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Die chirurgische Therapie der pharmakoresistenten Temporallappenepilepsie: neue Implikationen und translationale Ansätze im klinischen Management

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Die folgenden aufgelisteten fünf Originalarbeiten liegen der kumulativen Habilitationsschrift zu Grunde, welche die wesentlichen Ergebnisse der Publikationen zusammenfasst und diskutiert.

1. **Borger V**, Hamed M, Taube J, Aydin G, Ilic I, Schneider M, Schuss P, Güresir E, Becker A, Helmstaedter C, Elger CE, Vatter H. Resective temporal lobe surgery in refractory temporal lobe epilepsy: prognostic factors of post-operative seizure outcome. *J Neurosurg.* 2021;135(3):760-769.(IF: 5.1)

2. **Borger V***, Schneider M*, Taube J, Potthoff AL, Keil VC, Hamed M, Aydin G, Ilic I, Solymosi L, Elger CE, Güresir E, Fimmers R, Schuss P, Helmstaedter C, Surges R, Vatter H. Resection of piriform cortex predicts seizure freedom in temporal lobe epilepsy. *Ann Clin Transl Neurol.* 2021;8(1):177-189. (IF: 4.5)

3. **Borger V,** Hamed M, Bahna M, Rácz A, Ilic I, Potthoff AL, Baumgartner T, Rüber T, Becker A, Radbruch A, Mormann F, Surges R, Vatter H, Schneider M. Temporal lobe epilepsy surgery: Piriform cortex Resection impacts seizure control in the long-term. *Ann Clin Transl Neurol.* 2022 Jul 1. doi: 10.1002/acn3.51620. Online ahead of print. (IF: 4.5)

4. Bahna M, Hamed M, Ilic I, Salemdawod A, Schneider M, Rácz A, Baumgartner T, Güresir E, Eichhorn L, Lehmann F, Schuss P, Surges R, Vatter H, **Borger V.** The necessity for routine intensive care unit admission following elective craniotomy for epilepsy surgery: a retrospective single-center observational study. *J Neurosurg.* 2022:1-7. (IF: 5.1)

5. **Borger V**, Hamed M, Ilic I, Potthoff AL, Rácz A, Schafer N, Güresir E, Surges R, Herrlinger U, Vatter H, Schneider M, Schuss P. Seizure outcome in temporal glioblastoma surgery: lobectomy as a supratotal resection regime outclasses conventional gross-total resection. *J Neurooncol.* 2021;152(2):339-346. (IF: 4.1)

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Meiner Familie

Abkürzungsverzeichnis

AED	Anti-epileptic drugs
ASA	American Society of Anesthesiologists
ATL	Anteriore temporale Lobektomie
CA	Cornu ammonis
COVID-19	Coronavirus disease 2019
CPR	Cardio-pulmonale Reanimation
DM	Diabetes mellitus
EEG	Elektroenzephalographie
FDG-PET	Flour-18-Desoxyglukose-Positronen-Emissions-Tomographie
fMRT	funktionelle Magnetresonanztomographie
GCS	Glasgow coma scale
GTR	Gross total resection
HG	Hippcampusgliose
HS	Hippocampussklerose
Hz	Hertz
ICU	Intensive care unit
ILAE	International League against Epilepsy
i.v.	intravenös
LEAT	Long-term epilepsy-associated tumors
ml	Milliliter
MOGHE	Mild malformation of cortical development
MRg-LITT	Magnetresonanz gesteuerte Laser interstitielle Thermotherapie
MRT	Magnetresonanztomographie
mTLE	mesiale Temporallappenepilepsie
PiC	piriformer Cortex
SEEG	Stereo-Elektroenzephalographie
SPECT	Single-Photon-Emissionscomputertomographie
Std.	Stunde
TLE	Temporallappenepilepsie
TRE	Tumor related epilepsy
tsSAHE	transsylvische selektive Amygdalohippocampektomie

2. Einleitung

2.1 Temporallappenepilepsie: Definition, Entstehung und Verlauf

Die Temporallappenepilepsie ist eine der häufigsten Epilepsieformen, die beim Menschen diagnostiziert wird (Engel, 2008; Semah et al., 1998). Ihre erste Erwähnung fand diese Form der Anfälle durch die Beschreibungen von Hughlings-Jackson (Taylor and Marsh, 1980). Zur Entstehung der Temporallappenepilepsie existieren in der heutigen wissenschaftlichen Literatur mehrere Hypothesen. Die in den epilepsiechirurgischen Serien am häufigsten beschriebene Form ist die mesiale Temporallappenepilepsie. Diese Form der Temporallappenepilepsie ist gleichzeitig auch eine der häufigsten fokalen Epilepsien (Blumcke et al., 2017). Wobei es hier anzumerken ist, dass in den letzten Jahren in den meisten epilepsiechirurgischen Zentren der Anteil der Patienten mit mesialen Temporallappenepilepsien rückläufig ist (Jehi et al., 2015). Eine Hippocampussklerose ist das histopathologische Substrat der mesialen Temporallappenepilepsie (Blumcke et al., 2017). Gemäß der Klassifikation der International League Against Epilepsy (ILAE) werden histologisch drei Subtypen unterschieden. ILAE Typ 1 ist gekennzeichnet durch einen ausgeprägten Zellverlust und eine Gliose im CA1 und CA4 Segment des Hippocampus. Mit etwa 60-80 % ist dies die häufigste Form. ILAE Typ 2 geht mit einem ausgeprägten Zellverlust und einer Gliose hauptsächlich im CA1 Segment des Hippocampus einher. ILAE Typ 3 ist durch Zellverlust und Gliose vorwiegend im CA4 Segment des Hippocampus gekennzeichnet (Blumcke et al., 2013). Die genaue Genese der Hippocampussklerose ist unklar. Es wird angenommen, dass zu deren Entstehung solche Ereignisse wie komplizierte Fieberkrämpfe, Traumen, intrakranielle Infektionen oder Hypoxien beitragen (de Lanerolle et al., 2003). Neben der „klassischen“ mesialen Temporallappenepilepsie unterscheidet man weitere sog. läsionelle Temporallappenepilepsien, welche durch andere strukturelle Veränderungen als eine Hippocampussklerose induziert werden. Hierzu zählen z.B. solche Läsionen wie fokale kortikale Dysplasien, Cavernome und arteriovenöse Malformationen, eine heterogene Gruppe von sog. long-term epilepsy-associated neuroepithelial tumors (LEAT): Astrozytome, Gangliogliome, angiozentrische Gliome, pleomorphe Xanthoastrozytome, dysembryoplastische neuroepitheliale Tumoren (Blumcke et al., 2016; Lamberink et al., 2020; West et al., 2015). Eine in der

aktuelleren Literatur neu beschriebene und noch relativ wenig erforschte Gruppe stellen die sog. mild malformation of cortical development with oligodendroglial hyperplasia and epilepsy (MOGHE) dar (Gaballa et al., 2021; Najm et al., 2022; Urbach et al., 2022). Die genaue Inzidenz der läsionellen Temporallappenepilepsien lässt sich nur schwer beziffern. In den großen epilepsiechirurgischen Serien können außer der Hippocampussklerosen bei etwa 56% der Patienten histopathologisch strukturelle Veränderungen nachgewiesen werden (Blumcke et al., 2017). Ätiologisch von den strukturellen Temporallappenepilepsien sind die sog. aläsionellen Temporallappenepilepsien abzugrenzen. Hierbei handelt es sich um eine Subgruppe an Patienten in welchen sich histopatholgisch keine Läsion nachweisen lässt. In diesem Zusammenhang findet man häufig eine weitere Definition, nämlich die der sog. Magnetresonanz Tomografie (MR)-negativen Temporallappenepilepsien. In den großen Epilepsiezentren beträgt der Anteil an MR-negativen Temporallapen-epilepsien etwa 20-30% (Carne et al., 2004; Tellez-Zenteno et al., 2010). Es handelt sich hierbei um Patienten mit Temporallappenepilepsien und gleichzeitig unauffälligen MRT-Befunden ohne Nachweis einer strukturellen Läsion. Aufgrund des immensen Fortschrittes in der MR-Diagnostik einerseits aber auch zunehmenden Anzahl an sog. post-processing Tools andererseits, welche die Analyse und Auswertung der MR-Bildgebung immer genauer und präziser ermöglichen, unterliegt dieses Definitionskonzept in der letzten Zeit einem gewissen Wandel. Denn durch den o.g. Fortschritt lassen sich die strukturellen Läsionen in der ehemals unauffälligen MRT-Bildgebung nun doch immer häufiger nachweisen. Es ist zu erwarten, dass der Anteil dieser Subgruppe an Patienten in Zukunft deutlich weniger wird.

2.2 Klinische prächirurgische Anfallsdiagnostik und Selektion geeigneter Patienten für einen epilepsiechirurgischen Eingriff

Neben den Fortschritten in der Diagnostik von Epilepsien hat sich mit der Einführung von einigen neuen antikonvulsiven Medikamenten auch die pharmakologische Therapie der Epilepsien verbessert. Ungeachtet dieser Entwicklungen bleibt der Anteil der Patienten mit sog. pharmakoresistenten Epilepsien konstant. Bei der Temporallappenepilepsie beträgt dieser Anteil weiterhin etwa 30% der Patienten (Choi et al., 2008; Engel, 2008). Gemäß ILAE-Definition liegt eine

pharmakoresistente Temporallappenepilepsie vor, wenn bei dem Patienten trotzt Behandlung mit zwei geeigneten antikonvulsiven Präparaten (in Mono- und/oder Kombinationstherapie) in adäquaten Dosierung bei guter Verträglichkeit keine Anfallskontrolle erzielt werden konnte.

Liegt eine pharmakoresistente Temporallappenepilepsie vor, sollte der Patient an ein geeignetes Epilepsiezentrum überwiesen und einer epilepsiechirurgische Evaluation unterzogen werden. Diese besteht aus multimodaler klinischer, elektroklinischer, neuropsychologischer, radiologischer, nuklearmedizinischer und ggf. auch genetischer Diagnostik. Das übergeordnete Ziel der prächirurgischen Evaluation besteht darin, den die Epilepsie generierenden Fokus möglichst präzise zu definieren und die Konkordanz der klinischen, elektroklinischen, radiologischen und neuropsychologischen Befunde zu überprüfen. Ist ein Anfallsgenerator nachzuweisen und liegt die Konkordanz der o.g. Befunde vor, kann dem Patienten, eine grundsätzliche neurochirurgische Operabilität des Anfallsgenerators vorausgesetzt, eine epilepsiechirurgische Behandlung offeriert werden (Wiebe et al., 2001). Am Anfang einer jeden prächirurgischen Evaluation steht die Analyse der Anfallssemiologie. Etwa 90% der Patienten mit mesialen Temporallappenepilepsie leiden an fokalen bewusst erlebbaren Anfällen (sog. Auren). Am häufigsten sind epigastrische Auren, die relativ spezifisch für Anfälle aus dem mesialen Temporallappen sind. Häufig beobachtet man einen Übergang einer epigastrischen Aura in einen automotorischen Anfall. Die automotorischen Anfälle können auch isoliert von Auren als eigenständiges Initialsymptom (fokale nicht bewusst erlebbare Anfälle) auftreten. Der Ablauf der automotorischen Anfälle ist relativ monoform und ist gekennzeichnet von Innehalten und Verharren der Patienten zu Beginn des Anfalls, dann gefolgt von motorischen Phänomenen wie orale Automatismen (Kauen, Schmatzen, Schlucken) und seltener Handautomatismen wie Nesteln und Gestikulieren. Eher selten ist eine sekundäre Generalisierung der Anfälle in Form von tonisch-klonischen Anfällen zu beobachten. Die Anfallssemiologie bei nicht mesialen läsionellen Temporallappenepilepsien ist durch die Lokalisation der Läsion im Temporallappen geprägt. Eine eindeutige Zuordnung ist hier zuweilen nicht ohne Weiteres möglich. Ähnlich verhält es sich bei den aläsionellen Temporallappenepilepsien. Die Anfallsursprungszone kann hier temporomesial, temporolateral oder –polar aber auch extratemporal ausgedehnt sein. Zur weiteren Eingrenzung oder Lokalisierung des Anfallsursprungs kommt der weiterführenden

apparativen Diagnostik eine besondere Rolle zu. In erster Linie ist hier die Ableitung eines Oberflächen-EEG kombiniert mit einer Video-Aufzeichnung zu nennen. Im Oberflächen-EEG lassen sich in der Regel abhängig von der Lokalisation des Anfallsgenerators typische EEG-Anfallsmuster sowie auch typische interiktuale EEG-Befunde aufzeichnen. So zeigen bis zu 94% der Patienten mit einer mesialen Temporallappenepilepsie im Anfall im EEG ein Muster mit anterioren temporalen, regulären rhythmischen 5-9 Hz-Aktivität (Risinger et al., 1989). Im interiktualen EEG zeigt sich eine temporale intermittierende rhythmische Verlangsamung im ipsilateralen Temporallappen und anteriore temporale epilepsietypische Potentiale (ETPs). Typisch sind auch sog. Typ-1-Spikes (Baumgartner et al., 1995). Das interiktuale EEG von Patienten mit nicht mesialen läsionellen Temporallappen-epilepsie zeigt typischerweise eine polymorphe Delta-Aktivität und temporale Spikes. Häufig (bis zu 30%) ist hier auch ein Normalbefund vorliegend. Des weiteren lassen sich bei diesen Patienten häufiger neokortikale temporale Spitzen aufzeichnen. Die iktalen EEG-Muster zeigen regionale temporale, hemisphärische oder auch nicht lateralisierte Anfallsaktivität (O'Brien et al., 1996; Pfander et al., 2002). Während bei der mesialen und läsionellen Temporallappenepilepsie häufig schon in der MRT-Bildgebung läsionstypische Befunde erhoben werden können und somit die Konkordanz der Befunde zur Verifikation des Anfallsgenerators hergestellt werden kann, ist die elektroklinische Differentialdiagnostik von aläsionellen Temporallappenepilepsien zuweilen aufwendiger. Eine Möglichkeit dies zu bewerkstelligen ist die Durchführung einer invasiven Anfallsdiagnostik mittels Stereo-EEG (SEEG). Hierbei werden in der Regel stereotaktisch Rahmen basiert oder Robotor assistiert Tiefenelektroden zwecks EEG-Ableitung in die Zielstrukturen im Hirn implantiert (Gonzalez-Martinez et al., 2014; Guenot et al., 2001). In größeren Epilepsiezentren werden etwa 20% der Patienten einer invasiven EEG-Diagnostik unterzogen mit eher steigenden Tendenz (Borger et al., 2021a; Tonini et al., 2004; Zumsteg and Wieser, 2000). Zur Planung der SEEG-Implantation ist die Aufstellung einer Hypothese über die Lokalisation des mutmaßlichen Anfallsgenerators obligat (Luders et al., 2006; Palmini, 2006). Dies erfolgt im multimodalen Setting unter Berücksichtigung der Anfalls-Semiologie, Befunden des Oberflächen-(Video)-EEG, radiologischen Untersuchungen (MRT, ggf. fMRT) und z.B. auch nuklearmedizinischen Untersuchungen (SPECT, FDG-PET). Anschließend erfolgt das Ausarbeiten und die Erstellung des SEEG-Implantations-Schemas. Bei dem

SEEG kommen sog. Tiefenelektorden zum Einsatz. Hierdurch lässt sich die elektrische (Anfalls-) Aktivität der in der Tiefe des Hirns (z.B. temporomesial) lokalisierten Zielstrukturen ableiten und analysieren. Durch die oberflächlichen kortikalen Kontakte der Tiefenelektroden, lässt sich gleichzeitig auch die kortikale iktuale und interiktuale Aktivität ableiten (Schiller et al., 1998). Dieser Ansatz ermöglicht das Analysieren des epileptogenen Netzwerkes und trägt zunehmend zum Verständnis der Epilepsie als eine Netzwerkerkrankung des Gehirns bei (Cossu et al., 2005). So ist es auch nicht verwunderlich, dass der Einsatz von SEEG zunehmend die Implantation von sog. Grid-Elektroden in der invasiven prächirurgischen Diagnostik ablöst (Cardinale et al., 2016; Tandon et al., 2019). So lassen sich z.B. Propagationsmuster der epileptischen Entladungen in ihre bevorzugten Projektionsareale besser darstellen. So dient vermutlich die Amygdala mit ihren Projektionen insbesondere in den hinteren Inselkortex als eine entscheidende Hub-Region für mesiale temporale Anfälle. Auch der Hippocampus besitzt einen typischen Fingerabdruck seiner elektrischen Aktivität. Das ermöglicht im SEEG eine Diskrimination zwischen einem hippocampalen und einem extrahippocampalen Anfallsursprung (Baumgartner et al., 2020). Das Verstehen des epileptogenen Netzwerkes und möglichst präzise Lokalisation des Anfallsgenerators innerhalb dieses Netzwerkes ist entscheidend, ob ein Patient*in geeignet für einen epilepsiechirurgischen Eingriff ist. Für den Erfolg eines solchen epilepsiechirurgischen Eingriffes ist eine möglichst vollständige Resektion aller Anfallsgeneratoren innerhalb des Netzwerkes von großer Bedeutung (Kahane and Bartolomei, 2010).

