



RESEARCH ARTICLE

Temporal lobe epilepsy surgery: Piriform cortex resection impacts seizure control in the long-term

Valeri Borger¹ , Motaz Hamed¹, Majd Bahna¹, Áttila Rácz², Inja Ilic¹, Anna-Laura Potthoff¹, Tobias Baumgartner², Theodor Rüber² , Albert Becker³, Alexander Radbruch⁴, Florian Mormann², Rainer Surges², Hartmut Vatter¹ & Matthias Schneider¹

¹Department of Neurosurgery, University Hospital Bonn, Bonn, Germany

²Department of Epileptology, University Hospital Bonn, Bonn, Germany

³Section for Translational Epilepsy Research, Institute of Neuropathology, Medical Faculty, University of Bonn, Bonn, Germany

⁴Department of Neuroradiology, University Hospital Bonn, Bonn, Germany

Correspondence

Valeri Borger, Department of Neurosurgery, University Hospital Bonn/Venusberg-Campus 1, 53127 Bonn, Germany. Tel: 0049 228 287 16500; Fax: 0049 228 287 11366; E-mail: valeri.borger@ukbonn.de

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Abstract

Objective: Recently, we showed that resection of at least 27% of the temporal part of piriform cortex (PiC) strongly correlated with seizure freedom 1 year following selective amygdalo-hippocampectomy (tsSAHE) in patients with mesial temporal lobe epilepsy (mTLE). However, the impact of PiC resection on long-term seizure outcome following tsSAHE is currently unknown. The aim of this study was to evaluate the impact of PiC resection on long-term seizure outcome in patients with mTLE treated with tsSAHE. **Methods:** Between 2012 and 2017, 64 patients were included in the retrospective analysis. Long-term follow-up (FU) was defined as at least 2 years postoperatively. Seizure outcome was assessed according to the International League against Epilepsy (ILAE). The resected proportions of hippocampus, amygdala, and PiC were volumetrically assessed. **Results:** The mean FU duration was 3.75 ± 1.61 years. Patients with ILAE class 1 revealed a significantly larger median proportion of resected PiC compared to patients with ILAE class 2–6 [46% (IQR 31–57) vs. 16% (IQR 6–38), $p = 0.001$]. Resected proportions of hippocampus and amygdala did not significantly differ for these groups. Among those patients with at least 27% resected proportion of PiC, there were significantly more patients with seizure freedom compared to the patients with <27% resected proportion of PiC (83% vs. 39%, $p = 0.0007$). **Conclusions:** Our results show a strong impact of the extent of PiC resection on long-term seizure outcome following tsSAHE in mTLE. The authors suggest the PiC to constitute a key target volume in tsSAHE to achieve seizure freedom in the long term.

Introduction

Temporal lobe epilepsy (TLE) is one of the most common entities of epilepsy. In approximately 30% of patients, epilepsy is refractory to drug treatment.^{1,2} Since the first randomized controlled trial by Wiebe et al. has shown significantly improved outcomes with epilepsy surgery over drug treatment in refractory TLE, resective temporal lobe surgery has become a reasonable option for treatment in these patients.³ The surgical approach via transylvian selective amygdalo-hippocampectomy (tsSAHE) aims to perform a lesionectomy of mesiotemporal structures avoiding trauma to the adjacent healthy temporal neopallial

areas and to the vasculature.^{4–6} During the last years, novel minimally invasive technologies such as laser interstitial thermotherapy (LITT) are increasingly gaining interest.^{7–9} Despite the rising utility of these minimally invasive treatment methods, the surgical treatment still remains the standard of care in drug-resistant epilepsy.^{10,11} In the treatment for mesial TLE (mTLE), the reported seizure freedom rates offered for tsSAHE range between 60% and 70%. Beyond these successfully treated cases, there is a considerable amount of patients with persistent seizures after resective epilepsy surgery.¹² The reasons behind failure of surgery remain controversial. In the study reported by Galovic et al., a strong evidence for the association of piriform

cortex (PiC) resection with surgical seizure outcome in patients with TLE who underwent a standard anterior temporal lobe (ATL) resection was shown.¹³ In a recently published study, we found that resection of at least 27% of the temporal part of PiC strongly correlated with seizure freedom 1 year following tsSAHE.¹⁴ However, the impact of PiC resection on long-term seizure outcome following tsSAHE is currently unknown. The aim of this study was to evaluate the impact of PiC resection on long-term seizure outcome after tsSAHE in patients with mTLE.

