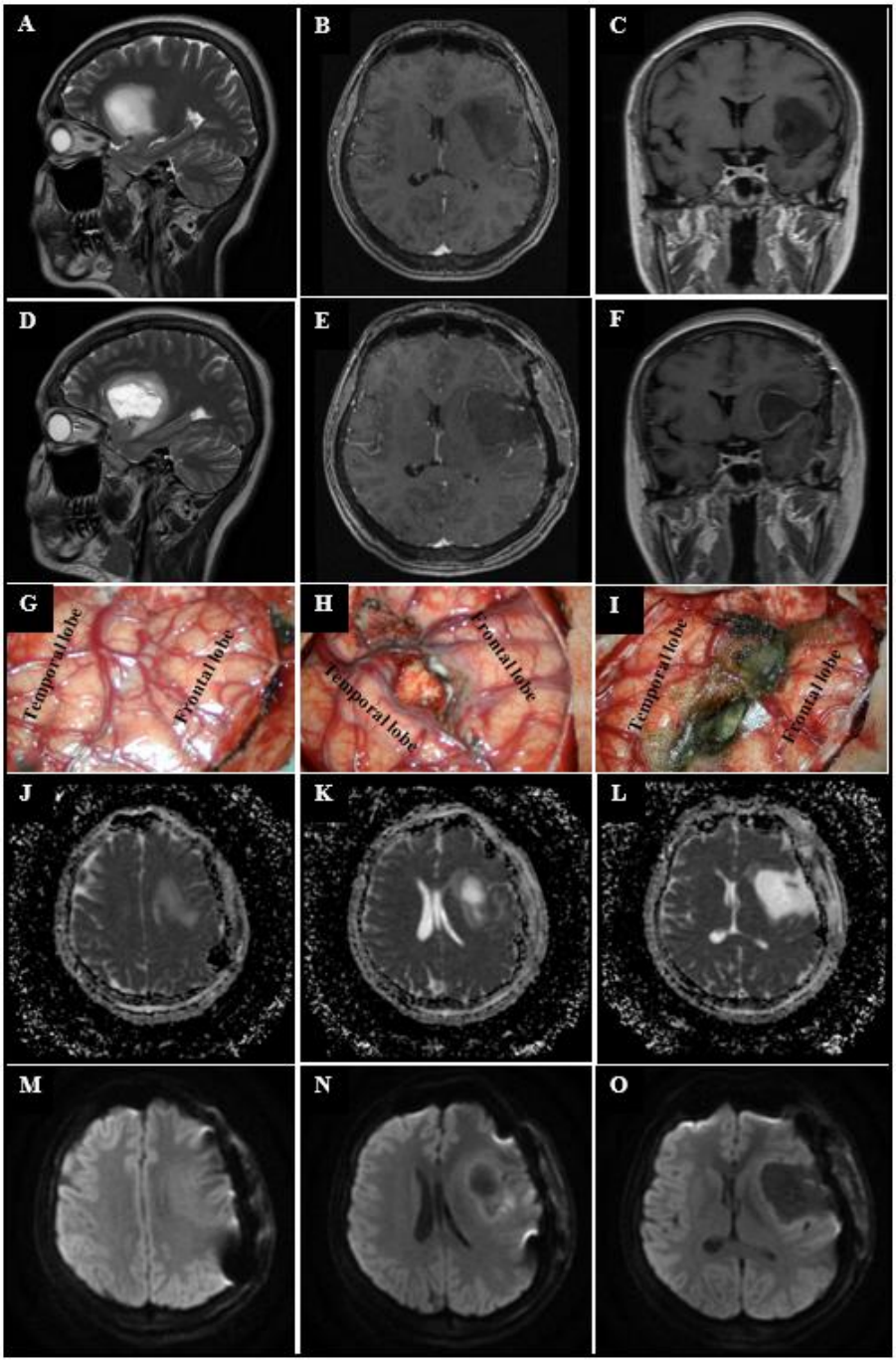


Fig. 1 Perioperative imaging and intraoperative views of transsylvian–transinsular resection of an insular glioma. A–C Preoperative magnetic resonance imaging demonstrating the insular lesion on sagittal T_2-weighted (A), axial T_1-weighted (B), and coronal T_1-weighted (C) images. D–F Corresponding postoperative sagittal T_2-weighted (D), axial T_1-weighted (E), and coronal T_1-weighted (F) images showing the resection cavity. G–I Intraoperative microscopic views illustrating exposure of the Sylvian fissure (G), development of the transsylvian corridor toward the insular region (H), and the operative cavity following tumor resection (I). The frontal and temporal lobes are labelled for anatomical orientation. J–L Postoperative axial apparent diffusion coefficient maps and M–O corresponding diffusion-weighted images at three levels through the operative region, showing the resection cavity and surrounding tissue for assessment of postoperative diffusion changes