2.3 Therapeutische epilepsiechirurgische Implikationen bei Pharmakoresistenz

Die Epilepsiechirurgie stellt bei Vorliegen einer pharmakoresistenten Temporallappenepilepsie und Eignung des*r Patienten*in für den neurochirurgischen Eingriff eine sehr wichtige Therapieoption dar. Nicht zuletzt konnte in mehreren randomisierten Studien die deutliche Überlegenheit der Epilepsiechirurgie gegenüber einer rein medikamentösen Therapie bei einer pharmakoresistenten Temporallappenepilepsie belegt werden (Dwivedi et al., 2017; Engel et al., 2012; Wiebe et al., 2001). So ist es auch nicht verwunderlich, dass die sog. Standardresektion in Form der klassischen vorderen Temporallappenresektion das

am häufigsten angewandte Operationsverfahren ist (Spencer et al., 1984). Hierbei wird der polare und laterale Neocortex gefolgt von temporomesialen (Amygdala, Hippocampus) und temporobasalen (entorhinaler Cortex, Gyrus parahippocampales) Strukturen reseziert. Die neocortikale Resektion erstreckt sich in der Regel auf etwa 4,5 cm nach hinten ab dem Temporalpol auf der sprachdominanten Seite und etwa 6,5 cm auf der nicht dominanten Seite. Die Resektion des Hippocampus wird in der Regel mit 2 - 3,5 cm ab Spitze des Temporalhorns des Seitenventrikels ausgedehnt. In der Literatur findet man auch Angaben zum Resektionausmaß des Hippocampus bis zur Ebene der Vierhügelplatte, mindestens sollte der Hippocmapus bis zur Ebene des Sulcus laterales des Hirnstamms reseziert werden (Borger et al., 2021a; Yasargil et al., 1993). Eine randomisierte Studie von Schramm et al. zeigte keinen Einfluss des größeren Resektionsausmaßes des Hippocampus von 3,5 cm gegenüber von 2,5 cm auf das postoperative Anfallsoutcome. Es zeigte sich jedoch, dass mit zunehmenden Resektionsausmaß die postoperativen neurokognitiven Defizite deutlicher ausgeprägt waren (Schramm et al., 2011a, b). Die Betrachtungen und Analysen der neurokognitiven Auswirkungen epilepsiechirurgischer Eingriffe führte zu der Erkenntnis, dass hierdurch bei einer Temporallappenepilepsie häufig bereits vorbestehende Defizite verstärkt oder aber solche auch neu verursacht werden können. Die entsprechenden Arbeiten hierzu konnten auch zeigen, dass das „Opfern“ von intaktem temporalen Neocortex durch die klassische anteriore Temporallappen-resektion bei einer rein temporomesialen Pathologie zu vermeid-baren kognitiven Einschränkungen führt, insbesondere bei Eingriffen in der sprachdominanten Hemisphäre (Helmstaedter, 2013). Diese Erkenntnisse haben die Entwicklung von möglichst selektiven Resektionstechniken im Temporallappen bei rein mesialen Pathologien angestoßen. Bei diesen sog. selektiven Amygdalohippocampektomien werden unter Schonung des temporalen Neocortex gezielt die Amygdala, der uncale Cortex, der entorhinale Cortex und der Hippocampus mit dem anteiligen Gyrus parahippocampales reseziert. Zur Durchführung der selektiven mesialen Resektionen wurden in der Literatur verschiede Techniken, die sich aus dem Zugang ableiten, beschrieben. Der transsylvische Zugang wurde von Yasagil et al. 1993 beschrieben (Yasargil et al., 1993). Trotz der Selektivität bietet dieser Zugang eine verhältnismäßig gute Übersicht, erfordert aber vom Neurochirurgen ein hohes Maß an Erfahrung und mikrochirurgischen vaskulären Skills. Ein weiterer Aspekt, der auch bei der Beratung

der Patienten zu berücksichtigen ist, ist eine mögliche Affektion der sog. Meyer'schen Schlaufe der Sehstrahlung, die in einer Quadrantenanopsie resultiert. Ein Zugangsweg, welcher die Sehstrahlung meidet, liegt der subtemporalen Resektionstechnik zugrunde. Dieser Zugang erlaubt jedoch nur eingeschränkte Sicht nach uncal und kann mitunter durch die individuelle Anatomie der temporobasalen Venen limitiert sein (Clusmann et al., 2002; Park et al., 1996). Ein weiterer die Sehstrahlung schonender Zugang ist die subokzipitale, suprazerebelläre transtentorielle Resektion (Serra et al., 2020; Yonekawa et al., 2001). Die Limitation liegt hierbei in der deutlich eingeschränkten Sicht und Zugangsmöglichkeit zu den anteromesialen Strukturen wie Amygdala und Uncus (Lafazanos et al., 2015). Eine relativ weit verbreitete und mit guter Übersichtlichkeit assoziierte Resektionstechnik ist die über den lateralen transkortikalen Zugang (Dorfer et al., 2020; Olivier, 2000). Die laterale kortikale Inzision lässt sich durch den Einsatz moderner mikrochirurgische Techniken optimal und möglichst minimal invasiv durchführen. Liegt eine epileptogene Läsion (z.B. Cavernom, Gangliogliom) ohne Involvierung der temporomesialen Strukturen vor, so erfolgt in der Regel eine Läsionektomie. Hierbei wird gezielt und möglichst schonend für das umliegende Hirngewebe die Läsion reseziert. Einen anderen Ansatz verfolgen die vor allem in den letzten Jahren aufkommenden sog. minimal-invasiven ablativen Verfahren. Diese Technik kommt meist ohne eine größere Schädeleröffnung (Trepanation) aus und macht sich die Fortschritte in der modernen direkten bildgestützten Navigation oder Thermometrie zunutze. So erfolgt bei der MR-gesteuerten Laser interstitiellen thermalen Therapie (MRg-LITT) die thermale Ablation der mesialen Zielstrukturen (Amygdala, Uncus und Hippocampus) durch eine Laser-Sonde, welche stereotaktisch sehr zielgenau eingebracht werden kann. Im Anschluss erfolgt die Kontrolle der Lage der Laser-Sonde mittels MRT. Die Überwachung der Ablation kann in Echtzeit mittels MR-Thermometrie durchgeführt werden. Die geplante Ablation lässt sich mithilfe der Planungssoftware im Vorfeld simulieren und bei Bedarf können auch Bereiche festgelegten werden, welche von der Thermoablation ausgespart werden sollen (Wu et al., 2019). Eine weitere Methode ist die Radiofrequenzthermoablation, die jedoch in der Behandlung der Temporallappenepilepsie nur eine untergeordnete Rolle spielt. Durch die Verfahren wie MRg-LITT verspricht man sich die Schwelle zur invasiven Therapie bei den Patienten zu senken und so mehr geeignete Kandidaten einer chrirugischen Behandlung zuzuführen. Des Weiteren zeigen die Daten-Analysen

erster größerer Kohorten zumindest im kürzeren Beobachtungszeitraum von bis zu 2 Jahren eine geringere Inzidenz von therapieassoziierten Gesichtsfelddefekten und bessere Preservation von kognitiven Funktionen (Sprachfunktion und visuelles Gedächtnis) im Vergleich zu den klassischen resektiven Verfahren. Das Anfallsoutcome im Hinblick auf die erreichten Raten von Anfallsfreiheit scheint bei MRg-LITT mit ca. 60% den Ergebnissen von resektiven OP-Verfahren mit ca. 70-80% unterlegen zu sein (Brotis et al., 2021; Liu et al., 2021). Es fehlen hier jedoch noch Langzeit-Daten und Daten aus prospektiven Vergleichsstudien.

2.4 Zielsetzung

Die folgenden Kapitel stellen die Ergebnisse von insgesamt fünf retrospektiven klinischen Arbeiten dar. Das Ziel der Arbeiten war, die Ergebnisse der epilepsiechirurgischen Behandlung von Patienten mit pharmakoresistenten Temporallappenepilepsien an einem großen Epilepsie-Zentrum, wie Universitätsklinikum Bonn, zu analysieren. Ein Fokus liegt dabei auf der Betrachtung des erzielten Anfallsoutcomes und der Faktoren, welche diesen beeinflussen. Als sekundäre Parameter werden die Komplikationsrate, die visuellen Defizite (Gesichtsfelddefekte) sowie das neurokognitive Outcome analysiert. Ein wichtiger Aspekt bei der Betrachtung des erzielten Anfallsoutcomes ist die Tatsache, dass etwa 30% der Patienten postoperativ nicht anfallsfrei werden. Eine der möglichen Ursachen hierfür, wie auch zentrumseigene Daten zeigen, ist die unzureichende Resektion von Zielstrukturen innerhalb des Temporallappens. Dieser Analyse widmet sich eine Arbeit mit dem Ziel bisher in einer Form unterrepräsentierte Bereiche des mesialen Temporallappens zu beschreiben und die Korrelation deren Resektionsausmaßes mit der Anfallsfreiheit nach selektiven Amygdalohippocampektomien zu analysieren. In einer weiteren Arbeit wird diese Korrelation im Hinblick auf die erzielte Anfallsfreiheit im Langzeitverlauf analysiert. Diese Erkenntnisse sollen vor allem vor dem Hintergrund der immer mehr aufkommenden sog. minimalinvasiven Verfahren helfen, die traditionellen und etablierten resektiven epilepsiechirurgischen Verfahren weiter zu optimieren, um eine noch bessere postoperative Anfallskontrolle zu erreichen. Bei diesen Betrachtungen darf auch das unmittelbare postoperative klinische Management der epilepsiechirurgischen Patienten vor allem vor dem Hintergrund der zunehmenden Verknappung der intensivmedizinischen Ressourcen und der Suche nach Einsparpotentialen nicht

außer Acht gelassen werden. Der Fokus der vierten Arbeit liegt auf der Analyse der Notwendigkeit der intensivmedizinischen post-operativen Überwachung von Patienten nach epilepsiechirurgischen Eingriffen. Eine der Besonderheiten und auch der Stärken des klinischen Managements der epilepsiechirurgischen Patienten sind der hohe Maß an Standardisierung sowohl präoperativ als auch im Hinblick auf die angewandten operativen Verfahren. Ein weiteres Ziel war diese in unserem Zentrum vorhandenen Erfahrungen auf andere klinische Versorgungsbereiche der operativen Neurochirurgie zu übertragen. Diesem Aspekt widmet sich die fünfte Arbeit und betrachtet die Auswirkungen und die Unterschiede im Anfallsoutcome bei Patienten mit temporalen Glioblastomen und einer symptomatischen Epilepsie wenn diese einer Glioblastomresektion nach epilepsiechirurgischen Gesichtspunkten in Form einer anterioren temporalen Lobektomie im Vergleich zu klassischen onkologischen gross total resection unterzogen werden. Eine derartige innerklinische Translation kann durch Übertragung synergetischer Effekte auch Schwerpunkt übergreifend zur Verbesserung der operativen Versorgung der Patienten innerhalb eines großen neurochirurgischen Zentrums beitragen.

3. Ergebnisteil

3.1 Borger V, Hamed M, Taube J, Aydin G, Ilic I, Schneider M, Schuss P, Güresir E, Becker A, Helmstaedter C, Elger CE, Vatter H. Resective temporal lobe surgery in refractory temporal lobe epilepsy: prognostic factors of postoperative seizure outcome. *J Neurosurg.* 2021;135(3):760-769.

Zielsetzung der Arbeit - Eingriffe am Temporallappen sind die häufigsten durchgeführten epilepsiechirurgischen Operationen. Trotz der sorgfältigen präoperativen Selektion und nachgewiesener Wirksamkeit der Epilepsiechirurgie bleibt es weiterhin schwierig, Merkmale oder Faktoren herauszufinden, die dazu führen, dass keine Anfallsfreiheit bei den operierten Patienten erreicht wird. Das Ziel dieser Arbeit war solche Faktoren zu identifizieren.

Methoden und Ergebnisse - Hierzu wurde die intstitutseigene Kohorte von 184 (eingeschlossen 164) Patienten mit pharmakoresistenter Temporallappenepilepsie retrospektiv untersucht. Alle Patienten wurden einer standardisierten prächirurgischen Evaluation unterzogen. Ausgewertet wurden klinische, radiologische, neuropsychologische histopathologische sowie perioperative Parameter. Die Einzelheiten sind den pp. 761-762 (Borger et al., JNS 2021) der angefügten Originalpublikation zu entnehmen. Die durchschnittliche Dauer der Epilepsie betrug 19,1 Jahren und das durchschnittliche Alter der Patienten zum Zeitpunkt der OP war 36,1 Jahren. Hinsichtlich des Anfallsoutcomes waren 75,2% der Patienten nach 12 Monaten post-operativ anfallsfrei. Die Zusammenfassung der Ergebnisse und wesentlicher Charakteristika der Patienten ist in Tabelle 1 dargestellt (Borger et al.; JNS 2021, p. 763). Als Anfallsoutcome bestimmende Faktoren konnten die Histopathologie und das Resektionsausmaß bzw. –Vollständigkeit gezeigt werden. Die Ergebnisse der präoperativen kognitiven Performance des untersuchten Patientenkollektivs sind in Fig. 1, (Borger et al., JNS 2021, p. 765) und der Vergleich der Entwicklung des visuellen und des verbalen Gedächtnisses im prä- und postoperativen Verlauf in Fig. 2, (Borger et al., JNS 2021, p. 765) der Originalpublikation dargestellt.

Schlussfolgerungen - Als Kernaussage dieser Arbeit zeigte die multivariate logistische Regressionsanalyse den histologischen Nachweis einer Hippocampusgliose sowie eine inkomplette Resektion der (temporo)-mesialen

Zielstrukturen als unabhängige Prädiktoren für eine ausbleibende postoperative Anfallsfreiheit.

JNS

Atlas

CLINICAL ARTICLE

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Resective temporal lobe surgery in refractory temporal lobe epilepsy: prognostic factors of postoperative seizure outcome

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OBJECTIVE Temporal lobe epilepsy (TLE) is one of the most common forms of epilepsy. In approximately 30% of patients, seizures are refractory to drug treatment. Despite the achievements of modern presurgical evaluation in recent years, the presurgical prediction of seizure outcome remains difficult. The aim of this study was to evaluate the seizure outcome in patients with drug-refractory TLE who underwent resective temporal lobe surgery (rTLS) and to determine features associated with unfavorable postsurgical seizure outcome.

METHODS Patients with medically refractory TLE who underwent rTLS between 2012 and 2017 were reviewed from the prospectively collected epilepsy surgery database. A retrospective analysis of clinical, radiological, neuropsychological, histopathological, and perioperative findings of 161 patients was performed. The patients were divided into two groups according to seizure outcome (group I, International League Against Epilepsy [ILAE] class 1; group II, ILAE class ≥ 2). For identification of independent risk factors for unfavorable postoperative seizure outcome (ILAE class ≥ 2), a multivariate logistic regression analysis was performed.

RESULTS Seizure freedom (ILAE class 1) was achieved in 121 patients (75.2%). The neuropsychological evaluation demonstrated that losses in cognitive performance were more pronounced in verbal memory after resections in the left temporal lobe and in nonverbal memory after right-sided resections, whereas attention improved after surgery. Overall, postoperative visual field deficits (VFDs) were common and occurred in 51% of patients. There was no statistically significant difference in the incidence of VFD in patients with selective surgical procedures compared to the patients with nonselective procedures. The lack of MRI lesions and placement of depth electrodes were preoperatively identified as predictors for unfavorable seizure outcome.

CONCLUSIONS rTLS is an effective treatment method in patients with refractory TLE. However, patients with a lack of MRI lesions and placement of depth electrodes prior to rTLS are at higher risk for an unfavorable postsurgical seizure outcome.

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KEYWORDS epilepsy surgery; hippocampal gliosis; temporal lobe epilepsy; seizure outcome

Temporal lobe epilepsy (TLE) is one of the most common forms of epilepsy, first described by Hughlings-Jackson. In approximately 30% of patients, seizures are refractory to drug treatment.[1] Since the first randomized controlled trial by Wiebe et al. showed significantly improved outcomes with epilepsy surgery over drug treatment in refractory TLE, resective temporal lobe surgery (rTLS) has been a reasonable option for treatment in these patients.[2] In a meta-analysis including 32 studies with 2250 patients, Engel et al. reported that after rTLS, seizure freedom was achieved in 65% of patients with TLE.[3] In a recently published review, Englot and Chang reported that the existing data favoring surgery for appropriately selected candidates with refractory

ABBREVIATIONS AHE = amygdalohippocampectomy; ATL = anterior temporal lobectomy; CA = cornu ammonis; CI = confidence interval; DCS-R = Diagnostikum für Zerebralschäden–Revised; EEG = electroencephalography; FCD = focal cortical dysplasia; HG = hippocampal gliosis; HS = hippocampal sclerosis; ILAE = International League Against Epilepsy; OR = odds ratio; rTLS = resective temporal lobe surgery; sAHE = selective AHE; TLE = temporal lobe epilepsy; VFD = visual field deficit; VLMT = verbal learning and memory test.

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TLE are convincing and suggest that a cure is possible in some patients with this disorder.[4] Despite this fact and all achievements of modern presurgical evaluation in recent years, the presurgical prediction of seizure outcome remains difficult. The aim of this study was to evaluate seizure outcome in patients with drug-refractory TLE who underwent rTLS at our center and to determine features associated with unfavorable postsurgical seizure outcome.

Methods

Population and Presurgical Evaluation

Patients with TLE who underwent rTLS between 2012 and 2017 were reviewed from the prospectively conducted epilepsy surgery database at our center. The formation of this database was approved by the local ethics committee. Given the retrospective nature of the study, written informed consent was not required.

During the studied period, rTLS was performed in a total of 184 patients. There were 23 cases lost to follow-up; the most common reason was treatment of patients from abroad who moved back to their countries after surgery. These patients did not complete the follow-up visits at our center. Because we included only patients with completed follow-up at 12 months after rTLS, complete data sets for 161 consecutive patients were available. All patients suffered from medically refractory TLE and had undergone adequate treatment with at least two first-line antiepileptic drugs. A retrospective analysis of clinical, radiological, histopathological, and perioperative findings was performed.