Methods

Patients

Patients with TLE who had undergone rTLS between 2012 and 2017 were reviewed from the prospective conducted epilepsy surgery database at our department. The conduction of the database has been approved by the local ethics committee (application number: 404/17). Given the retrospective nature of the study, a written informed consent was not required. As the long-term seizure outcome is the focus of the current study, patients were included in the analysis, if a follow-up (FU) of at least 2 years was available after epilepsy surgery. All patients suffered from medically refractory mTLE and had undergone adequate treatment with at least two first-line antiepileptic drugs (AEDs). All patients were presurgically assessed in the department of epileptology and were considered to be suitable for surgery. Following the completed evaluation, the extent of resection was determined in every individual candidate by the interdisciplinary epilepsy surgery conference. The tsSAHE was performed in 103 consecutive patients. According to the inclusion criteria, a total of 64 patients with long-term FU and completed dataset were included in the analysis.

Surgical procedure

All surgical procedures of tsSAHE were performed in a highly standardized fashion by three certified epilepsy surgeons (H. V., V. B., M. H.). The goal of surgery was to remove mesiotemporal target structures that entail presumed seizure focus. As previously described, for SAHE, exclusively the transsylvian approach as described by Yasargil et al. with several modifications was used by all neurosurgeons.^{5,14,15}

Imaging and volumetric analysis

All MRI studies were performed pre- and postoperatively at the same 3.0 Tesla scanner (Achieva TX, Philips Healthcare, Best, the Netherlands) with identical scanning

protocols. All patients underwent MRI within 2–3 days postoperatively in order to detect the extent of resection of desired structures. The pre- and postoperative scans were measured as a pair by two independent and blinded raters. For postoperative assessment, the same landmarks were used and preoperative outlines were transposed onto postoperative scans. The detailed protocol for the volumetric analysis was described by our group in a previously published study.¹⁴

Seizure outcome analysis

Seizure outcome was assessed at last available FU visit according to the International League against Epilepsy (ILAE) classification. Patients were divided into two groups according to the seizure outcome (group I: ILAE class 1; group II: ILAE class ≥ 2). The ILAE class 1 outcome was considered favorable, the ILAE class ≥ 2 outcome was considered unfavorable. Furthermore, an evaluation regarding complete withdrawal or reduction of AEDs was performed. Reduction was defined as a withdrawal of at minimum one AED during the FU.

Statistics

Data analyses were performed using the computer software package SPSS (version 25, IBM Corp., Armonk, NY) and PRISM. Categorical variables were analyzed in contingency tables using Chi-square test or Fisher's exact test. The Mann–Whitney-*U* test was chosen to compare continuous variables, as the data were mostly not normally distributed. Results with $p < 0.05$ were considered statistically significant. For identification of independent factors associated with reduction or withdrawal of AEDs, a stepwise backward logistic regression analysis was performed. The results of the analysis were presented as odds ratio (OR) with a 95% confidential interval (CI).

Results

Patient baseline characteristics

Between 2012 and 2017, 103 patients with pharmacoresistant mTLE had undergone tsSAHE at the authors' institution. Patient chart review yielded long-term FU information for 64 patients. The mean FU duration for these 64 patients was 3.75 years (SD \pm 1.61 years) with a range 2–9 years. Postoperative long-term seizure freedom in terms of ILAE class 1 was achieved in 43 of 64 patients (67%).

The patient cohorts with favorable and unfavorable seizure outcomes showed homogeneous distribution regarding sex distribution, age at epilepsy onset, site of surgery,

Table 1. Baseline patient characteristics stratified according to the long-term seizure outcome¹.

	ILAE class 1 (n = 43)	ILAE class 2–6 (n = 21)	p value
Sex			0.11
Female	25 (58)	7 (33)	
Male	18 (42)	14 (67)	
Age at epilepsy onset (mean yrs ± SD)	19 ± 14	14 ± 11	0.15
Age at surgery (mean yrs ± SD)	39 ± 14	38 ± 14	0.79
FU duration (mean yrs ± SD)	3.7 ± 1.4	3.8 ± 1.9	0.64
Site of surgery			0.44
Left	22 (51)	13 (62)	
Right	21 (49)	8 (38)	
Preoperative MRI findings			
Unilateral hippocampal sclerosis	37 (87)	15 (71)	0.18
No lesion	4 (9)	4 (19)	0.42
Hippocampal gliosis	1 (2)	0 (0)	1.0
Unspecific hippocampal lesion	1 (2)	2 (10)	0.25
Histology of hippocampus			
Hippocampal sclerosis	37 (86)	15 (71)	0.18
Hippocampal gliosis	5 (12)	6 (29)	0.15
Others	1 (2)	0 (0)	1.0

ILAE, International League Against Epilepsy; SD, standard deviation; yrs, years.