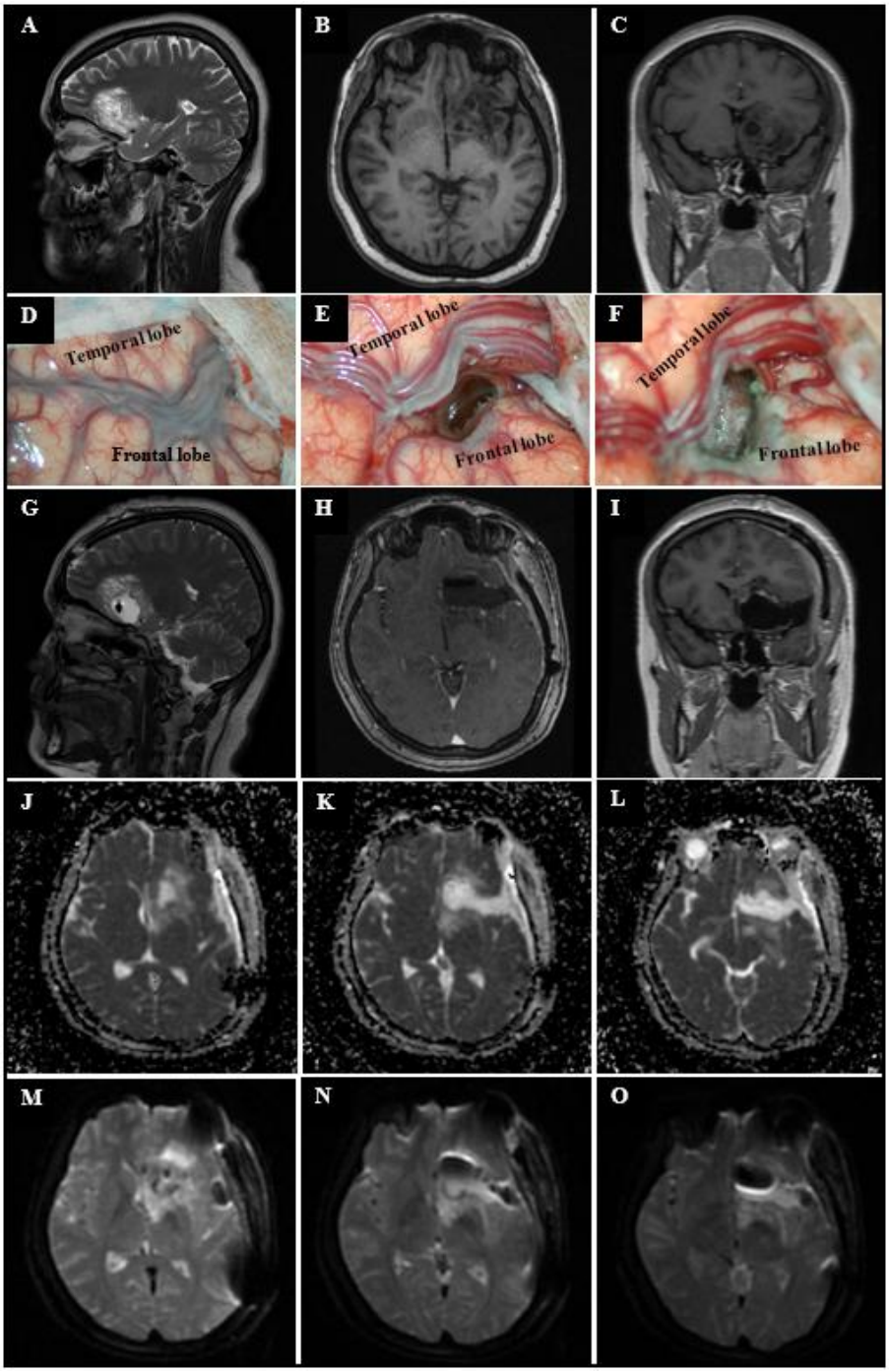


Fig. 2 Imaging and microsurgical findings in an illustrative case of insular glioma resection via a transsylvian–transinsular approach. A–C Preoperative magnetic resonance imaging demonstrating the insular lesion on sagittal T_2-weighted (A), axial T_1-weighted (B), and coronal T_1-weighted (C) images. D–F Intraoperative microscopic views showing exposure of the Sylvian fissure between the frontal and temporal lobes (D), opening of the transsylvian corridor (E), and the operative cavity following tumor resection (F). The frontal and temporal lobes are labelled for anatomical orientation. G–I Postoperative sagittal T_2-weighted (G), axial T_1-weighted (H), and coronal T_1-weighted (I) images demonstrating the resection cavity. J–L Postoperative axial apparent diffusion coefficient maps and M–O corresponding diffusion-weighted images depicting the operative bed and surrounding tissue for assessment of postoperative diffusion changes. Panels B, D, and H are reproduced or adapted from the authors' previous FEES report [17]

Exploratory analysis showed a negative association between posterior insular resection volume and ΔUTC (Spearman ρ = −0.314; p = 0.038; n = 44). DWI/ADC images were evaluable in 44 patients, with new restricted diffusion recorded in 7/44 (15.9%). The nondiagnostic examinations in two patients were not classified as showing absence of restricted diffusion.

The subgroup with insula-confined resection and no new restricted diffusion, including no thin rim of restriction around the resection cavity, comprised 30 patients. Among the 28 patients in this subgroup with paired UTC measurements, median ΔUTC was −2 [−2; −1] points. UTC decreased in 22 patients, remained unchanged in five, and increased in one.

Follow-up outcomes

The T_2–T_5 challenge tests were performed at median postoperative days 28, 91, 188, and 358, respectively. Paired comparisons with baseline for UTC and cough count at C* were available for 41, 43, 40, and 37 patients, respectively. The corresponding numbers for PCF were 42, 43, 40, and 37. The corresponding results are summarized in Table 3.