All patients were preoperatively assessed in the department of epileptology in a similar fashion and were considered to be suitable for surgery.[5,6] The evaluation included detailed history of seizures, medical history, high resolution 3-T MRI, neuropsychological assessment, and video-electroencephalography (EEG) monitoring using continuous recordings. In patients with absent or several lesions on MRI, PET and SPECT were performed to identify a seizure focus. In cases with inconclusive findings, invasive EEG monitoring was performed using stereotactically implanted depth electrodes.[7]

Surgical Procedures

All surgical procedures were performed while patients were under general anesthesia using intraoperative neuronavigation and intraoperative neurophysiological monitoring with motor evoked and somatosensory evoked potentials. The goal of surgery was to remove temporal and temporomesial structures, including the lesion depicted on MRI or anatomical area with presumed seizure focus.

Histopathological Examination

The resected tissue was obtained from all patients in this study. Standardized neuropathological analysis was performed in all preserved specimens by local neuropathologists. The histopathological findings were differentiated into three categories. First were hippocampal pathologies such as hippocampal sclerosis (HS) or hippocampal gliosis (HG) according to the International League Against Epilepsy (ILAE) classification.[8] Next were pathologies within the temporal lobe without the involvement of the hippocampus, such as gliosis, ganglioglioma, cavernoma, and focal cortical dysplasia (FCD). The diagnosis of HG was histologically confirmed as reactive astrogliosis without neuronal loss within the resected hippocampus. Neoplastic lesions were classified according to the WHO classification.[9] The FCD was classified according to the new ILAE classification.[10] The last category was no specific pathological changes.

Surgical Outcome Analysis

After rTLS, the outcome was assessed during follow-up visits at 6 and 12 months. Patients with a follow-up period less than 12 months were not included in this study. At the 12-month visit, all patients underwent a thorough clinical examination, evaluation of seizure outcome, video-EEG recording, 3-T MRI, and neuropsychological reassessment. The postoperative seizure outcome was assessed according to the ILAE classification.[11] The patients were divided into two groups according to seizure outcome: group I (ILAE class 1) and group II (ILAE class ≥ 2).

Surgically associated complications were assessed during the postoperative course of treatment. The clinically relevant events requiring surgical revision, such as bleeding complications and surgical site infections, were analyzed. Furthermore, relevant newly occurring neurological deficits such as motor deficits, aphasia, and cranial nerve palsy were assessed and analyzed.

All patients underwent MRI within 2–3 days postoperatively to detect the extent of resection of desired structures. Incomplete resection was determined in cases in which a substantial remnant of target tissue was not reached by resection as confirmed by postoperative MRI, whether it was from imprecise delimitation or surgical and functional limitation. The target structures were different according to the surgical procedure. In candidates who underwent selective amygdalohippocampectomy (sAHE) or anterior temporal lobectomy (ATL) with amygdalohippocampectomy (ATL with AHE), the resection was stated as incomplete if mesial temporal structures such as the hippocampus, amygdala, or superior part of the uncus were insufficiently removed. In patients who underwent temporal lesionectomy or ATL without AHE, the resection was incomplete if any parts of the epileptogenic lesion were not addressed by the surgery. After completion of the presurgical evaluation, the extent of resection and the desired structures that were intended to be removed were defined by the responsible epileptologist and reviewed by the interdisciplinary epilepsy surgery conference. In cases where needed, resection masks were generated and included in the intraoperative neuronavigation. Following surgery, the resection was matched with the presurgical resection mask to confirm the proper extent of resection. The postoperative MRI was performed in each patient within 2–3 days to confirm the extent of resection of addressed structures or lesions and rule out surgical complications such as bleeding, infarction, and damage to brain tissue along the surgical approach. The postsurgical MR images were analyzed by experienced neuroradiologists.

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Neuropsychological Assessment

The neuropsychological evaluation focused on tests of verbal and nonverbal memory representing temporal lobe functions. In addition, attention and executive functions, visuospatial abilities, and language and motor functions were considered. Verbal memory was measured via the verbal learning and memory test (VLMT). For visual learning, the Diagnostikum für Zerebralschäden–Revised (DCS-R) was applied. Parallel versions of the VLMT and DCS-R were used to minimize practice effects at the follow-up. Attention was assessed by the EpiTrack screening tool and the d2 Aufmerksamkeitsbelastungstest. Language assessment comprised the BNT and the Token Test. Visuospatial abilities were evaluated via Leistungspruefsystem subtest 7 and Wechsler Adult Intelligence Scale block design. The tests and their references are described in previous articles.[12] Pre- and postoperative test results from each cognitive domain were summarized and classified into a 5-point scale, ranging from severely impaired to above average (severely impaired = 0, at least two test scores > 2 standard deviations below the mean of the normative sample; impaired = 1, at least two test scores > 1 standard deviation below the mean; borderline = 2, one test score below the mean; unimpaired = 3, no test score > 1 standard deviation below the mean; above average = 4, at least two test scores > 1 standard deviation above the mean). The distance between two subsequent categories approximately corresponds to one standard deviation from the mean standardized score across all test scores of the respective domain.

Ophthalmological Examination

Visual fields were examined in each patient pre- and postoperatively using kinetic Goldmann perimetry. A new postoperatively diagnosed visual field deficit (VFD) was classified as a superior quadrantanopia or homonymous hemianopia.

Statistical Analysis

Statistical data analysis was performed using the SPSS software package (IBM SPSS Statistics for Windows, version 25.0., IBM Corp.). Associations between parametric variables were analyzed using an unpaired, two-tailed Student t-test. For analysis of associations between nonparametric variables, the Mann-Whitney U-test was used. Associations of categorical variables were compared using the chi-square or Fisher exact test. Results with p values < 0.05 were considered statistically significant. For identification of independent risk factors for unfavorable postoperative seizure outcome (ILAE class ≥ 2), a multivariate logistic regression analysis was performed including the variables with significant p values in univariate analysis. The results of the analysis were presented by logistic regression as odds ratio (OR) with a 95% confidence interval (CI).

Results

Population and Presurgical Evaluation

In total, data from 161 patients who underwent rTLS for TLE were included in this analysis. There were 85 males (52.8%). The surgery was performed in 81 patients (50.3%) on the left side and in 80 (49.7%) on the right. The mean age at epilepsy onset was 17.32 ± 13.09 years, and the mean age at surgery was 36.1 ± 14.96 years. The mean duration of epilepsy was 19.1 ± 13.77 years. According to seizure outcome, 121 patients were assigned to group I (ILAE class 1) and 40 to group II (ILAE class ≥ 2). Regarding basic clinical characteristics such as age at seizure onset, age at surgery, duration of epilepsy, and side of surgery, there were no statistically significant differences (Table 1). During the presurgical evaluation, the invasive evaluation using depth electrodes was performed in significantly more patients in group II compared to group I (15 [37.5%] vs 21 [17.4%], p = 0.015). The analysis of preoperative MRI revealed the evidence of HS as the most common radiological pathology in both groups (79 [65.3%] in group I vs 20 [50.0%] in group II, nonsignificant difference). The distribution of other lesions is shown in Table 1. A negative MR image without any lesions was found significantly more often in group II compared with group I (8 [20%] vs 6 [5%], p = 0.007).

Surgical Procedures

Overall, the leading surgical procedure performed was transsylvian sAHE in 91 of 161 patients. The ATL with AHE was performed in 30 of 161 patients and without AHE in 15 of 161 patients. In 20 of 161 patients, a tailored lesionectomy without AHE was performed followed by lesionectomy with AHE in 5 of 161 patients. As shown in Table 2, the analysis revealed no differences related to surgical procedure between the two outcome groups.

Histopathological Examination

The overview of the histopathological findings is shown in Table 1. There were significantly more patients with HS in the group with favorable seizure outcome (77 [63.6%] in group I vs 17 [42.5%] in group II, p = 0.026). Furthermore, the prevalence of HG was significantly higher in group II compared with group I (11 [27.5%] vs 10 [8.3%], p = 0.05). In regard to other histopathological findings, the groups did not differ significantly (Table 1).

Surgical Outcome Analysis

Of the 161 patients, at 6- and 12-month follow-up visits after rTLS a favorable seizure outcome with seizure freedom (ILAE class 1) was achieved in 121 patients (75.2%). The proportion of patients with ILAE class 2–6 was not significantly different for each ILAE class at the 6- and 12-month follow-ups, respectively (Table 3). The analysis of surgical complications revealed an overall complication rate of 11.8%. The overall rate of revision surgery was 8.1% (Table 2). Surgical site infections were the most frequent complication (in 9 [5.6%] of 161 patients), followed by bleeding complications (6 [3.7%] of 161 patients). The comparison of the two outcome groups revealed no significant differences, either for overall complication rate or rate of surgical revision, or for bleeding complications and infections in each group (Table 2). Transient motor neurological deficits such as paresis and hemiparesis occurred

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TABLE 1. Patient demographics and characteristics according to ILAE seizure outcome class

Characteristic	Overall	Group I (ILAE class 1)	Group II (ILAE class 2–6)	p Value
No. of patients	161	121	40	
Sex, n (%)				
Male	85 (52.8)	62 (51.2)	23 (57.5)	NS
Female	76 (47.2)	59 (48.8)	17 (42.5)	NS
Mean age at epilepsy onset ± SD, yrs	17.32 ± 13.09	17.9 ± 13.59	15.56 ± 11.4	NS
Mean duration of epilepsy ± SD, yrs	19.1 ± 13.77	19.06 ± 13.8	19.4 ± 13.71	NS
Mean age at surgery ± SD, yrs	36.1 ± 14.96	36.66 ± 15.53	34.58 ± 13.12	NS
Site of surgery, n (%)				NS
Lt	81 (50.3)	56 (46.3)	25 (62.5)	NS
Rt	80 (49.7)	65 (53.7)	15 (37.5)	NS
Invasive presurgical evaluation w/ depth electrodes, n (%)	36 (22.4)	21 (17.4)	15 (37.5)	0.015
Preop MRI findings, n (%)				
Unilateral HS	99 (61.5)	79 (65.3)	20 (50.0)	NS
Hippocampal lesions other than HS	27 (16.8)	20 (16.5)	7 (17.5)	NS
Temporal lesion w/o hippocampal involvement	21 (13.0)	16 (13.2)	5 (12.5)	NS
No lesion	14 (8.7)	6 (5.0)	8 (20.0)	0.007
Histology of hippocampus, n (%)				
HS	94 (58.4)	77 (63.6)	17 (42.5)	0.026
HG	21 (13.0)	10 (8.3)	11 (27.5)	0.005
Histology of TL tissue w/o hippocampus, n (%)				
Temporal gliosis	11 (6.8)	6 (5.0)	5 (12.5)	NS
Ganglioglioma	9 (5.6)	7 (5.8)	2 (5.0)	NS
Cavernoma	6 (3.7)	5 (4.1)	1 (2.5)	NS
FCD type I	2 (1.2)	2 (1.7)	0 (0.0)	NS
Other	6 (3.7)	5 (4.1)	1 (2.5)	NS
No specific histopathological changes	12 (7.4)	9 (7.4)	3 (7.5)	NS

NS = nonsignificant; TL = temporal lobe.

in 8 (4.9%) of 161 patients and were not significantly different between groups I and II (6 [4.9%] vs 2 [5%], nonsignificant). The postoperative MRI showed that desired extent of resection was significantly often not achieved in group II compared to group I (4 [10%] in group II vs 2 [1.7%] in group I, $p = 0.034$).

Neuropsychological Outcome

Before surgery, visual memory was impaired in 66% of patients, followed by verbal memory, language, and attention in approximately 50% each. Visuospatial functions were affected in 39% of cases. Preoperatively, there were no significant differences in performance between left and right TLE ($p = 0.29$–0.80; Fig. 1).

Group-level analysis, by means of repeated-measures ANOVA, revealed an interaction effect of visual memory and surgical side ($F [1,99] = 4.752$, $p = 0.032$, $\eta^2 = 0.046$). Patient performance was worse after right-sided resections (Fig. 2, left). A significant main effect of surgery ($F [1,101] = 10.831$, $p < 0.01$, $\eta^2 = 0.097$) and a significant main effect of surgical side ($F [1,101] = 4.379$, $p < 0.05$, $\eta^2 = 0.042$) were found for verbal memory. There was a trend for an interaction of side and surgery ($F [1,101] = 3.127$, $p = 0.08$, $\eta^2 = 0.03$; Fig. 2, right). Attention significantly improved after surgery ($F [1, 99] = 12.561$, $p < 0.01$, $\eta^2 = 0.113$). Language and visuospatial abilities did not show significant changes.

Consistent with the group-level analysis, individual-level analysis indicated that verbal memory decline was more frequent after left rTLS (63%) than after right rTLS (38%). Visual memory was worse for 48% of the patients after right-sided and for 25% after left-sided resections ($\chi^2 [6] = 11.373$, $p < 0.05$). Deteriorations of visuospatial abilities and language were noted in 14%–19% of cases. Attention improved after surgery (39% vs 16%). Figure 3 displays the number of patients with significant individual changes, corrected for floor effects.

Postoperative Visual Field Impairment

Overall, postoperative VFDs were common and occurred in 82 (51%) of 161 patients. The most frequent VFD was superior quadrantanopia (40%). Homonymous hemianopia occurred in 11% of the patients. There was no statistically significant difference in the overall incidence rate of VFD in patients with selective versus nonselective procedures, either for superior quadrantanopia or for homonymous hemianopia (Table 4).

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TABLE 2. Distribution of surgical modality and complications during the perioperative course of treatment according to seizure outcome

Variable	Overall	Group I, n = 121	Group II, n = 40
Surgery modality			
sAHE	91 (56.5)	67 (55.4)	24 (60.0)
ATL w/ AHE	30 (18.6)	21 (17.3)	9 (22.5)
ATL w/o AHE	15 (9.3)	11 (9.1)	4 (10.0)
LE w/ AHE	5 (3.1)	4 (3.3)	1 (2.5)
LE only	20 (12.5)	18 (14.9)	2 (5.0)
Overall surgical complications	19 (11.8)	12 (9.9)	7 (17.5)
Bleeding complication	6 (3.7)	4 (3.3)	2 (5.0)
Surgical site infection	9 (5.6)	5 (4.1)	4 (10.0)
Overall revision surgery	13 (8.1)	8 (6.6)	5 (12.5)

LE = lesionectomy.
Data are given as number (%). All statistical comparisons between the two groups for each variable were nonsignificant.

Multivariate Logistic Regression Analysis

We performed a stepwise multivariate logistic regression analysis using the variables "invasive preoperative evaluation," "evidence of a lesion in preoperative MRI," "histopathological evidence of HS," "histopathological evidence of HG," and "extent of resection on postoperative MRI" to find independent predictors for unfavorable seizure outcome (ILAE class ≥ 2). The analysis showed that the histopathological evidence of HG (OR 4.99, 95% CI 1.9–13.1, p = 0.001) and incomplete resection (OR 9.08, 95% CI 1.6–52.5, p = 0.014) were independent and significant predictors for unfavorable seizure outcome after rTLS in TLE (Table 5).

Discussion

Resective epilepsy surgery is an established treatment option in patients with focal refractory epilepsy, particularly those with TLE.[2] However, although it is effective, it has been demonstrated that seizure freedom rates decrease over time after surgery.[13] There are studies reporting that surgical treatment for TLE fails to provide a seizure-free outcome in 20%–30% of these patients.[14,15] The reasons behind failure of surgical treatment are multiple and comparison with existing data is difficult because of methodological issues. In this study, we tried to identify factors associated with unfavorable seizure outcome in patients with TLE who underwent rTLS. In the present study, a favorable seizure outcome (ILAE class 1) was achieved in 75% of patients 1 year after surgery, which is consistent with published data.[16–20] Schmeiser et al. reported on a series of 458 patients with TLE who were treated with different surgical approaches. They found no differences in short- and long-term seizure outcomes in regard to surgical approach.[16] Other studies addressing this aspect have shown comparable results regarding the seizure outcome between standard temporal lobectomy and sAHE.[21,22] The systematic review and meta-analysis by Josephson et al. shows that ATL is slightly more effective than sAHE regarding seizure outcome.[18] Some authors have reported that sAHE may carry the risk of seizure recurrence in patients with an unrecognized lateral temporal epileptogenic zone.[23] The analysis in this current series revealed that surgical modality did not have an impact on seizure outcome. The overall complication rate in our series was 11.8%, and a revision surgery was required in 8.1% of all patients. However, the reported complication rates are difficult to compare due to different surgical approaches, different underlying pathologies, and heterogeneous study populations. Surgical site infections were the most common complications (5.6%) in our series, followed by bleeding complications (3.7%). The reported rate of infections ranges between 1.5% and 8.5%.[24,25] The occurrence rate of new postoperative motor deficits (hemiparesis) as reported by Erba et al.[25] was 4.3%, and 1.2% in the series by Schmeiser et al.[16] In our series, hemiparesis occurred in 4.9% of patients and was completely resolved in all patients during the observation period. With respect to newly occurring neurological deficits, the comparison of patients with favorable and unfavorable outcomes in our series revealed no impact on seizure outcome. VFDs are a common side effect after TLS. Due to inconsistent and different definitions, the reported rate of VFDs has a very wide range (between 1.5% and 69%).[24] In their study, Schmeiser et al. reported on a large cohort of patients suffering from TLE (overall rate of 73%).[26] In patients who underwent ATL the overall rate was 83%, and in patients who underwent transsylvian sAHE the rate was 74%. In the current series, the overall rate of postoperative VFD is consistent with the reported literature. However, our results did not reveal any differences between selective and nonselective surgical procedures. Due to the fact that at our institution the sAHE was performed exclusively via a transsylvian approach, there are some limitations with regard to comparability of the data with other studies.

As mesiotemporal and neocortical structures play an important role in memory function, postoperative memory impairment is a major sequela after rTLS. In the current series, left TLE patients were generally more impaired

TABLE 3. Seizure outcome according to ILAE classification at 6- and 12-month follow-up visits

Follow-Up (mos)	ILAE Classification						
	1	2	3	4	5	6	Total
6	121 (75.2)	9 (5.6)	11 (6.8)	10 (6.2)	8 (5.0)	2 (1.2)	161
12	121 (75.2)	10 (6.2)	8 (5.0)	10 (6.2)	10 (6.2)	2 (1.2)	161

Data are given as number (%).