¹Values represent number of patients unless otherwise indicated (%).

and preoperative MRI characteristics among others (Table 1).

Postoperative histological analysis yielded hippocampal sclerosis in 52 of 64 patients (81%) with 37 of 52 patients (71%) reaching ILAE class 1 and 15 of 52 patients (28%) reaching ILAE class 2–6 long-term seizure outcome ($p = 0.18$).

Extent of temporal PiC resection correlates to postoperative seizure freedom in the long term

Patients with favorable long-term seizure outcome exhibited a median resected proportion of temporal PiC volumes of 46% (IQR 31–57) compared to 16% (IQR 6–38) for patients with unfavorable long-term seizure outcome ($p = 0.001$). Compared with this, resected proportions of hippocampus and amygdala as commonly known target structures in tsSAHE did not reveal significant differences between the groups of favorable and unfavorable seizure outcome and showed expectably high values [hippocampus: 82% (IQR 72–88) for ILAE class 1 vs. 76% (IQR 69–91) for ILAE class 2–6 ($p = 0.71$); amygdala: 100% (IQR 100–100) vs. 100% (IQR 100–100) ($p = 0.77$)] (Table 2).

Preoperative volumes of PiC, hippocampus, and amygdala as tsSAHE target structures did not significantly

Table 2. Extent of temporal piriform cortex resection predicts postoperative seizure outcome in the long-term¹.

	Resected proportion ¹ [median (IQR)]		
	ILAE class 1 (n = 43)	ILAE class 2–6 (n = 21)	p value
Piriform cortex	46 (31–57)	16 (6–38)	0.001
Hippocampus	82 (72–88)	76 (69–91)	0.71
Amygdala	100 (100–100)	100 (100–100)	0.77

ILAE, International League Against Epilepsy; IQR, interquartile range.

¹Values indicated in %.

differ between the groups of favorable and unfavorable long-term seizure outcome (Table 3).

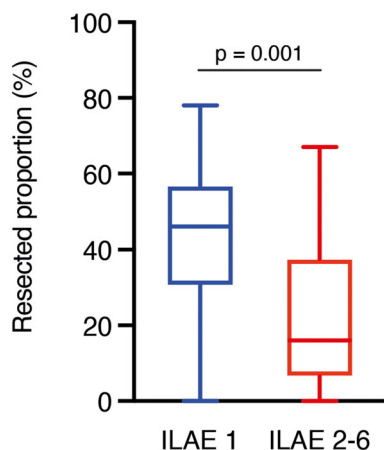
According to the results of our previous study, we further analyzed long-term seizure outcome based on the predefined cut-off value of 27% as proportion of PiC resection which had been shown to correlate to significantly improved seizure outcome in the short-term FU.¹⁴ In accordance to this approach, 34 of 41 patients (79%) with favorable postoperative long-term seizure outcome (ILAE class 1) showed resection of more than 27% of PiC volume. Compared with this, 14 of 21 patients (67%) with postoperative persistent or deteriorated seizures (ILAE class 2–6) showed resection of <27% of the of PiC volume ($p = 0.0007$) (Figs. 1, 2; Table 4). The evaluation of the AED therapy revealed a complete withdrawal of AED only in 3 (7%) patients. All these patients were seizure-free postoperatively and the proportion of PiC resection was above the cut-off value of 27%. In one of these patients, the AEDs were withdrawn 1 year postoperatively, and in two patients after 2 years, respectively. Furthermore, we performed an analysis of the subgroup of patients in whom a reduction of AEDs was achieved and compared this subgroup to the subgroup of patients with unchanged continued AED medication. The analysis revealed that in total, AEDs were reduced or stopped in 34 (53%) out of 64 patients. Among seizure-free patients, AEDs were reduced or withdrawn in 30 (70%) out of 43 patients. If compared seizure-free patients with reduced or withdrawn AEDs with patients on unchanged AED medication, we found no statistically significant difference regarding the typical demographics and characteristics, except the FU duration (Table S1). Of note, there is a trend toward more patients with a resected amount of PiC above the cut-off value of 27% in the subgroup of patients with reduced or withdrawn AEDs. In the next step, we divided the whole patient cohort into two groups according to the cut-off value of 27% of PiC resection. In total, resection of $\geq 27\%$ of PiC volume was achieved in 41 (64%) out of 64 patients compared to 23 (36%) out of 64 patients with resection proportion <27%. The

Table 3. Overview of preoperative volumes of tsSAHE target structures¹.