Table 3. Within-patient changes from baseline at subsequent visits

Visit	UTC and cough, n	ΔUTC, points	Holm-adjusted p	Δcough count	PCF, n	ΔPCF, L/min
T_2 — 4 weeks	41	−1 [−1; 0]	<0.001	−2 [−3; −1]	42	−2 [−18; 21]
T_3 — 3 months	43	0 [−1; 0]	<0.001	−1 [−2; 0]	43	−2 [−12.5; 5]
T_4 — 6 months	40	0 [0; 0]	0.043	0 [−1; 0]	40	+5 [−4.25; 9.25]
T_5 — 12 months	37	0 [0; 0]	1.000	0 [−1; 1]	37	−3 [−11; 3]

Values are presented as the median [first quartile; third quartile] of individual differences. Each visit was compared with T_0 using paired observations. Holm adjustment was applied to the four UTC sign tests at T_2–T_5.

Although median ΔUTC was 0 points at T_3, the individual distribution showed a decrease in 20/43 patients, no change in 22/43, and an increase in 1/43. At T_5, the corresponding numbers were 5/37, 26/37, and 6/37. Median cough counts at C* at T_2, T_3, T_4, and T_5 were 1 [0; 2], 2 [1; 3], 3 [2; 3.25], and 3 [2; 4], respectively. The median KPS score was 90 [80; 90] at all four follow-up visits.

After surgery, combined chemotherapy and radiotherapy was prescribed for 26 patients, radiotherapy for seven, and chemotherapy for three; 10 patients remained under observation. Among the 36 patients who received treatment, treatment started at a median of 35.5 [32; 39.25] days after surgery. Six cases of progression and three deaths were recorded during follow-up. The numbers of patients who missed the T_2–T_5 visits were 4, 2, 4, and 6, respectively; the numbers who had died before the corresponding visits were 0, 1, 2, and 3.

Swallowing function and testing safety

Baseline FEES findings were available for all 46 patients. A PAS score of 1 was recorded in 39 patients and a score of 2 in seven; no baseline aspiration was identified. At T_1, aspiration, defined as PAS 6–8, was identified in eight of the 42 patients examined (19.0%). Silent aspiration, defined as PAS 8, was recorded in three of these eight patients, representing 7.1% of patients who underwent FEES at T_1.