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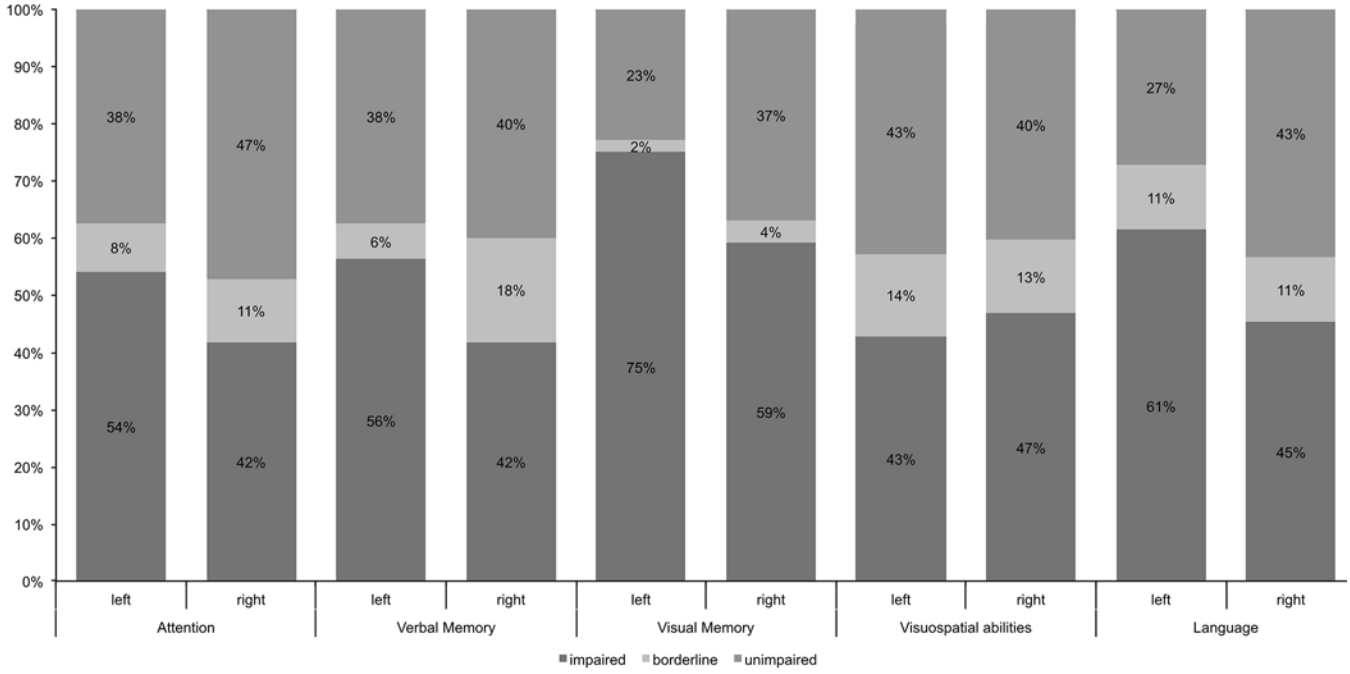

FIG. 1. Comparative histogram demonstrates the results of the preoperative cognitive performance. The results from each cognitive domain are summarized and classified into a 5-point scale ranging from severely impaired to above average. The values represent cumulative percentage of performance categories in each tested cognitive domain according to the side of the TLE. Impaired = cumulative percentages of impaired and severely impaired performance categories; unimpaired = cumulative percentages of unimpaired and above-average performance categories; borderline = percentages of borderline performance categories. Visual memory was impaired in 66% of patients, followed by verbal memory, language, and attention in approximately 50% each, respectively. Visuospatial functions were affected in 39% of cases. Preoperatively there were no significant differences in performance between left and right TLE ($p > 0.29–0.80$).

than right TLE patients, and verbal learning and memory deteriorated similarly in both groups. Language and visuospatial abilities did not show significant changes. Our findings are consistent with comparable previously published studies in which deterioration of verbal memory has been observed after left-sided resections and visual memory deterioration has been observed after right-sided resections.[16,27] Selective attention significantly improved after surgery, which could be due to the relatively high number of seizure-free patients in our study cohort.[28]

In a meta-analysis on a total of 3511 patients reported by Tonini et al., the authors found that intracranial monitoring was a predictor for unfavorable seizure outcome.[29] In accordance with these results, in the current series we found significantly more patients in the group with unfavorable seizure outcome who underwent invasive presurgical evaluation with depth electrodes. Interestingly, in multivariate logistic regression analysis in our series, this variable failed to be an independent predictor for an unfavorable seizure outcome. According to published data,

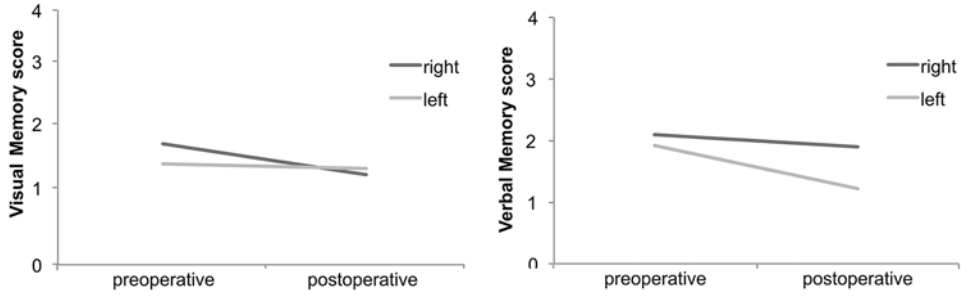

FIG. 2. Performance in visual and verbal memory before and after surgery according to the side of the resection. Group-level analysis revealed an interaction effect of visual memory and surgical side ($F [1,99] = 4.752$, $p = 0.032$, $\eta^2 = 0.046$). Patient performance was worse after right-sided resections than after left-sided resections (*left*). In addition, a significant main effect of surgery ($F [1,101] = 10.831$, $p < 0.01$, $\eta^2 = 0.097$) and a significant main effect of surgical side ($F [1,101] = 4.379$, $p < 0.05$, $\eta^2 = 0.042$) was found for verbal learning and memory. There was a trend for an interaction of side and surgery ($F [1,101] = 3.127$, $p = 0.08$, $\eta^2 = 0.03$) (*right*).

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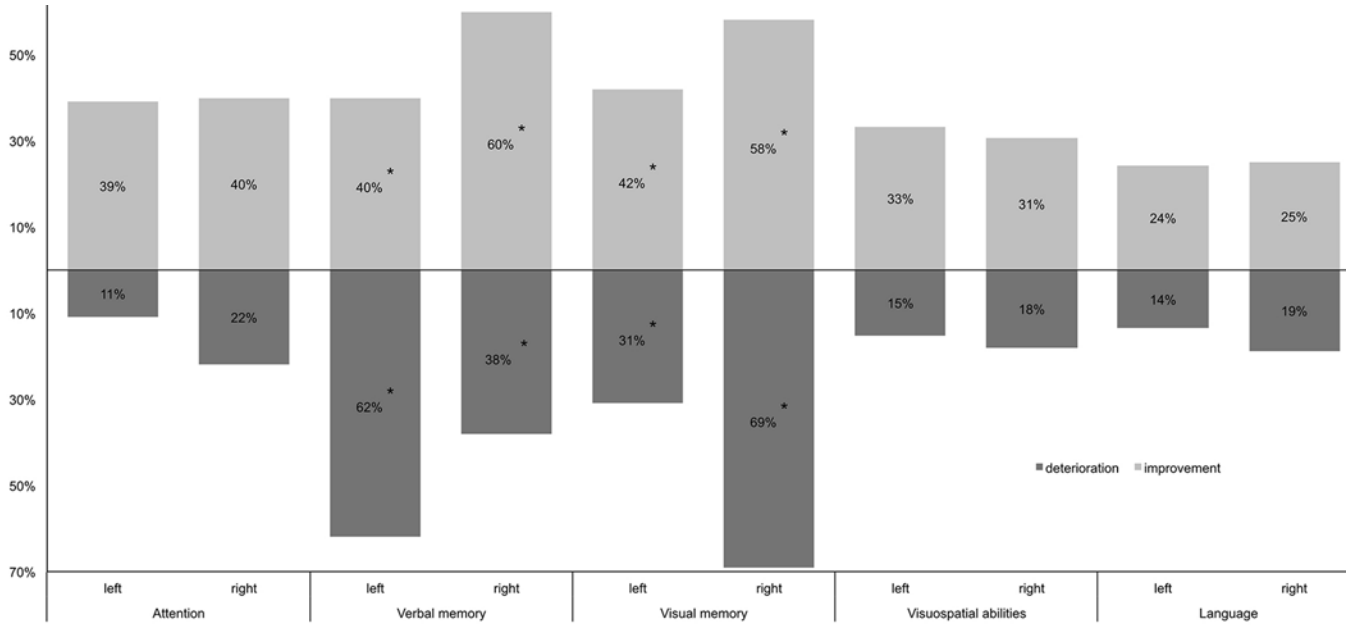

FIG. 3. Postoperative changes in performance categories according to side of resection. The histogram displays the number of patients with significant individual changes, corrected for floor effects. To account for floor effects, patients with the lowest possible baseline score without postoperative change were filtered. We identified 13 patients with floor effects in verbal memory, 15 patients in visual memory, 3 patients in attention, 2 patients in visuospatial abilities, and 1 in the language domain. This revealed a higher rate of postoperative decline in verbal memory after left-sided resections (χ^2 [2] = 9.160, p = 0.01). The other findings remained the same as in the whole sample. Considering ceiling effects, the results were not significantly different from the results obtained from the whole sample. The bars for verbal and visual memory exclude patients with floor effects. The *asterisks* represent significant postoperative changes.

about 20%–30% of patients with TLE have normal MRI without epileptogenic lesions.[30,31] The reported rates of seizure-free outcome following rTLS in these patients varied widely, between 20% and 80%.[32,33] In our studied population, the overall rate of patients with MRI-negative TLE was 8.7%. There were significantly more patients (20%) with negative MRI in the group with unfavorable seizure outcome compared to the 5% in the group with favorable seizure outcome. In contrast to the data published by Tonini et al., in the multivariate logistic regression analysis in the present series, negative MRI also failed to be an independent prognostic factor for unfavorable seizure outcome. These findings suggest that a normal MRI and the need for invasive presurgical evaluation are not always associated with worse postoperative seizure outcome. This suggestion can be supported by data reported by Sotero de Menezes et al.[34] and Roberts et al.[35] showing that seizure outcome in patients with normal MRI is comparable to that in patients with abnormal MRI. Ivanovic et al. showed similar results in their analysis.[33]

Regarding the histopathological findings, there are several studies suggesting that HS and its distinct pattern may predict surgical outcome in patients with TLE.[36–38] According to the ILAE Task Force, neuronal loss may affect all of the areas of the cornu ammonis (CA; HS ILAE type 1), predominantly CA1 (HS ILAE type 2), or predominantly CA4 (HS ILAE type 3).[8] Another pattern described in surgical specimens is astrogliosis without neuronal loss, and it is called "no hippocampal sclerosis, gliosis only." It is unclear whether HG precedes neuronal loss leading to HS or whether it is a distinct disease entity. The data evaluating the impact of HG on seizure outcome

TABLE 4. Occurrence of VFDs according to surgical procedures

Variable	Surgical Procedures		
	Overall	Selective	Nonselective
No. of procedures	161	91	70
No VFD	79 (49)	39 (43)	40 (57)
VFD w/ superior quadrantanopia	65 (40)	43 (47)	22 (32)
VFD w/ homonymous hemianopia	17 (11)	9 (10)	8 (11)
Total	161 (100)	91 (100)	70 (100)

Data are given as number (%). All comparisons of VFDs between surgical groups were nonsignificant.

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TABLE 5. Multivariate logistic regression analysis of factors related to unfavorable seizure outcome (ILAE class 2–6)

Factor Analyzed	Seizure Outcome		Multivariate Analysis		
	Group I, n = 121	Group II, n = 40	OR	95% CI	p Value
Invasive presurgical evaluation w/ depth electrodes	21 (17.4%)	15 (37.5%)	2.01	0.8–5.1	0.144
Preop MRI w/o lesion	6 (5%)	8 (20%)	1.44	0.3–6.5	0.633
Histopathological evidence of HS	77 (63.6%)	17 (42.5%)	1.60	0.7–3.8	0.295
Histopathological evidence of HG	10 (8.3%)	11 (27.5%)	4.99	1.9–13.1	0.001
Incomplete resection	2 (1.7%)	4 (10%)	9.08	1.6–52.5	0.014

in patients with TLE following resective surgery is scarce. The majority of the literature is focused on evaluation of the impact of HS on postsurgical seizure outcome. However, the identification of HG as an independent predictor for lack of seizure freedom in our series is an aspect that is underrepresented in the literature. Since ILAE developed a consensus classification of HS, several reports have been published to rule out the impact of subtypes of HS on postoperative seizure outcome. In their recently published series on 307 cases with TLE and HS, Gales et al. found no clear correlation between HS subtype and epilepsy surgery outcome.[39] Similar results were found by Deleo et al.[40] and Savitr Sastri et al.,[41] who showed no significant difference in short-term seizure outcome between patients with different HS subtypes. In their recently published series, Hattingen et al. found that patients with hippocampal "gliosis only" according to the ILAE classification have distinct histopathological and MRI patterns compared with HS.[42] In the current series, we did not distinguish between patient HS subtypes and seizure outcome. However, the analysis of histopathological features in our series revealed HS as the most frequent pathology. Furthermore, there were significantly more patients with HS in the group with favorable seizure outcome. In contrast, HG was found significantly more often in patients with unfavorable outcome. Yet, only HG was identified to be an independent predictor for unfavorable outcome in the multivariate logistic regression analysis. These findings may support the suggestion made by Hattingen et al., who identified HG as a distinct entity in patients with TLE. In our opinion, this finding is important given that several reports have recently been published describing features with the potential to distinguish between HG and HS on preoperative MRI using novel methods of neuroimaging.[43] Further progress in neuroimaging may allow us to detect the underlying pathology within the hippocampus more precisely on the preoperative scan. Thus, the fact that HG independently predicts seizure outcome is novel in relationship to prior publications.

The insufficient resection of epileptogenic structures is an obvious reason for continued seizures after epilepsy surgery.[29,44] The resection may prove difficult with structures involving eloquent brain area or those not easy to access surgically. There are several series reporting that further resection of residual epileptogenic structures can result in a seizure-free outcome.[12,45] This fact supports the suggestion that a subgroup of patients fail rTLS for TLE because of incomplete resection of mesial temporal structures. In accordance with these results, the analysis in our series shows significantly more patients with incomplete resection on postoperative MRI in the group with unfavorable seizure outcome. The data in the current study also revealed the evidence of HG and an incomplete resection of the epileptogenic lesion as independent predictors of unfavorable postoperative seizure outcome. Furthermore, the analysis shows that even though there were nonsignificant differences, there was a much higher proportion of gliosis in the specimen obtained from temporal lobe tissue among patients without effects on the hippocampus and with unfavorable seizure outcome compared to the seizure-free group. This could be caused by the fact that neocortical temporal lesions without clearly circumscribed pathology are less resectable. Thus, such lesions might possibly have worse results for reasons related to the lesion itself, not to the surgery.

Study Limitations

The present study has several limitations. One of the strengths of the present series is a relatively large study population, which was treated at a high-volume center in a standardized fashion. Our study suffers from the risk of bias inherent to retrospective cohort analysis. Even though data analysis was retrospective, data acquisition was prospective. However, the implementation of standardized neurosurgical approaches and strict variable definitions might mitigate some of the shortcomings of a retrospective study design.

Conclusions

Our analysis shows that rTLS is an effective treatment method in patients with refractory TLE. However, patients with a lack of lesions on MRI and placement of depth electrodes prior to rTLS are at higher risk for an unfavorable postsurgical seizure outcome. Therefore, these facts should be carefully taken into account, and each of these patients needs an individual approach during the selection process for surgery.

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Disclosures

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Author Contributions

Conception and design: Borger, Vatter. Acquisition of data: Borger, Hamed, Taube, Aydin, Ilic, Schneider, Becker. Analysis and interpretation of data: Borger, Taube, Helmstaedter, Vatter. Drafting the article: Borger. Critically revising the article: Schuss, Güresir, Becker, Helmstaedter, Elger, Vatter. Reviewed submitted version of manuscript: Hamed, Taube, Aydin, Ilic, Schneider, Schuss, Güresir, Becker, Helmstaedter, Elger, Vatter. Approved the final version of the manuscript on behalf of all authors: Borger. Statistical analysis: Borger, Taube. Administrative/technical/material support: Helmstaedter, Elger, Vatter.

Supplemental Information

Previous Presentations

Parts of this work were presented orally at the 69th Annual Meeting of the German Society of Neurosurgery in Münster, Germany, June 3–6, 2018, and at the 13th European Congress on Epileptology in Vienna, Austria, August 26–30, 2018.

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3.2 **Borger V**, Schneider M, Taube J, Potthoff AL, Keil VC, Hamed M, Aydin G, Ilic I, Solymosi L, Elger CE, Güresir E, Fimmers R, Schuss P, Helmstaedter C, Surges R, Vatter H. Resection of piriform cortex predicts seizure freedom in temporal lobe epilepsy. *Ann Clin Transl Neurol.* 2021;8(1):177-189.