	Volumes ¹ [median (IQR)]		p-value
	ILAE class 1 (n = 59)	ILAE class 2–6 (n = 23)	
Piriform cortex	0.52 (0.42–0.62)	0.51 (0.37–0.62)	0.76
Hippocampus	1.81 (1.55–2.38)	1.96 (1.49–2.49)	0.34
Amygdala	1.05 (0.88–1.22)	1.03 (0.88–1.51)	0.32

ILAE, International League Against Epilepsy; IQR, interquartile range; tsSAHE, transsylvian selective amygdalo-hippocampectomy.

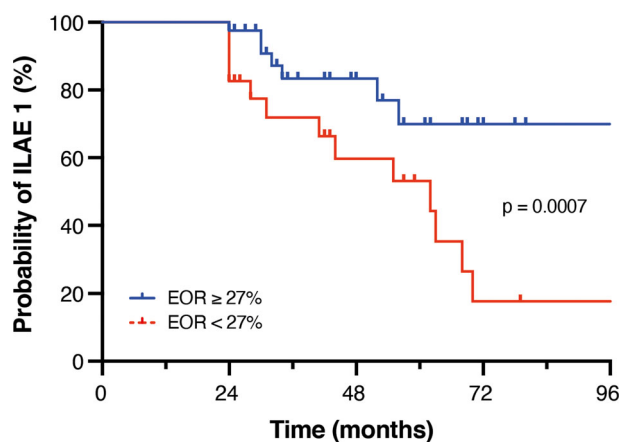
¹Values indicated in mL.

**Figure 1.** Box Whisker plots depict long-term seizure outcome dependent on the proportion of temporal piriform cortex resection. ILAE, International League Against epilepsy.

comparison of these two groups revealed that in patients with resection of $\geq 27\%$ of PiC volume, AEDs were reduced or withdrawn in a significantly higher amount of patients [28 (68%) vs. 6 (26%), $p = 0.0017$]. For identification of independent factors for reduction or withdrawal of AEDs, we performed a stepwise backward logistic regression analysis using the variables “gender”, “site of the surgery”, “evidence of a lesion on pre-op. MRI”, “histological evidence of hippocampal sclerosis”, and “resected proportion of PiC volume”. The analysis identified the resection of $\geq 27\%$ of PiC volume as the only significant and independent predictor for reduction or withdrawal of AEDs in the long term (OR 7.7; CI 2.4–24.6; $p = 0.001$).

Discussion

Resection of the PiC has been shown to be associated with the seizure outcome following epilepsy surgery in patients suffering from mTLE. In the study by Galovic

**Figure 2.** Kaplan–Meier analysis for long-term seizure outcome stratified for the indicated extent of piriform cortex resection. EOR, extent of resection in %; ILAE, International League Against epilepsy.**Table 4.** Long-term seizure outcome dependent on the proportion of temporal piriform cortex resection¹.

	ILAE class 1 (n = 43)	ILAE class 2–6 (n = 21)	p value
EOR <27	9 (21)	14 (67)	0.0007
EOR ≥ 27	34 (79)	7 (33)	

EOR, extent of resection in %; ILAE, International League Against Epilepsy.

¹Values represent number of patients (%).

et al. reporting on individuals suffering from TLE and underwent standard ATL, seizure freedom was achieved in 60% of patients if at least 50% of PiC had been resected in ATL.¹³ In the recently published study, we showed that a removal of at least 27% of PiC was required to achieve seizure freedom at 12 months in 96% of patients following tsSAHE.¹⁴ However, the impact of PiC resection on long-term seizure outcome has not been evaluated for tsSAHE, so far. In the current series, we for the first time present results on the impact of extent of PiC resection on long-term seizure outcome in candidates suffering from mTLE and surgically treated using tsSAHE. Our analysis revealed a significantly higher resected proportion of PiC in patients with favorable long-term seizure outcome. Additionally, the resection of at least 27% of the PiC was associated with a high rate (79%) of seizure freedom in long-term FU. These findings are in line with previously reported series on patients with mTLE following tsSAHE.^{10,16} In the present study, we for the first time show that an extent of PiC resection above 27% of PiC volume is the only independent significant predictor for reduction or withdrawal of AEDs during the long-term FU following tsSAHE. The analysis of further