No PAS 6–8 scores were recorded among the selected patients examined at T_2, T_3, and T_4 (14, 15, and 13 patients, respectively). These findings apply specifically to the examined subgroups. No FEES data were available at T_5.

A total of 253 capsaicin challenge sessions were performed. At T_2, one session was stopped because of transient headache, which resolved after test cessation and observation. This patient's PCF measurement was retained in the analysis, but UTC(C*) and cough count at C* were unavailable because the challenge did not reach C*. No other test-related adverse events were recorded.

Sensitivity analysis for missing outcomes

UTC decreased in 36 of the 46 patients with an available baseline UTC assessment who were alive at T_1. Of the two patients without a T_1 UTC(C*) measurement, one had a baseline UTC >0 and the other had a baseline UTC = 0. Under boundary scenarios accounting for the missing observation in which a decrease was possible, the proportion with a decrease in UTC ranged from 36/46 (78.3%) to 37/46 (80.4%). The patient with a baseline UTC = 0 was not classified as having a decrease in either scenario. Outcomes after death were not imputed.

DISCUSSION

In this cohort, urge-to-cough and capsaicin-evoked cough responses decreased in the early period after transsylvian–transinsular resection of insular gliomas. At the same individual reference concentration, the median paired change in UTC was −2 points, with a decrease observed in 36 of the 44 evaluable patients. By contrast, the median paired change in maximal voluntary peak cough flow was +3 L/min, with a 95% confidence interval of −15 to +12 L/min. These findings suggest that voluntary motor performance alone may not adequately characterize postoperative cough function. The principal contribution of this study is the characterization of postoperative changes in these functions through repeated assessment of UTC, evoked cough, and voluntary cough in the same patients.

Comparing UTC at a fixed individual concentration, C*, equal to each patient's baseline C_2 threshold and unchanged at subsequent visits, is important to the interpretation of this finding. Experimental studies have identified distinct neural responses associated with capsaicin stimulus intensity and perceived urge-to-cough; UTC ratings obtained at different stimulus levels may therefore have different implications [4]. Our approach maintains the same nominal stimulus concentration for within-patient comparisons. The reduction in UTC and evoked cough, together with the shift in C_2 toward higher concentrations, is consistent with an early decrease in responsiveness to capsaicin. However, these measures represent different functional components: UTC is a conscious sensory rating, whereas C_2 and C_5 are thresholds defined by the cough motor response [1, 10]. Because C_5 values not reached at the maximum exposure are censored, they cannot be interpreted as exact numerical thresholds or as evidence of complete loss of the cough response.

Previous physiological observations provide a biological rationale for assessing sensory and motor responses separately. Davenport and colleagues showed that UTC may occur at concentrations below those required to elicit cough [1]. However, another study in healthy individuals found that some participants coughed before reporting an isolated UTC sensation; thus, self-reported UTC is not an obligatory or universal precursor to every cough [3]. Accordingly, the reduction in sensory ratings observed here should not be equated with complete loss of the cough reflex. Concurrent measurement of UTC and evoked cough provides complementary information about conscious perception of the stimulus and the resulting motor response.

Functional imaging studies suggest a potential central mechanism for these clinical observations. Capsaicin-evoked UTC has been associated with activity in a distributed network encompassing the insula and other sensory, cingulate, and motor regions [4, 9]. The neural substrates of evoked cough and its voluntary suppression are also not identical: Mazzone and colleagues associated the posterior insula with evoked cough and a network involving the anterior insula with cough suppression [8]. Our findings are consistent with the hypothesis that insular resection may affect sensory processing or sensorimotor integration within this network. However, the present design cannot distinguish whether reduced UTC reflects altered central perception, peripheral afferent signaling, or their interaction. Functional activation alone is also insufficient to establish any particular insular region as a unique and necessary 'cough center'.

The PCF findings require cautious interpretation in this context. Producing a maximal voluntary cough on command and coughing in response to an inhaled stimulus are different tasks. Studies in Parkinson disease have shown that voluntary cough airflow and timing measures may be associated with penetration or aspiration during swallowing [11], underscoring the need to consider aspects of cough motor performance beyond peak flow alone. In our study, a confidence interval for PCF change that includes zero, together with the absence of an observed association between ΔUTC and ΔPCF, does not establish equivalence of motor function or independence of the sensory and motor systems. These findings provide a rationale for investigating potentially divergent changes, but do not demonstrate sensorimotor dissociation.