Zielsetzung der Arbeit - Die Ergebnisse der vorausgegangen Arbeit zeigten, dass eine unvollständige Resektion der mesilaen Zielstrukturen ein unabhängiger Prädiktor für ausbleibende Anfallsfreiheit ist. In der neueren Literatur zeigt sich eine Evidenz dafür, dass das Resektionsausmaß des piriformen Cortex, eine bis dato in der einschlägigen Literatur unterrepräsentierte mesiale Zielstruktur, bei einer anterioren temporalen Lobektomie unterzogenen Patienten mit TLE signifikant mit der Rate an postoperativen Anfallsfreiheit assoziiert ist. Daten zum Einfluss des Resektionsausmaßes des piriformen Cortex auf das Anfallsoutcome nach transsylvischen selektiven Amygdalohippocampektomien (tsSAHE) existieren bis dato nicht. Das Ziel dieser Arbeit war, diesen Zusammenhang zu untersuchen.
Methoden und Ergebnisse – von den 103 mittels tsSAHE im Zeitraum zwischen 2012 und 2017 behandelten Patienten mit pharmakoresistenten TLE wurden 82 Patienten in die retrospektive Analyse eingeschlossen. Das Resektionsaumaß der Zielstrukturen (Amygdala, Hippocampus, piriformer Cortex) wurde jeweils durch manuelle Volumetrie der prä- und postoperativen MRT-Bildgebung ermittelt. Ferner wurde der Einfluss des Resektionsausmaßes der o.g. Zielstrukturen auf das postoperative Anfallsoutcome 12 Monate nach der OP analysiert. Als sekundäre end-points wurden das neurokognitive Outcome, sowie die Rate an perioperativen Komplikationen und neuen postoperativen neurologischen Defiziten in Abhängigkeit zum größeren Resektionsausmaß des piriformen Cortex evaluiert. Die Untersuchung zeigte, dass postoperativ anfallsfreie Patienten mit einem mediane Anteil von 51% vs. 13% signifikant größeres Resektionsausmaß des piriformen Cortex aufwiesen als nicht anfallsfreie Patienten (siehe Figure 1, p. 181, Borger et al., ACTN 2021). Die ROC-Analyse des jeweiligen Resektionsausmaßes der untersuchten Zielstrukturen zeigte, dass im Vergleich nur das Resektionsausmaß des piriformen Cortex significant zur Anfallsfreiheit beitrug und eine Resektion von knapp 27% des Volumens des piriformen Cortex hierfür notwendig war (Figure 4, Table 5, p. 184, Borger et al., ACTN 2021). Im Hinblick auf die sekundären end-points zeigtemn sich keine signifikanten Unterschiede zwischen den Patienten mit einem größeren (≥

26,4%) Resektionsausmaß des piriformen Cortex und solchen mit einem Resektionsausmaß < 26,4%.

Schlussfolgerungen – Diese Arbeit zeigt eine starke Evidenz für den Einfluss des Resektionsausmaßes des piriformen Cortex auf die postoperative Anfallsfreiheit 12 Monate nach einer tsSAHE bei gleichzeitig nicht signifikant höherem Risiko für das Auftreten von perioperativen Komplikationen oder neuen neurologischen Defiziten und gleichbleibenden Risikoprofil bezüglich der Neurokognition. Daher sollte einer möglichst ausgedehnten Resektion des piriformen Cortex während der tsSAHE seitens der Epilepsiechirurgen eine größere Aufmerksamkeit und Beachtung geschenkt werden.

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RESEARCH ARTICLE

Resection of piriform cortex predicts seizure freedom in temporal lobe epilepsy

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Abstract

Objective: Transsylvian selective amygdalo-hippocampectomy (tsSAHE) represents a generally recognized surgical procedure for drug-resistant mesial temporal lobe epilepsy (mTLE). Although postoperative seizure freedom can be achieved in about 70% of tsSAHE, there is a considerable amount of patients with persisting postoperative seizures. This might partly be explained by differing extents of resection of various tsSAHE target volumes. In this study we analyzed the resected proportions of hippocampus, amygdala as well as piriform cortex in regard of postoperative seizure outcome. **Methods**: Between 2012 and 2017, 82 of 103 patients with mTLE who underwent tsSAHE at the authors' institution were included in the analysis. Resected proportions of hippocampus, amygdala and temporal piriform cortex as target structures of tsSAHE were volumetrically assessed and stratified according to favorable (International League Against Epilepsy (ILAE) class 1) and unfavorable (ILAE class 2–6) seizure outcome. **Results**: Patients with favorable seizure outcome revealed a significantly larger proportion of resected temporal piriform cortex volumes compared to patients with unfavorable seizure outcome (median resected proportional volumes were 51% (IQR 42–61) versus (vs.) 13 (IQR 11–18), $P = 0.0001$). Resected proportions of hippocampus and amygdala did not significantly differ for these groups (hippocampus: 81% (IQR 73–88) vs. 80% (IQR 74–92) ($P = 0.7$); amygdala: 100% (IQR 100–100) vs. 100% (IQR 100–100) ($P = 0.7$)). **Interpretation**: These results strongly suggest temporal piriform cortex to constitute a key target resection volume to achieve seizure freedom following tsSAHE.

Introduction

Temporal lobe epilepsy (TLE) is one of the most common entities of epilepsy, first described by Hughlings-Jackson in 1898.[1] In approximately 30% of patients, seizures are refractory to drug treatment.[2,3] 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 (rTLS) has become a reasonable option for treatment in these patients.[4] Especially for the treatment of mesial TLE (mTLE), a selective amygdalo-hippocampectomy via the transsylvian approach (tsSAHE) was introduced.[5] The aim of this approach was to perform a lesionectomy of mesiotemporal structures avoiding trauma to the adjacent healthy temporal neopallial areas and to the vasculature.[6] Despite reported seizure freedom rates between 60% and 70%, there is a considerable amount of patients with continued seizures after epilepsy surgery.[7] The reasons behind failure of surgery for mTLE are diverse and vary between cases. In the previous decades, many efforts were made to identify a sufficient

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resection extent of mesiotemporal structures.[8–12] However, results from these studies have been conflicting and the issue of optimal extent of resection remains controversial.[13]

A recently published study by Galovic et al. reported strong evidence for the association of piriform cortex resection with surgical seizure outcome in patients with TLE who underwent a standard anterior temporal lobe (ATL) resection.[14] Thus, extended removal of the piriform cortex has been shown to significantly increase the probability of becoming seizure free. Against this backdrop, the piriform cortex seems to constitute a novel key target volume for ATL resections. However, the impact of piriform cortex resection in the setting of transsylvian SAHE for treatment of mTLE is still unknown. Therefore, the aim of this study was to investigate whether the extent of piriform cortex resection might significantly contribute to postoperative seizure outcome in the course of tsSAHE.

Methods

Patient population and presurgical evaluation

Patients with TLE who underwent rTLS between 2012 and 2017 were reviewed from the prospectively kept epilepsy surgery database at our hospital. The establishment of this database was approved by the local ethics committee. Informed consent was not sought as a retrospective design was used.

During the studied period, rTLS was performed in a total of 184 patients. For patients suffering from unilateral mTLE, in our center the tsSAHE is the first-line surgical treatment option. The rationale for surgical procedure selection was based on the magnetic resonance imaging (MRI)-documented pathological lesion as well as putative epileptogenic tissue volumes as suggested in the course of preoperative clinical and electroencephalographical evaluation as previously described for our interdisciplinary epilepsy center.[15]

All patients were presurgically assessed in the department of epileptology and were considered to be suitable for surgery.[16–18] The evaluation included detailed history of seizures, medical history, high resolution structural 3.0 Tesla MRI, neuropsychological assessment,[19] and video-electroencephalography (EEG) monitoring using continuous recordings. In patients with absent or several lesions on MRI – the latter defined as any coexistent extratemporal lesion beyond the ipsilateral temporal lobe that had undergone surgery for tsSAHE – positron emission tomography (PET) and single-photon emission computed tomography (SPECT) were performed in order to identify a seizure focus. In cases with nonconclusive findings, invasive EEG monitoring was performed using stereotactically implanted depth electrodes.[20] Following completed evaluation, the extent of resection was determined in every individual candidate by the interdisciplinary epilepsy conference.

Accordingly, the tsSAHE was performed in 103 consecutive patients. To establish a uniform code of study quality, we only included patients with (a) at least completed 12 months of follow-up after surgery; (b) available pre- and postsurgical structural magnetic resonance imaging (MRI) scans acquired according to the identical scanning protocol and (c) tsSAHE that was performed as a highly standardized surgical procedure by three neurosurgeons (H.V., V.B., M.H.). Considering the abovementioned inclusion criteria, 12 patients were lost to follow-up and nine patients had limited postoperative MRI-protocols. A total of 82 eligible patients were included in the analysis. All patients suffered from medically refractory mTLE and had undergone adequate treatment with at least two first-line antiepileptic drugs (AED).

Surgical procedure of transsylvian selective amygdalo-hippocampectomy

All surgical procedures were performed under general anesthesia using intraoperative neuronavigation and intraoperative neurophysiological monitoring with motor evoked potentials (MEP) and somatosensory evoked potentials (SSEP). The goal of surgery was to anatomically remove mesiotemporal target structures that entail presumed seizure focus. For SAHE, exclusively the transsylvian approach as described by Yasargil et al.[6] with several modifications was used by all neurosurgeons. The surgery was performed as a highly standardized procedure. Shortly described, the patient is positioned supine, the head is fixed in Mayfield-Clamp turned 45° to the opposite side, and the vertex is tilled 5–10° to the bottom. A standard pterional craniotomy was performed. Attention was paid to extend the frontal margin of the bone flap to the mediopupillar line. After opening of the dura, the proximal sylvian fissure was dissected and the sylvian fossa was exposed. In the next step, the deep sylvian vein and limen insulae were identified and a small pial incision into the piriform cortex, 2–3 mm lateral to the M_1 segment and lateral to the deep sylvian vein, was performed. The resection of the superior and lateral parts of the amygdala was performed using neuronavigation and ultrasound suction system (CUSA) just along the lateral border and ventral to the tip of the temporal horn until the temporobasis was reached. From this point, the further resection of amygdala and uncus was performed using CUSA or Penfield dissector, until the pial and

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arachnoid membranes, adjacent to the crural and ambient cisterns, was reached. The temporal horn was then opened using a dissector and the coroidal point was identified followed by resection of the anterior part of the hippocampus. The body of the hippocampus was then resected en bloc and obtained for histopathological analysis. The resection of dorsal parts of the hippocampus was extended until the level of the tectum.

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 volumetric analysis was performed by A.-L.P. and M.S. after training and under continuous supervision provided by V.C.K. and L.S. (8 and 25 years of experience in tumor volumetry) using commercially available software (Intellispace 8.0, Philips Healthcare, Best, the Netherlands). V.C.K. checked and analyzed data for accuracy and methodological consistency afterwards. The volumes of amygdala, hippocampus and piriform cortex were obtained from presurgical and postsurgical 1mm isovoxel 3D T1-weighted MPRAGE scans. The resected proportions of amygdala, hippocampus and piriform cortex were then calculated in each individual. In this series, the segmentation and volumetry of hippocampus, amygdala and piriform cortex were manually performed by trained raters under continuous supervision by experienced neuroradiologists. Each hippocampus was traced in coronal, axial and sagittal plane. The entire length of each hippocampus was manually outlined to anatomic landmarks. The anterior border of the hippocampus was defined by distinguishing from amygdala by the presence of the alveus or the cerebrospinal fluid (CSF) of the lateral ventricle (e.g. uncal recess).[21,22] The posterior border was reached when the fornices were visible in their full length in sagittal plane. The anterior mesial border was defined by the posterior portions of the uncal fissure whereas the posterior mesial border was made up by the open end of the hippocampal fissure. The CSF of the lateral ventricle defines the lateral boundary of the hippocampus. The white matter of the parahippocampal gyrus below the subiculum defines the inferior limit. The manual volumetrical segmentation of the amygdala was performed according to existing protocols.[23] In short, the posterior border was defined in the coronal plane by the alveus that appears inferiorly to the amygdala and the head of the hippocampus, which is inferior-medial. The axial plane was used to identify the medial and lateral border. The ambient cistern limited the medial boundary. The lateral border was defined by the inferior horn of the lateral ventricle. For the identification of the inferior border, the amygdala was traced in the coronal slices. The tentorial indentation was a demarcation line between amygdala and entorhinal cortex. The anterior limit was defined at the level of the closure of lateral sulcus, which could easily be found in the axial sections.

For volumetric analysis of piriform cortex, we basically employed the work reported by Vaughan and Jackson. Thus, the human piriform cortex was subdivided in a frontal and a temporal part. In the temporal lobe, the piriform cortex becomes contiguous to periamygdaloid cortex both anatomically and functionally, and posteriorly extends to overlie the amygdala complex. Medially, piriform cortex limits to the entorhinal cortex with the sulcus semiannularis as its border. In the frontal lobe, the piriform cortex extends from the fundus of the entorhinal sulcus, and is limited medially by the olfactory tubercle and the lateral olfactory tract. The extent of the piriform cortex in the posterior – anterior direction in coronal plane begins at the level of the opening of the hippocampal fissure. From this level, the anterior limit is at the level of the limen insulae. The frontal part of the piriform cortex was definded in accordance to Vaughan and Jackson[24] as a triangular region, which starts from the fundus of the endorhinal sulcus and is bounded medially by the olfactory tubercle and the lateral olfactory tract. The boundary between the superior medial border of the amygdala and piriform cortex is represented by the periamygdaloid cortex (PAC) area. Given by the fact, that in the MR imaging, the discrimination between PAC and piriform cortex is not possible, we grouped the piriform cortex and PAC together for further volumetric analysis. This approach is feasible because both these areas are closely connected both spatially and functionally and were also previously reported by Conçalves Pereira et al.[25]

Due to its eloquent localization and inherent risk of vascular damage, the frontal part of the piriform cortex was not intended for resection during tsSAHE. Given by this fact, we consequently excluded the frontal part of the piriform cortex for volumetric analysis.

Seizure outcome analysis

Seizure outcome was assessed during follow-up visits at 6 and 12 months. At the 12 months visit, all patients underwent thorough clinical examination, evaluation of seizure outcome, Video-EEG recording, high resolution

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structural 3 Tesla MRI, and neuropsychological reassessment. Postoperative seizure outcome was assessed according to the ILAE classification.[26] 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 unfavorable.

Statistical analysis

Statistical data analysis was performed using software package SPSS (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Associations between parametric variables were analyzed using unpaired, two-tailed Student t-test. The Mann-Whittney-U test was chosen to compare continuous variables as the data were largely not normally distributed. Associations of categorical variables were compared using Chi-square test or Fisher exact test. Results with $P < 0.05$ were considered to be statistically significant. For identification of independent risk factors for unfavorable postoperative seizure outcome (ILAE class ≥ 2), a two-level logistic regression analysis was performed including the variables with significant *P*-values in univariate analysis. The results of the analysis were presented as odds ratios (OR) with 95% confidential interval (CI). Finally, receiver operating characteristic (ROC) analysis was performed to explore the power of the resulting model.

Neuropsychological assessment

The neuropsychological evaluation focused on tests of verbal and nonverbal memory representing temporal lobe functions. In addition, attention and executive functions, visuo-spatial abilities, language and motor functions were considered. Verbal learning and memory were measured via the VLMT, a German adaptation of the Rey Auditory Verbal Learning Test.[27] For nonverbal learning and memory the revised version of the DCS-R was applied.[28] Parallel versions of the VLMT and DCS-R were employed to minimize practice effects at the follow-up. Attention was assessed by the EpiTrack[29] and a letter cancellation task. Language assessment comprised confrontation naming and a comprehension task (Token Test). Evaluation of visuo-spatial abilities was carried out by administering mental rotation and WAIS block design. The tests and their references are described in previous articles.[30]

Pre- and postoperative test results from each cognitive domain were summarized and classified into a five-point scale ranging from severely impaired to above average (severely impaired = 0, at least two test scores > 2SD below the mean of the normative sample; impaired = 1, at least two test scores > 1SD below the mean; borderline = 2, one test score below the mean; unimpaired = 3, no test score > 1SD below the mean; above average = 4, at least two test scores > 1SD above the mean). The distance between two subsequent categories approximately corresponds to one SD from the mean standardized score across all test scores of the respective domain.[31]

Statistical analysis

The neuropsychological outcome was defined as the intraindividual change of cognitive categories from pre- to postoperative assessment. Therefore, we subtracted the postoperative from the preoperative category score per domain. A positive value indicated improvement, a negative value indicated deterioration, a value of zero indicated no change.[30] To investigate postoperative changes depending on the side of surgery we performed chi-square tests for each cognitive domain (attention, verbal memory, visual memory, language). In addition, language was examined with separate repeated measures analyses of variance with raw scores from the Token Test, Boston Naming Test and phonemic fluency as within-subjects factors and side of surgery as the between-subjects factor. We chose nonparametric tests, since our data were not normally distributed. To predict which factors influence the postoperative cognitive outcome, separate multiple linear regressions (enter method) were calculated for each cognitive domain. As potential predictors we included the extent of resection of piriform cortex, baseline performance, seizure freedom, and side of surgery as independent variables.

Results

Patient characteristics

Between 2012 and 2017, 82 patients with drug-resistant mTLE underwent tsSAHE at the authors' institution. Postoperative seizure freedom in terms of ILAE class 1 could be achieved for 59 patients (72%) (Table 1).

Side of surgery did not significantly impact the postoperative seizure outcome: 30/42 patients (71%) were seizure free after left tsSAHE and 29/40 patients (73%) were seizure free after right tsSAHE ($P = 1.0$).

In the course of pre-surgical evaluation, invasive diagnostics using depth electrodes were performed in 12 patients (20%) within the ILAE class 1 group and nine patients (39%) within the ILAE class 2–6 group ($P = 0.1$). The histopathological analysis revealed that 52 out of 67 (88%) patients with hippocampal sclerosis had a favorable outcome, compared to seven out of 15 (47%) patients with gliosis or other pathology. Piriform cortices did not exhibit any identifiable preoperative MRI lesions. Coexistent MRI lesions comprised extratemporal gliosis in 9/59 patients (15%) and gray-white differentiation disorders in 5/59

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Table 1. Baseline patient characteristics according to ILAE class seizure outcome[1].