potential predictors of seizure outcome in the current series such as patient's demographics, underlying pathology, and extent of resection of other target volumes did not show any correlation with the long-term seizure outcome. However, the observed superiority in long-term seizure outcome for the extensively resected patients might partly be driven by additional Wallerian degenerative processes. Wallerian degeneration is known to occur predominantly in the first months following ATL on the left side, while degenerative changes after ATL on the right side are reported to continue throughout the entire first-year postop.¹⁷ Though contralateral hippocampus body atrophy following ipsilateral ATL or ipsilateral SAH has even been shown to occur as early as postoperative day #1, the extent of degeneration is measured as low as 1.3% at this early postoperative time point. Hippocampal atrophy is known to further progress up to a 13% reduction level¹⁸ therefore constituting a persistent degeneration and adaptive plasticity process within the first months after surgery. In the present study, postoperative residual PiC volumes were assessed based on MRI scans performed within 48 h after tsSAHE. Given the close time span between surgery and postoperative MRI performance, the confounding impact of Wallerian degeneration on the measurement of the extent of PiC resection and therefore on the seizure outcome in the short-term can be disregarded. However, the observed superiority in long-term seizure outcome for the extensively resected patients might partly be driven by additional Wallerian degenerative processes. With regard to extended PiC resection to significantly improve favorable seizure outcome, the current study supports the hypothesis that the PiC may profoundly be involved in genesis and propagation of seizures in the temporal lobe. Since the minimally invasive procedures such as LITT are increasingly gaining interest, the access to the novel ablative target volumes in the mesial temporal lobe is becoming an area of focus.^{7,8,19} In the recently published study, Liu *et al.* showed that additional trajectory to achieve more extensive ablation of hippocampus, amygdala, and PiC in LITT procedures is more likely associated with seizure freedom.²⁰ Despite the progress in the field of minimally invasive surgical techniques, the selective epilepsy surgery procedures including tsSAHE remain effective and safe treatment options in mTLE. In terms of long-term seizure outcome following tsSAHE, our data strongly indicate that an effort to access and remove the temporal part of the PiC should be made by the neurosurgeon during the surgery.

Limitations

It should be noticed that the present study has individual limitations. The retrospective design carries the risk of

bias inherent to retrospective cohort analysis. In addition, our data represent a single-center experience. One of the strengths of the present series is the fairly homogeneous study population consisting of candidates with mTLE. Another strength is the highly standardized fashion in which the surgical procedure (tsSAHE) was performed in all patients. The imaging used for volumetric analysis was obtained from the same MRI scanner according to the standardized scanning protocol in all individuals. Despite the retrospective nature of data analysis, patients were treated according to the decision of the interdisciplinary epilepsy surgery conference and data acquisition was prospective. However, the implementation of a standardized neurosurgical approach and strict definition of inclusion criteria and variables analyzed in the current series might mitigate some of the shortcomings of a retrospective study design.

Conclusion

The present study demonstrates a strong impact of the extent of PiC resection on long-term seizure outcome following tsSAHE in mTLE. The authors suggest the PiC to constitute a key target volume in tsSAHE to achieve seizure freedom in the long term.

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Author Contributions

V. B. and M. S. have performed conception of the study, statistical analysis, and interpretation of the data. V. B. and M. S. were involved in designing and writing the draft of the manuscript. H. V. supervised the whole process of analysis and writing of the manuscript. All co-authors made substantial contributions to the conception of the study, the treatment and recruitment of the patients, and data collection. A. B., F. M., T. R., Á. R., and T. B. revised the manuscript critically. All co-authors approved the final version. A.-L. P. and M. S. performed volumetric analysis after training and under continuous supervision provided by A. R. The collection of patient data was performed by M. B. and I. I. R. S. is responsible for the presurgical evaluation. The surgical procedures were performed by H. V., V. B., and M. H.

Conflict of Interests

The authors declare that they have no conflict of interest.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Comparison of seizure-free patients with reduced or withdrawn AED and seizure-free patients on unchanged AED therapy in the long term*.