The negative association between resection volume within the posterior insular region and ΔUTC is of anatomical interest but requires cautious interpretation. The association was modest ($\rho = -0.314$), and the analysis was exploratory. The volume of overlap between the resection and a region delineated relative to the central insular sulcus does not represent the volume of resected posterior insular cortex alone; the finding therefore cannot be directly equated with functional injury to an isolated cortical structure. A study of swallowing recovery after stroke also reported findings involving white matter connectivity and the anterior insula [5]. Although that study is not a direct model of UTC or glioma resection, it supports interpreting airway-protective functions within a broader network framework. Our anatomical finding generates a hypothesis for further topographic studies rather than providing an established criterion for altering surgical boundaries.

Ischemic injury is an important alternative explanation for functional changes after insular surgery. A comparison of transsylvian and transcortical approaches evaluated postoperative diffusion restriction and its anatomical distribution alongside neurological outcomes [12]. In our cohort, UTC also decreased in the subgroup with resection confined to the insular region and no new diffusion restriction. This observation suggests that new restriction detectable on DWI/ADC may not fully explain the early sensory change. Nevertheless, the subgroup analysis does not exclude microscopic injury, edema, transient disruption of functional connectivity, or general perioperative effects.

Interpretation must also account for the fact that nondiagnostic DWI examinations in two patients were not classified as negative.

During follow-up, UTC and evoked cough measures approached baseline values at the group level, but this trend does not imply uniform individual recovery. Although median ΔUTC was zero at 3 months, 20 of 43 patients still had lower values than at baseline. At 12 months, among the 37 patients assessed, five had lower values, 26 had unchanged values, and six had higher values. Thus, a group median approaching baseline is distinct from every patient returning to their initial state. Resolution of transient surgical effects, compensation, or reorganization may explain recovery, but these mechanisms were not directly investigated. Oncological treatment, progression, missed visits, and death also altered the composition of the group assessed over time.

The swallowing safety findings underscore the clinical relevance of investigating UTC. Early FEES identified aspiration in eight of 42 patients and silent aspiration in three. The center's previous prospective FEES study also described impaired swallowing safety after insular glioma surgery [17]. The present study extends this work through direct measurement of cough sensation and performance in a cohort that also included additional eligible patients. Because 22 of the 46 patients were also included in the previous FEES study, the FEES observations in the present analysis should not be interpreted as an independent replication of the earlier study. In Parkinson disease, greater dysphagia severity has been associated with lower UTC and attenuated evoked cough [15], but an association observed in another disease cannot be assumed to hold in an insular glioma cohort. Our results do not establish an individual-level association between reduced UTC and aspiration or its predictive accuracy. Silent aspiration detected by FEES is not a direct measure of UTC; these assessments address related clinical questions using different methods.

Methodological strengths include paired comparisons with baseline, a fixed individual stimulus, parallel assessment of sensory and motor measures, and follow-up extending to one year. In bounding scenarios accounting for missing early UTC outcomes, the proportion of patients with a decrease ranged from 78.3% to 80.4%, indicating that the two missing measurements did not change the direction of the principal finding. This analysis does not establish the magnitude or clinical importance of the effect and does not resolve selection bias during later follow-up. Although standardization of capsaicin challenge testing is important for comparability [10], the safety observations in this cohort apply only to patients considered clinically fit for testing and cannot establish safety for all patients in the early postoperative period.

Clinically, these findings support further investigation of the sensory component of cough when assessing function after insular glioma resection. Maximal voluntary peak cough flow alone should not be regarded as a comprehensive measure of airway sensitivity or swallowing safety. However, the present data are insufficient to define a clinical risk threshold for UTC, base feeding decisions on UTC, or modify the extent of surgical resection. Future multicenter studies should jointly examine prespecified anatomical analyses, measurement reproducibility, clinically meaningful changes in UTC, and associations among UTC, FEES findings, and respiratory outcomes. Such work would clarify the practical significance of the observed physiological changes for patients.

Limitations

The single-center cohort of 46 patients limits generalizability to other centers, surgical approaches, and patient populations. The absence of a control group prevents attribution of the observed changes specifically to insular resection. Although within-patient comparisons with baseline account for some

individual variability, they do not separate the general effects of surgery and the perioperative period. Histological heterogeneity and the lack of reported molecular subtype data limit detailed analysis of the relationship between tumor biology and functional outcomes. The requirement to understand instructions and complete the assessments may have resulted in underrepresentation of patients with severe neurological impairment. The smaller numbers in subgroup analyses further reduce the precision of anatomical comparisons.