Characteristics	ILAE class 1 (n = 59)	ILAE class 2 –6 (n = 23)	P Value
Sex			
Male, n (%)	28 (47)	14 (61)	0.33
Female, n (%)	31 (53)	9 (39)	
Age at epilepsy onset (mean years ± SD)	16.8 ± 14.2	17.0 ± 12.1	
Duration of epilepsy (mean years ± SD)	22.7 ± 13.2	20.0 ± 16.4	
Age at surgery (mean years ± SD)	39.2 ± 14.1	36.2 ± 14.2	
Site of surgery			
Left, n (%)	30 (51)	12 (52)	1.0
Right, n (%)	29 (49)	11 (48)	
Invasive presurgical evaluation with depth electrodes n (%)	12 (20.3)	9 (39)	0.1
Preoperative MRI findings			
Unilateral hippocampal sclerosis, n (%)	52 (88.1)	16 (69.6)	0.06
No lesion, n (%)	4 (6.8)	5 (21.7)	0.11
Hippocampal gliosis, n (%)	1 (1.7)	2 (8.6)	0.19
Unspecific hippocampal lesion	2 (3)	0 (0)	1.0
Coexistent lesions[2]	10 (17)	4 (21)	1.0
Histology of hippocampus			
Hippocampal sclerosis, n (%)	52 (88.1)	15 (65.2)	0.03
Hippocampal gliosis, n (%)	7 (11.9)	6 (26.1)	0.18
Others, n (%)	0 (0.0)	2 (8.7)	0.08
Peri- and postoperative complications	2 (3)	3 (13)	0.1

ILAE, International League Against Epilepsy; SD, standard deviation.
[1]Values represent number of patients unless otherwise indicated (%).
[2]Defined as any coexistent extratermporal lesion beyond the ipsilateral temporal lobe of surgery.

patients (8%). Peri- and postoperative complications were present in five out of 82 patients (6%) and accounted for postoperative bleeding in one case (1%) and postoperative wound infection and meningitis in four cases (5%). Further, peri- and postoperative unfavorable events did not significantly impact the postoperative seizure outcome: two out of 59 (3%) patients with ILAE class 1 and three out of 23 (13%) patients with ILAE class 2–6 (P = 0.1) exhibited surgery-associated complications. For further details on patient characteristics see Table 1.

Extent of temporal piriform cortex resection predicts postoperative seizure outcome

While volumetric analysis of pre- and postoperative target volumes did not yield significant differences in the resected proportions of hippocampus and amygdala for the ILAE class 1 and ILAE class 2–6 groups (hippocampus: 81% (IQR 73–88) for favorable versus (vs.) 80% (74–92) for unfavorable seizure outcome (P = 0.7); amygdala: 100% (100–100) vs. 100% (100–100) (P = 0.6)), patients with postoperative seizure freedom revealed a profound reduction in residual piriform cortex volumes. Thereby, patients with favorable seizure outcome exhibited a median resected proportion of 51% (42–61) compared to 13% (11–18) for patients with postoperative persisting or deteriorating seizures (P = 0.0001) (Fig. 1, Table 2).

Figure 2 illustrates the anatomical topography of hippocampus, amygdala and piriform cortex as target volumes in tsSAHE surgery. Examples of differing extents of piriform cortex resection are given in Figure 3. Preoperative volumes of abovementioned tsSAHE target structures did not significantly differ between the groups of favorable and unfavorable seizure outcome (Table 3). The volumetric analysis of tsSAHE target volumes according to affected side by the mTLE is shown in Tables S1 and S2. Additionally, we analyzed the impact of the extent of piriform cortex resection in patients with histological evidence of hippocampal sclerosis and in those without this pathology. Thereby, we did not find any significant correlation (Table 4). In order to check for a potential influence of hippocampal sclerosis and the extent of piriform cortex resection as variables both of which were significantly associated with postoperative seizure outcome in univariate analysis, a two-level logistic regression analysis including an interaction term was performed. Thereby,

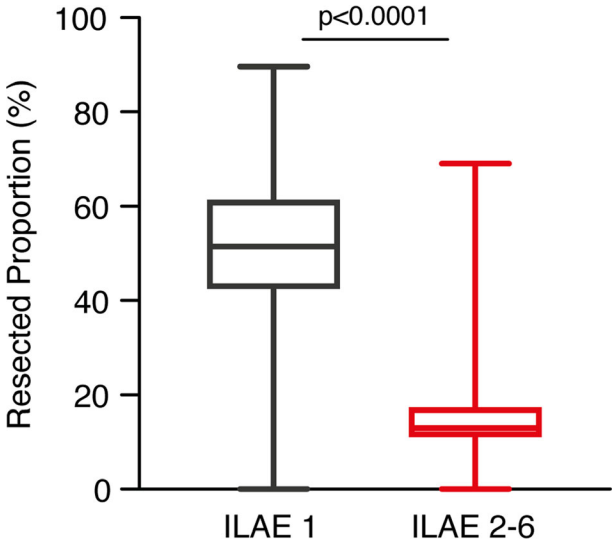

Figure 1. Box-Whisker Plots illustrate seizure outcome dependent on the proportion of temporal piriform cortex resection. ILAE, International League Against Epilepsy.

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Table 2. Extent of temporal piriform cortex resection predicts postoperative seizure outcome.

	Resected proportion[1] (median (IQR))		
	ILAE class 1 (n = 59)	ILAE class 2–6 (n = 23)	P Value
Piriform cortex	51 (42–61)	13 (11–18)	0.0001
Hippocampus	81 (73–88)	80 (74–92)	0.7
Amygdala	100 (100–100)	100 (100–100)	0.6

ILAE, International League Against Epilepsy; IQR, interquartile range.
[1]Values indicated in %.

we could not find any evidence for potential interactions between these two variables (P = 0.09).

The ROC analysis revealed that 50 out of 59 patients (85%) with postoperative seizure freedom (ILAE class 1) had undergone resection of more than 26.4% of preoperative temporal piriform cortex volumes. In comparison, 21 out of 23 patients (91%) with postoperative persistent or deteriorated seizures (ILAE class 2–6) exhibited resection of less than 26.4% of preoperative temporal piriform cortex volumes (Fig. 4, Table 5). As shown in Table 6, the extent of piriform cortex resection did not correlate with the new onset of neurological deficits including new visual field impairment.

Neurocognitive outcome

At baseline, cognitive impairments affected the majority of patients undergoing tsSAHE. Visual memory was most frequently impaired in 70% followed by verbal memory, language and attention in about 50% of the patients (Fig. 5). Postoperative assessments revealed that performance in verbal memory tasks dropped in 60% after left tsSAHE and in 27% after right tsSAHE ($X^2(2) = 6.87$, P = 0.032). Visual memory deteriorated in 33% after TLS regardless of side. In contrast, attention improved in 33%, language remained stable in 60% of the patients. Significant changes in language were found for phonemic fluency ($F(1,39) = 7.43$, $P < 0.05$, eta^2 = 0.01) and confrontation naming ($F(1,55) = 9.55$, $P < 0.05$, eta^2 = 0.15).

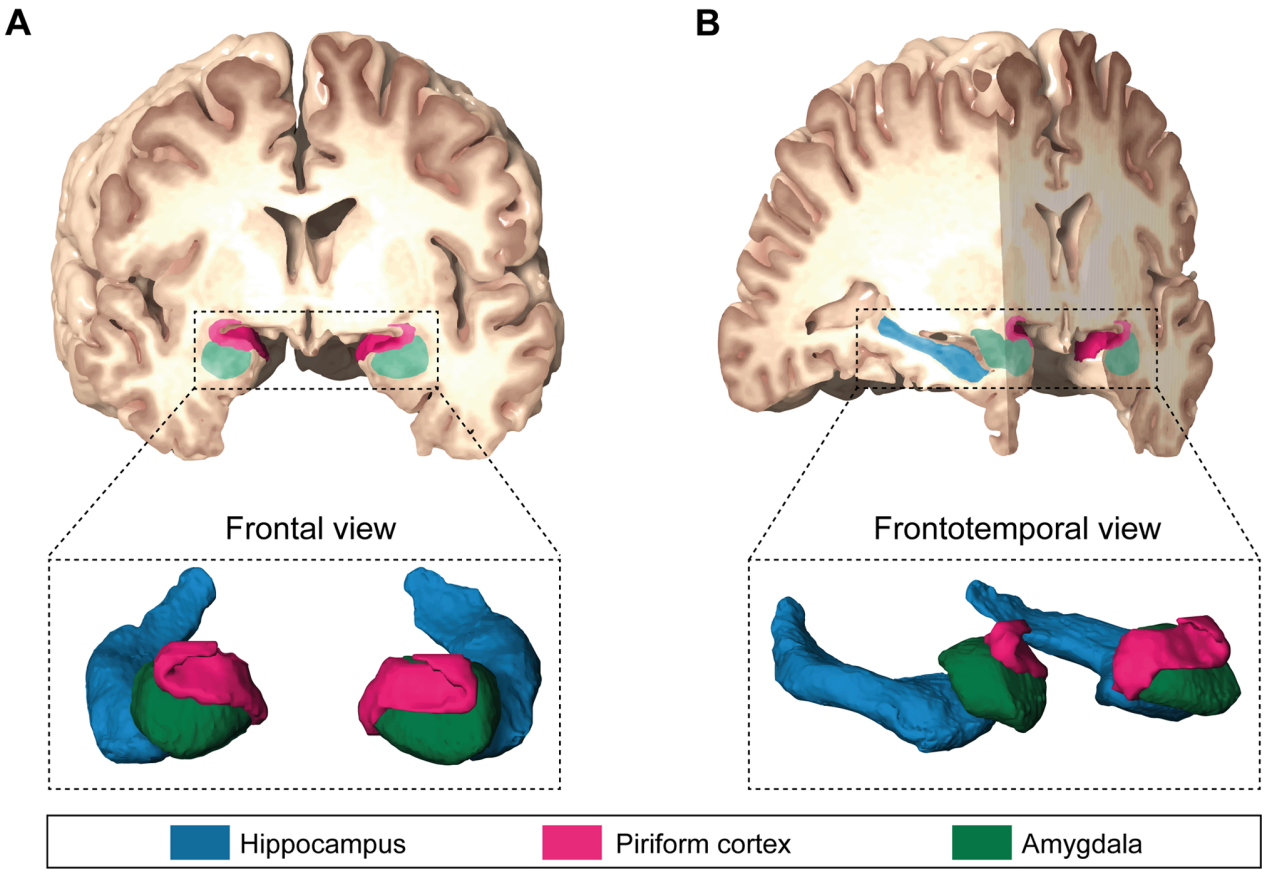

Figure 2. Illustration of anatomical topography of mesiotemporal target structures in tsSAHE. tsSAHE, transsylvian selective amygdalohippocampectomy.

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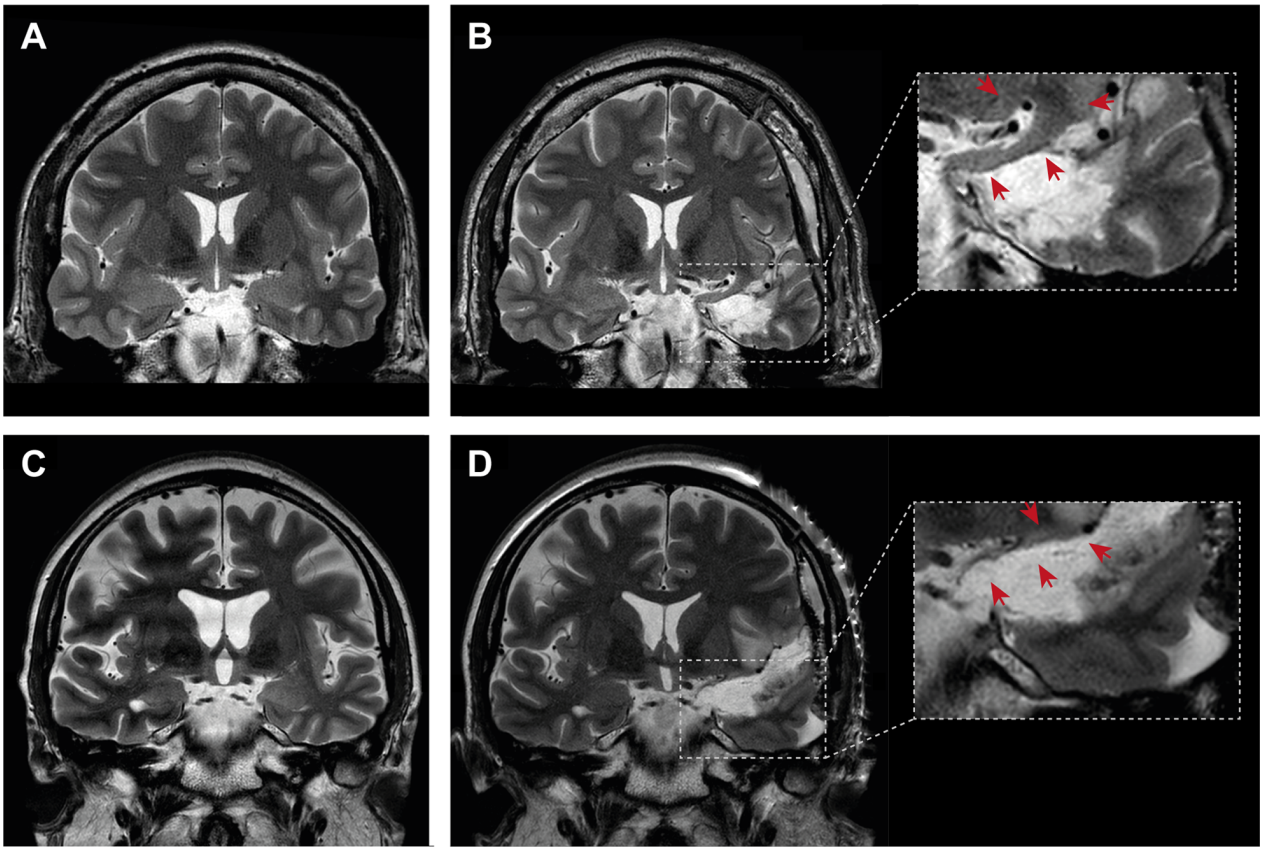

Figure 3. Representative coronal T2-weighted MRI of tsSAHE with differing extent of piriform cortex resection. Pre-(A) and postoperative (B) images show profound residual volume of piriform cortex compared to a high extent of piriform cortex resection for respective images (C) and (D). Red arrows in the enlarged sections point at postoperative residual piriform cortices.

Table 3. Preoperative volumetric analysis of tsSAHE target structures according to seizure outcome.

	Volumes[1] (median (IQR))		
	ILAE class 1 (n = 59)	ILAE class 2–6 (n = 23)	P Value
Piriform cortex	0.39 (0.31–0.47)	0.40 (0.32–0.51)	0.7
Hippocampus	1.81 (1.54–2.36)	1.99 (1.71–2.50)	0.2
Amygdala	1.05 (0.88–1.24)	1.12 (0.93–1.41)	0.2

ILAE, International League Against Epilepsy; SD, standard deviation; tsSAHE, transsylvian selective amygdalo-hippocampectomy.
[1]Values indicated in ml.

Table 4. Extent of piriform cortex resection dependent on postoperative histological analysis.

	Proportion of piriform cortex resection[1] (median (IQR))		
	ILAE class 1 (n = 59)	ILAE class 2–6 (n = 23)	P Value
Hippocampal sclerosis	50 (42–61)	13 (12–18)	0.0002
Hippocampal gliosis	62 (43–85)	13 (7–20)	0.0012

ILAE, International League Against Epilepsy; IQR, interquartile range; tsSAHE, transsylvian selective amygdalo-hippocampectomy.
[1]Values indicated in %.

Confrontation naming improved after right tsSAHE and deteriorated after left tsSAHE. Phonemic fluency improved from pre- to postoperative assessment. The pre- and postoperative memory profile for patients with a smaller resection extent (less than median) and for patients with a larger resection extent (more than median) is displayed in Figure 6.

According to regression analyses, baseline performance, surgical side, seizure outcome and extent of piriform cortex resection have proven to be good predictors of postoperative cognitive outcome explaining between 29% (attention) and 56% (language) of the variance (Table 7). Baseline performance is the best predictor for attention,

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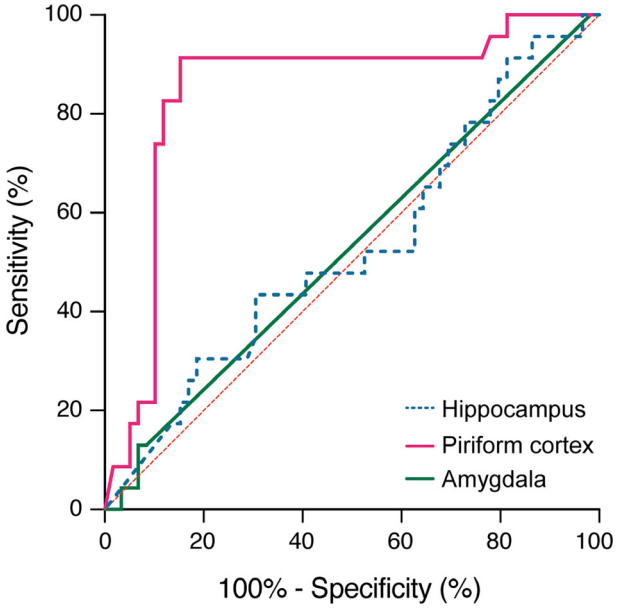

Figure 4. Illustration of the association between piriform cortex, amygdala and hippocampus as target structures and seizure outcome in tsSAHE. Receiver operating characteristic curves (ROC) reveals the piriform cortex as the only target volume in tsSAHE to significantly discriminate between favorable and unfavorable seizure outcome. tsSAHE, transsylvian selective amygdalo-hippocampectomy.