UTC is a subjective rating that may be influenced by attention, comprehension of instructions, and the patient's general condition. Although standardized Uzbek instructions and familiarization were used, the psychometric properties of the language version used and the reliability of repeated measurements were not reported. The minimal clinically important change in UTC has not been established in this population; statistical differences cannot be equated with meaningful functional changes for patients. A fixed individual C* concentration standardizes the comparison but does not control all factors affecting sensory ratings. Because C* was selected from a single baseline C_2 determination, test–retest variability and regression toward the mean may have influenced subsequent responses, particularly evoked cough counts at that concentration. Intubation, opioids and sedatives, respiratory status, neurological deficits, and postoperative edema must be considered when interpreting the results. No multivariable analysis separating the independent effects of these factors was reported; residual confounding therefore cannot be excluded.

The anatomical measure represents the volume of overlap between the resection and the posterior insular region, rather than posterior insular cortical loss alone. The observed association therefore cannot be interpreted as injury to a specific cortical center. The correlation between posterior insular resection volume and ΔUTC was exploratory, and the p value of 0.038 requires caution in the context of multiple analyses. Holm adjustment was applied to the follow-up UTC comparisons, but no overall correction across all exploratory analyses was reported. The subgroup without diffusion restriction identifies observations not explained by overt new diffusion abnormalities but does not exclude other perioperative or network effects. Nondiagnostic DWI in two patients also limits the completeness of the anatomical assessment.

A confidence interval for PCF change that includes zero does not confirm preservation of motor function, as the study was not designed using equivalence margins. Likewise, the absence of an observed correlation between UTC and PCF changes does not establish sensorimotor dissociation. These measures assess different functional components, and PCF depends on maximal voluntary effort. The observed differences should therefore be regarded as a basis for further investigation rather than a mechanistic conclusion. Censoring of C_5 values above the maximum concentration also limits estimation of the actual magnitude of the highest thresholds.

Long-term outcomes may be affected by missed visits, death, oncological treatment, and disease progression. Consequently, later medians approaching baseline do not imply uniform recovery across the entire cohort. Although a bounding sensitivity analysis was performed for T_1, it does not eliminate selection bias at later assessments. FEES was not performed in every patient at every follow-up visit; the absence of aspiration in selectively assessed groups cannot be generalized to the entire cohort. No model assessing an independent association between UTC change and aspiration was reported, and the number of aspiration events was limited. These data therefore do not establish a UTC threshold for predicting aspiration risk or an independent basis for clinical decision-making.

CONCLUSION

In this prospective cohort, transsylvian–transinsular resection of insular gliomas was followed by early reductions in urge-to-cough (UTC) and capsaicin-evoked cough responses at a fixed individual stimulus concentration. Among patients assessed during follow-up, group-level UTC and evoked cough measures approached baseline over 12 months, although individual trajectories varied. Voluntary peak cough flow showed no clear early group-level change; this finding does not establish preservation of cough motor function. The modest association between resection volume within the posterior insular region and UTC change remains exploratory. These findings support further evaluation of UTC as a complementary measure of postoperative cough function. Multicenter studies integrating reproducible sensory assessments, standardized anatomical mapping, and concurrent swallowing and respiratory outcomes are needed to establish the clinical significance of these changes and the potential value of UTC assessment in postoperative care.

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Author contributions

Jakhongirmirzo Yoldoshev: Conceptualization, data curation, formal analysis, and writing—original draft.

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Alvaro Campero: Supervision, validation, and visualization.

Ethics approval

This study was approved by the Ethics Committee of the Republican Specialized Scientific and Practical Medical Center of Neurosurgery, Tashkent, Uzbekistan (Protocol No. 10-2022).

Clinical trial number: not applicable.

Consent to participate

Written informed consent was obtained from all participants for participation in the study and the scientific use of anonymized clinical, radiological, and endoscopic data.

Consent for publication

Written informed consent was obtained from all patients for publication of anonymized clinical data and accompanying radiological and endoscopic images.

Data availability

Aggregate results are reported in this article. Requests for access to the underlying participant-level data should be directed to the corresponding author. Any sharing would be subject to applicable institutional requirements and participant confidentiality.