Table 5. Seizure outcome dependent on the proportion of temporal piriform cortex resection.

	Number of patients		
	ILAE class 1	ILAE class 2–6	Total
EOR < 26%	9	21	30
EOR ≥ 26%	50	2	52
Total	59	23	82

EOR, extent of resection; ILAE, International League Against Epilepsy.
$P < 0.0001$.

Table 6. New postoperative neurological deficits dependent on the extent of piriform cortex resection[1].

	EOR < 26% (n = 30)	EOR ≥ 26% (n = 52)	P Value
New transient motor deficit	0 (0)	1 (2)[2]	1.0
New transient aphasia	1 (3)	0 (0)	0.4
New visual deficit	17 (61)	33 (63)	0.6
quadrantanopsia	13 (43)	27 (52)	0.5
homonymous hemianopsia	4 (13)	6 (12)	1.0

EOR, extent of resection.
[1]Values represent number of patients unless otherwise indicated (%).
[2]transient hemiparesis.

memory and language. In addition, side of surgery also predicted the outcome of verbal memory. According to the β weights the extent of piriform cortex resection contributed little to the regression models.

Discussion

In this study, we presented results from one of the largest cohorts comparing preoperative and postoperative volumetric data on MRI exclusively in candidates suffering from mTLE and surgically treated using tsSAHE.[32] We showed that extended resection of piriform cortex profoundly predicts seizure freedom following tsSAHE in patients with mTLE.

In 1990 Siegel et al. provided the first study on 30 patients with TLE, who had undergone tsSAHE with the focus on the relationship between seizure outcome and volumetrically estimated amount of removal within temporomesial structures.[33] They found that smaller resection in the cranio-caudal axis was associated with a poorer seizure outcome. Furthermore, the authors concluded that incomplete resection of the parahippocampal gyrus and the subiculum results in less favorable seizure outcome.

Recently published data by Galovic et al. comparing the association between volumetrically calculated extent of resection in the course of ATL and seizure outcome in individuals suffering from TLE[14] suggest that seizure freedom was achieved in 60% of patients if at least 50% of piriform cortex had been resected. In contrast to the findings by Siegel et al., the analysis performed by Galovic et al. revealed no significant difference in the amount of resection of entorhinal cortex between seizure free patients and patients with continued seizures after ATL. The results of our series are in line with the findings made by Galovic and coworkers. However, in contrast with these findings, in the current series a removal of at least 26.4% of the temporal part of piriform cortex was required to achieve seizure freedom in 96% of patients following tsSAHE.

In their study, Galovic and coworkers used outlining methods for manual segmentation largely based on the publication reported by Conçalves Pereira et al. The authors reported, that particularly in the frontal lobe, the outlining of borders of piriform cortex could be difficult. Therefore, to obtain more reliable estimates of piriform cortex volumes, they focused on the temporal extention of the piriform cortex. It is important to recognize, that in the study reported by Conçalves Pereira et al., the MR images were acquired on 1.5 T MR scanner with a slice thickness of 1.5–2.0 mm. In contrast, we performed entire pre- and postoperative MR scans on a 3.0 T MR scanner with a slice thickness of 1.0 mm. A similar scan protocol was applied in the study by Galovic et al. According to

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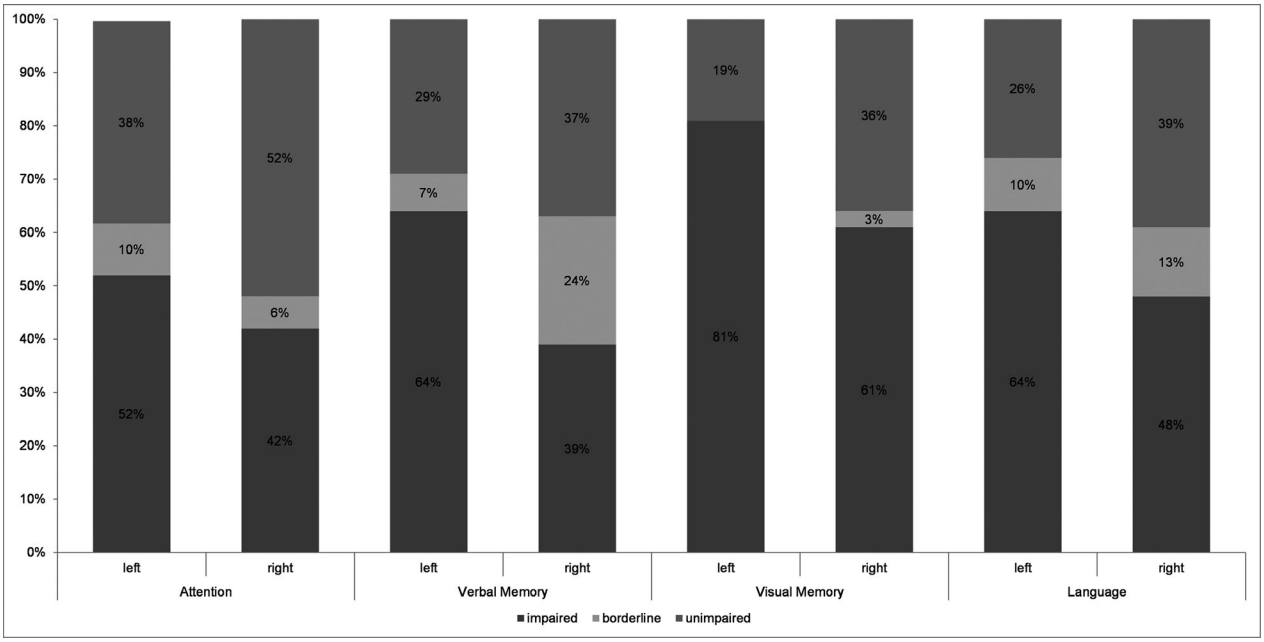

Figure 5. Histogram demonstrates the results of the preoperative cognitive performance. The results from each cognitive domain summarized and classified into a five-point scale ranging from severely impaired to above average. The values represent cumulative percentage of performance categories in each tested cognitive domain according to the side of the TLE.

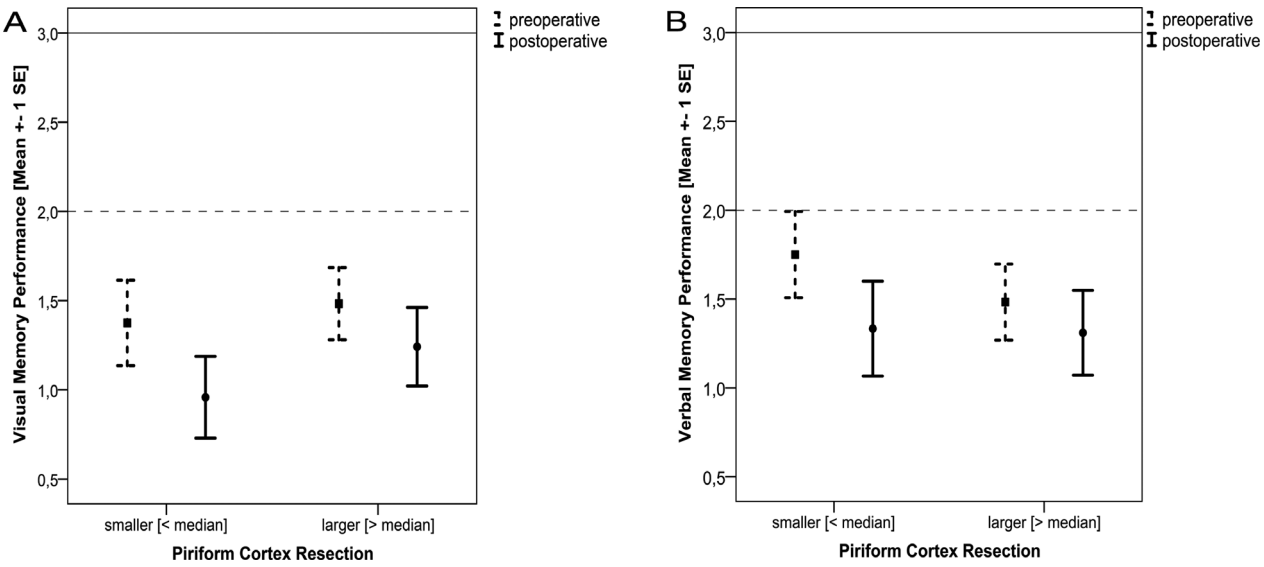

Figure 6. Performance in visual (A) and verbal memory (B) before and after surgery according to the extent of piriform cortex resection.

the work reported by Vaughan and Jackson, in our study we extended the outlining of the frontal part of the piriform cortex from the endorhinal sulcus to olfactorial tubercle limiting it by the lateral olfactorial tract. In contrast to our study, Galovic et al. included only 50–75% of this distance in the volumetric analysis. In light of this aspect, the segmentation and volumetry of the frontal part of the piriform cortex was performed slightly more extensively in our study, compared to the method used by Galovic et al.

The outlining of the temporal part of piriform cortex was performed in the same fashion as reported by Galovic et al. Of note is that the frontal part of the piriform cortex was not included for volumetric analysis in the

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Table 7. Results of regression analysis for prediction of postoperative neurocognitive outcome.

	$R^2_{adj.}$	*F*	*P*	Variable	*β*	*t*	*P*
Attention	0.29	7.07	<0.001	Baseline	0.50	4.39	<0.001
				Seizure freedom	0.11	0.29	0.77
				Surgical side	0.04	0.15	0.88
				Piriform cortex	0.01	1.94	0.06
Verbal memory	0.34	9.16	<0.001	Baseline	0.54	4.76	<0.001
				Surgical side	0.61	2.30	<0.05
				Seizure Freedom	−0.57	−1.49	0.14
				Piriform cortex	−0.01	−1.55	0.13
Visual Memory	0.51	14.85	<0.001	Baseline	0.73	7.57	<0.001
				Surgical side	−0.09	−0.43	0.67
				Seizure Freedom	0.01	0.02	0.98
				Piriform cortex	0.00	0.86	0.39
Language	0.56	17.83	<0.001	Baseline	0.60	7.10	<0.001
				Surgical side	0.33	1.96	0.06
				Seizure Freedom	−0.24	−1.04	0.30
				Piriform cortex	0.00	0.47	0.64

present series. This difference should be taken into account, when interpreting both these studies in regard of the required proportion of piriform cortex resection. However, the results of our study strongly support the evidence, that a more extensive resection of the temporal part of the piriform cortex is associated with a significantly higher chance to become seizure free after tsSAHE in mTLE.

Additionally, the abovementioned discrepancy in required amount of piriform cortex resection may be caused by the fact that the population in our series consists of candidates suffering from mTLE who represent a more homogeneous group of patients with a highly assumed seizure focus within the mesiotemporal structures. Therefore, extended resection of piriform cortex during tsSAHE in patients with mTLE might be more successful in removing the seizure foci compared to piriform cortex resection during ATL in patients with TLE.

Interestingly, a recent study of Wu et al. on laser interstitial thermal therapy (LITT) as a minimally invasive treatment for mesial temporal lobe epilepsy yielded superior seizure outcomes for ablation of more mesial and anterior located target structures than in the case of dorso-lateral tracts within the hippocampal body.[34] Notwithstanding reported data do not allow for distinct topographical analysis of piriform cortex volumes and therefore might partly explain worse overall seizure freedom rates compared to our series, these results may support the findings of strictly mesiotemporal located target volumes to significantly entail postoperative superior favorable seizure outcome rates.

In regard to neuropsychological outcome, the results in the current series are in line with previously reported studies.[19,35] Resection of piriform cortex was safe and there was no impact on neurocognitive performance in regard of extent of resection. Although the role of piriform cortex in initiation and propagation of seizures is well described in animal models, there is little evidence regarding the exact function of piriform cortex in humans.[36–38] Therefore, further research is required to correlate the extent of resection with both seizure as well as neurocognitive outcome.

Of note is that the resection of piriform cortex using the transsylvian approach for SAHE is more challenging for the surgeon due to several aspects. One of the main limitations is a narrow operative space and restricted visualization of the temporal part of the piriform cortex. There is often a need for additional dissection of the brain tissue or even retraction in order to attempt a better visualization of the operating field. These maneuvers may be risky as parts of basal ganglia, M_1 segment of the middle cerebral artery and other vessels traversing the anterior perforated substance could be affected. Despite this potential risk, our data strongly indicate that an effort to access and remove the temporal part of the piriform cortex should be made by the neurosurgeon during tsSAHE.

With regard to an extension of piriform cortex resection to significantly improve favorable seizure outcome, this study supports the hypothesis that the piriform cortex may profoundly be involved in the genesis of seizures in the temporal lobe. In addition to the evidence that the piriform cortex is a part of an epileptogenic network in rodent models,[39–44] there are several studies that provide evidence that piriform cortex might also be involved in the genesis and spreading of epileptic seizures in humans.[24,45,46] However, when analyzing the reasons

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associated with failure of epilepsy surgery in mTLE, the role of piriform cortex and its extent of resection during the surgical procedure were underestimated in the literature.

One of the strengths of the present series is the homogeneous study population consisting of candidates with mTLE. Another strength is that the surgical procedure (tsSAHE) was performed in a highly standardized fashion 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, data acquisition was prospective. Patients were not randomized, but treated according to the decision of the interdisciplinary epilepsy surgery conference. Beyond doubt this study has several limitations. Due to its retrospective design, our study suffers from the risk of bias inherent to retrospective cohort analysis. Additionally, the present data represent a single-center experience. 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.

This study provides strong evidence for temporal piriform cortex as a novel key target structure in tsSAHE surgery. With regard to a profound increase in the rate of postoperative seizure freedom following extended piriform cortex resection, the authors suggest a renewed and enhanced surgery regime. The resection strategy during tsSAHE should take into account the residual temporal piriform cortex volume as a pivotal predictor for postoperative seizure outcome in mTLE.

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Author Contributions

VB and MS conceived the study, statistical analysis, and interpretation of the data. VB and MS contributed equally to this work by designing and writing the draft of the manuscript. HV supervised the whole process of analysis and writing of the manuscript. All co-authors made substantial contribution to the conception of the study, the treatment and recruitment of the patients and data collection. EG and PS revised the manuscript critically. All co-authors approved the final version. RF supervised the statistical analysis and its interpretation. A-LP and MS performed volumetric analysis after training and under continuous supervision provided by VCK and LS. The neuropsychological assessment was performed and analyzed by JT and CH. The collection of patient data was performed by GA and II. CEE and RS are responsible for the presurgical evaluation. The surgical procedures were performed by HV, VB and MH.

Conflicts of Interest

The authors report no disclosures relevant to the manuscript.

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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. Table demonstrates the results of the volumetric analysis of tsSAHE target volumes in left-sided mTLE.
Table S2. Table demonstrates the results of the volumetric analysis of tsSAHE target volumes in right-sided mTLE.

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3.3 Borger V, Hamed M, Bahna M, Rácz A, Ilic I, Potthoff AL, Baumgartner T, Rüber T, Becker A, Radbruch A, Mormann F, Surges R, Vatter H, Schneider M. Temporal lobe epilepsy surgery: Piriform cortex Resection impacts seizure control in the long-term. *Ann Clin Transl Neurol.* 2022 Jul 1. doi: 10.1002/acn3.51620. Online ahead of print.

Zielsetzung der Arbeit – In der vorangehenden Arbeit konnte erstmalig der starke Zusammenhang zwischen Resektionsausmaß des piriformen Cortex und der postoperativen Anfallsfreiheit bei den mittels tsSAHE behandelten Patienten mit pharmakoresistenten TLE im kurz- bis mittelfristigen Verlauf von 12 Monaten nach stattgehabten OP gezeigt werden. Über den Einfluss des Resektionsausmaßes des piriformen Cortex auf die Anfallsfreiheit im Langzeitverlauf nach einer tsSAHE existieren keine Daten in der aktuellen Weltliteratur. Das Ziel dieser nun folgenden Arbeit war, diesen Einfluss zu analysieren.
Methoden und Ergebnisse – In diese retrospektive Analyse wurden insgesamt 64 Patienten mit pharmakoresistenten TLE eingeschlossen, welche zwischen 2012 und 2017 in unserem Epilepsie-Zentrum mittels einer tsSAHE epilepsiechirurgisch behandelt wurden. Der post-operative Beobachtungszeitraum betrug mindestens zwei Jahre. Der primäre end-point war der Einfluss des Resektionsausmaßes des piriformen Cortex auf das Langzeit-Anfallsoutcome. Das Resektionsausmaß wurde anhand der manuellen Volumetrie in der prä-und postoperativen MRT-Bildgebung ermittelt. Als sekundärer end-point wurde die Häufigkeit der Reduktion oder der vollständigen Absetzung der antikonvulsiven Medikation im Langzeitverlauf abhängig von den Faktoren „Geschlecht“, „Seite der OP“, „Nachweis einer Läsion im MRT“, „histologischer Nachweis einer Hippocampus-Sklerose“ und „Resektionsausmaß des piriformen Cortex“ mittels logistischer Regressionsanalyse ermittelt. Die Untersuchungen zeigen mit einem Median von 46% eine signifikant größere Proportion des resezierten piriformen Cortex bei Patienten mit Anfallsfreiheit im Langzeitverlauf verglichen zu den nicht anfallsfreien Patienten mit 16%, während sich der Resektionsanteil von Amygdala und Hippokampus nicht signifikant zwischen den beiden Patientengruppen unterschieden (siehe Figure 1, p. 4; Table 2 p. 3; Borger et al., ACTN 2022). Wenn man nun die Patienten in Abhängigkeit des Cut-off-Wertes des Resektionsausmaßes des piriformen Cortex von 27% betrachtet, so haben die Patienten mit einem Resektionsausmaß ≥ 27% im Langzeitverlauf eine signifikant

höhere Wahrscheinlichkeit für eine postoperative Anfallsfreiheit (siehe Figure 2, p. 4; Borger et al., ACTN 2022). Die multivariate Analyse zeigte, dass das Resektionsausmaß des piriformen Cortex von mindestens 27% der einzige signifikante und unabhängige Prädiktor für die Reduktion oder das Absetzen der antikonvulsiven Medikation im Langzeitverlauf war (p. 4; Borger et al., ACTN 2022).

Schlussfolgerungen – in dieser Arbeit konnte erstmalig der starke Einfluss des Resektionsausmaßes des piriformen Cortex auf die Anfallsfreiheit der mittels tsSAHE epilepsiechirurgisch behandelten Patienten nun auch im Langzeitverlauf gezeigt werden. Damit konnte die Bedeutung einer sorgfältigen Resektion dieser Struktur bei resektiven Temporallappen-Eingriffen nochmals bekräftigt werden.

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RESEARCH ARTICLE

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

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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 transsylvian 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

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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 ± 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,

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Table 1. Baseline patient characteristics stratified according to the long-term seizure outcome[1].

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

Table 2. Extent of temporal piriform cortex resection predicts postoperative seizure outcome in the long-term[1].

	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.
[1]Values indicated in %.

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 ≥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

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Table 3. Overview of preoperative volumes of tsSAHE target structures[1].

	Volumes[1] [median (IQR)]		
	ILAE class 1 (n = 59)	ILAE class 2–6 (n = 23)	p-value
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.
[1]Values indicated in mL.

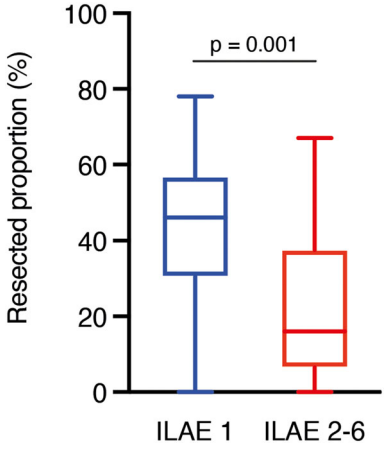

Figure 1. Box Whisker plots depict long-term seizure outcome dependent on the proportion of temporal piriform cortex resection. ILAE, International League Against epilepsy.

comparison of these two groups revealed that in patients with resection of ≥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 ≥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 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

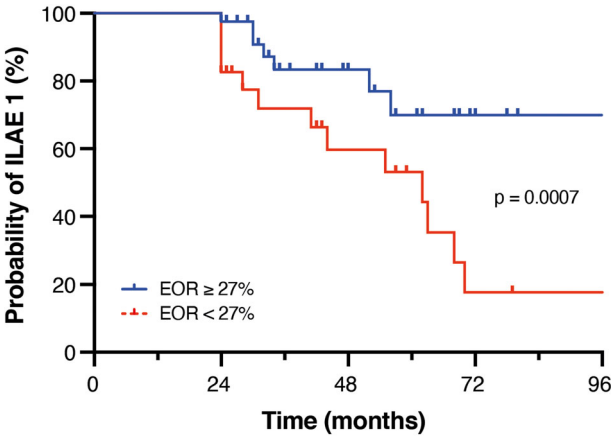

Figure 2. Kaplan–Meier analysis for long-term seizure outcome stratified for the indicated extent of piriform cortex resection. EOR, extent of resection in %; ILAE, International League Against epilepsy.

Table 4. Long-term seizure outcome dependent on the proportion of temporal piriform cortex resection[1].

	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.
[1]Values represent number of patients (%).

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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 predominantely 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 level[18] 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 cofounding 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*.

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3.4 Bahna M, Hamed M, Ilic I, Salemdawod A, Schneider M, Rácz A, Baumgartner T, Güresir E, Eichhorn L, Lehmann F, Schuss P, Surges R, Vatter H, **Borger V**. The necessity for routine intensive care unit admission following elective craniotomy for epilepsy surgery: a retrospective single-center observational study. *J Neurosurg.* 2022:1-7.

Zielsetzung der Arbeit – die aktuell in den meisten neurochirurgischen Zentren am häufigsten verbreitete Praxis sieht vor, dass Patienten nach kraniellen Eingriffen über eine offene Kraniotomie direkt post-operativ auf einer (Neuro-) Intensivstation überwacht werden. Insbesondere vor dem Hintergrund nicht zuletzt auch durch die COVID-19 Pandemie bedingten Verknappung der ICU-Ressourcen kann diese Praxis durchaus hinterfragt werden. Auch existieren bis dato keine verbindlichen Leitlinien. In dieser Arbeit haben wir untersucht, inwieweit bei epilepsiechirurgischen Patienten nach einer Kraniotomie eine intensivmedizinische Überwachung notwendig ist und welche perioperativen Risikofaktoren die Notwendigkeit einer solchen Überwachung vorhersagen können.
Methoden und Ergebnisse – In dieser retrospektiven Arbeit haben wir die intensivmedizinische Monitoring-Daten von insgesamt 266 Erwachsenen, welche einem elektiven epilepsiechirurgischen Eingriff über eine Kraniotomnie im Zeitraum zwischen 2012 und 2019 unterzogen worden sind, analysiert. Als ICU kritische Events wurden definiert: Verschlechterung des GCS-Scores um mehr als zwei Punkte, umgehende Verbringung in den OP wegen einer relevanten postoperativen Nachblutung, Notwendigkeit einer Reintubation, Stroke, Herzinfarkt, intravenöse Applikation einer hämodynamisch wirksamen Medikation, Notwendigkeit der kontinuierlichen i.v. – Applikation von Insulin, ultra frühe post-op. Anfälle, CPR, Tod. Eine Übersicht über die Kenncharakteristika der untersuchten Population zeigt Table 1, p. 3, (Bahna et al., JNS 2022); die Verteilung über die Art der durchgeführten Eingriffe zeigt FIG. 1, p. 3, (Bahna et al., JNS 2022). Die Analyse zeigte, das insgesamt 13 Patienten (4.9%) im frühen post-op. Verlauf ein Ereignis hatten, welches das Setting einer ICU benötigte (Table 2, p. 4, Bahna et al., JNS 2022). Die überwiegende Mehrheit dieser Ereignisse trat innerhalb der ersten 24 Std. post-op. auf. In der multivariaten Analyse konnten DM und intraoperativer Blutverlust ≥ 325ml als unabhängige Prädiktoren für die Notwendigkeit einer post-operativen ICU-Überwachung identifiziert werden (Table 3, p. 5, Bahna et al., JNS 2022).

Schlussfolgerung – die Daten der aktuellen Studie zeigen, dass die Inzidenz der klinischen Ereignisse im frühen post-operativen Verlauf, welche das Setting und die Ressorcen eine ICU benötigen, bei epilepsiechirurgischen Patienten ingesamt relativ niedrig ist. Auf der anderen Seite ist es möglich, prä- und perioperativ Faktoren zu idenzifizieren, welche eine solche Notwendigkeit vorherzusagen vermögen. Auf der Basis dieser Ergebnisse könnten eine weiterführende externe Validierung und Evaluation im prospektiven Setting die Grundlage für eine allgemeingültige Empfehlung bilden.

JNS

CLINICAL ARTICLE

The necessity for routine intensive care unit admission following elective craniotomy for epilepsy surgery: a retrospective single-center observational study

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OBJECTIVE Traditionally, patients who underwent elective craniotomy for epilepsy surgery are monitored postoperatively in an intensive care unit (ICU) overnight in order to sufficiently respond to potential early postoperative complications. In the present study, the authors investigated the frequency of early postoperative events that entailed ICU monitoring in patients who had undergone elective craniotomy for epilepsy surgery. In a second step, they aimed at identifying pre- and intraoperative risk factors for the development of unfavorable events to distinguish those patients with the need for postoperative ICU monitoring at the earliest possible stage.

METHODS The authors performed a retrospective observational cohort study assessing patients with medically intractable epilepsy (n = 266) who had undergone elective craniotomy for epilepsy surgery between 2012 and 2019 at a tertiary care epilepsy center, excluding those patients who had undergone invasive diagnostic approaches and functional hemispherectomy. Postoperative complications were defined as any unfavorable postoperative surgical and/or anesthesiological event that required further ICU therapy within 48 hours following surgery. A multivariate analysis was performed to reveal preoperatively identifiable risk factors for postoperative adverse events requiring an ICU setting.

RESULTS Thirteen (4.9%) of 266 patients developed early postoperative adverse events that required further postoperative ICU care. The most prevalent event was a return to the operating room because of relevant postoperative intracranial hematoma (5 of 266 patients). Multivariate analysis revealed intraoperative blood loss ≥ 325 ml (OR 6.2, p = 0.012) and diabetes mellitus (OR 9.2, p = 0.029) as risk factors for unfavorable postoperative events requiring ICU therapy.

CONCLUSIONS The present study revealed routinely collectable risk factors that would allow the identification of patients with an elevated risk of postsurgical complications requiring a postoperative ICU stay following epilepsy surgery. These findings may offer guidance for a stepdown unit admission policy following epilepsy surgical interventions after an external validation of the results.

https://thejns.org/doi/abs/10.3171/2021.12.JNS211799

KEYWORDS elective epilepsy surgery; medically intractable epilepsy; intensive care; healthcare resources

Traditionally, patients who undergo an intracranial neurosurgical approach are admitted to the intensive care unit (ICU) postoperatively, as close monitoring of these patients is considered to be important to identify postoperative complications requiring quick medical or neurosurgical intervention. On the other hand, many studies have shown that only a limited number of patients undergoing elective neurosurgical approaches may require intensive care interventions.[1–3] Furthermore, an appropriate and rapid postoperative transfer of patients to the normal ward seems to be advantageous for patients in terms of accelerating postoperative mobilization and reducing hospital length of stay and, consequently, the risk of hospital-related complications.[4,5] In addition, current limited healthcare resources, most notably ICU capacity and increased costs, demand wise management of this sector.[6,7] Along these lines, many studies have reported significant cost savings through limiting routine ICU ad-

ABBREVIATIONS ASA = American Society of Anesthesiologists; AUC = area under the curve; BP = blood pressure; DM = diabetes mellitus; GCS = Glasgow Coma Scale; ICU = intensive care unit; ROC = receiver operating characteristic.

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mission and implementing standard operating protocols to select those patients who may need ICU interventions postoperatively without threatening patient care.[3–8] However, there is as yet no standardized or consistent policy among neurosurgical departments for selecting the patients with an increased likelihood of developing adverse events requiring an ICU setting after elective craniotomy. In the majority of neurosurgical centers, this decision is based on available resources and individual interdisciplinary evaluation between anesthetists and the neurosurgical team after considering the patient's disease severity and accompanying conditions.

Neurosurgical epilepsy treatment represents a specific kind of elective supratentorial brain surgery involving slightly different patient characteristics, histological diagnoses, and morbidity. Furthermore, developments in epilepsy surgery techniques and neurological monitoring in recent decades have improved the safety of these procedures.[9,10]

We reviewed our institutional database to determine the safety of elective craniotomies for epilepsy surgery and to identify possible pre- and intraoperative risk factors that could predict the necessity for postoperative ICU admission among these patients.

Methods

Patients

All adult patients with medically intractable epilepsy who had undergone elective neurosurgical epilepsy treatment at our institution between 2012 and 2019 were eligible for the study. In order to reduce the heterogeneity of our cohort, the exclusion criteria were as follows: 1) patients who had undergone invasive diagnostic approaches, and 2) patients who had undergone functional hemispherectomy. The medical records of included patients were retrospectively examined and analyzed for this study. Each patient's surgery had been performed on the basis of comprehensive preoperative evaluation, including neurological examination, seizure semiology, long-term video-EEG monitoring, MRI, and invasive diagnostics if necessary. Furthermore, the indication for surgical treatment of these patients with medically intractable epilepsy was given at the interdisciplinary epilepsy surgery conference for every candidate.

We collected and entered into a computerized database (SPSS version 25, IBM Corp.) patient clinical information including age at surgery, sex, type of surgical approach, type of epilepsy (temporal lobe epilepsy vs extratemporal lobe epilepsy), age at epilepsy onset, epilepsy duration, functional status (American Society of Anesthesiologists [ASA] class), relevant accompanying comorbidities and conditions (such as diabetes mellitus [DM], coronary heart disease, hypertension, and obesity), intraoperative duration, estimated blood loss, use of blood transfusions, and surgical abnormalities as well as postoperative adverse events.

Postoperative Standards

After neurosurgical epilepsy treatment, patients are routinely moved to the recovery ward until being discharged to the ICU. During the stay in the recovery ward (1:1:1 patient/anesthesiologist/nurse ratio), the patients are monitored (oxygen saturation, heart rate, noninvasive blood pressure [BP]) and routinely checked for pupillary function, global motor function, and consciousness status.

In the interdisciplinary neurointensive care unit (either 1:3 or 1:2 patient/nurse ratio), the patients are further continuously monitored (oxygen saturation, heart rate, noninvasive BP, and routine blood gas analysis) and neurological examinations are performed by trained nurses on an hourly basis. The ICU course of each patient (including vital parameters, neurological examinations, physician orders, medication records, and event records) was collected and analyzed from either electronic or written inpatient medical records. In addition, all patients undergo MRI within the first 3 days postoperatively in order to determine complete resection of the target structure, in line with previous studies.[11,12] However, postoperative CT scanning is not routinely implemented in an uneventful postoperative course. In the case of a new neurological deficit, immediate CT scanning or even MRI is performed.[13,14]

Identification of Adverse Events

Critical events that required an ICU setting and/or interventions, which are typically not possible on a general neurosurgical ward or stepdown ward, were defined as a Glasgow Coma Scale (GCS) score decrease of more than 2 points, a need to return to the operating room because of clinically relevant postoperative hematoma, a need for reintubation, ischemic stroke, myocardial infarction, the use of intravenous hemodynamic medication, the use of an insulin drip, an ultra-early postoperative seizure, a need for cardiopulmonary resuscitation, and death within the first 48 hours postoperatively.

Statistical Analysis

To interpret the results of this study, data analysis was performed using SPSS Statistics (version 25, IBM Corp.). Fisher's exact test was applied to compare unpaired categorial and binary variables for the two groups, that is, the group needing the ICU and the group that did not. For continuous variables, the Mann-Whitney U-test was performed, as data were mostly not normally distributed (intraoperative duration, estimated blood loss, age at surgery, age at epilepsy onset, and epilepsy duration). The area under the curve (AUC), specificity, and sensitivity, as well as the cutoffs for the significant continuous variables in the Mann-Whitney U-test, were determined using the receiver operating characteristic (ROC) curve to explore the power of the resulting model. Finally, a multivariate analysis was performed to find independent predictors of the need for postoperative ICU admission (using a binary logistic regression analysis), including the variables with significant p values in the univariate analysis. The results of the analysis were presented as odds ratios with 95% confidential intervals. Statistical significance was defined as $p < 0.05$.

Results

Patient Characteristics

Overall, 266 patients (142 [53.4%] male, 124 [46.6%]

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TABLE 1. Summary of characteristics of 266 patients who underwent elective craniotomy for epilepsy surgery

Variable	Value
Sex	
M	142 (53.4)
F	124 (46.6)
Mean age at surgery in yrs	37.9 ± 13.4
ASA class	
I	25 (9.4)
II	225 (84.6)
III	16 (6.0)
ICU admission over prior 12 mos	3 (1.1)
BMI in kg/m^2	
<18.5	28 (10.5)
18.5–25	117 (44.0)
25.1–30	74 (27.8)
>30	47 (17.7)
DM	6 (2.3)
Hypertension	33 (12.4)
Mean length of surgery in mins	243 ± 67
Mean intraop blood loss in ml	292 ± 278
Need for intraop blood products	18 (6.8)
Intraop bleeding abnormalities & vulnerable cortex tissue	21 (7.9)

Values are expressed as number (%) or as mean ± standard deviation.

female) with medically intractable epilepsy were surgically treated at our institution between October 2012 and December 2019. The mean age at surgery was 37.9 ± 13.4 years (mean ± standard deviation), and the mean epilepsy duration was 20.5 years. In total, 47 (17.7%) of the 266 patients had a BMI of more than 30 kg/m^2. An ASA class of III was found in 16 (6.0%) of 266 patients. Twenty-five (9.4%) of the 266 patients had undergone a craniotomy of some kind in the past, and 3 (1.1%) of the 266 patients had been admitted to an ICU of some kind in the 12 months prior to our surgery. Further details regarding the baseline patient characteristics are shown in Table 1.

According to intraoperative course documentation, the mean surgery duration was 243 ± 67 minutes and the mean estimated blood loss was 292 ± 278 ml. The operating surgeons described intraoperative bleeding abnormalities in 21 cases (7.9%) as well as vulnerable cortex tissue in their operative reports. A total of 18 patients (6.8%) required transfusion of blood products intraoperatively (Table 1).

Among the 266 patients, 116 (43.6%) underwent transsylvian selective amygdalohippocampectomy. A temporal lobe resection was performed in 34 patients (12.8%), temporal lesionectomy with amygdalohippocampectomy in 22 (8.3%) and without amygdalohippocampectomy in 36 (13.5%), respectively. An extratemporal lesionectomy was performed in 58 patients (21.8%; Fig. 1).

Occurrence of Early Postoperative Adverse Events

Among the entire study population, a total of 13 patients (4.9%) experienced early postoperative adverse events that necessitated an ICU setting. The most common adverse event (5 patients [1.9%]) was the need to return to the operating room because of a clinically relevant postoperative hematoma. Five patients (1.9%) had a significant GCS score decrease of 2 or more points. Intravenous hemodynamic medication was required in 4 patients (1.5%) because of postoperative short-term volume depletion. An ultra-early postoperative focal to bilateral tonic-clonic seizure was observed in 4 patients (1.5%). Clinically relevant strokes within the first 48 hours occurred postoperatively in 2 patients (0.8%), and 2 patients (0.8%) required an in-

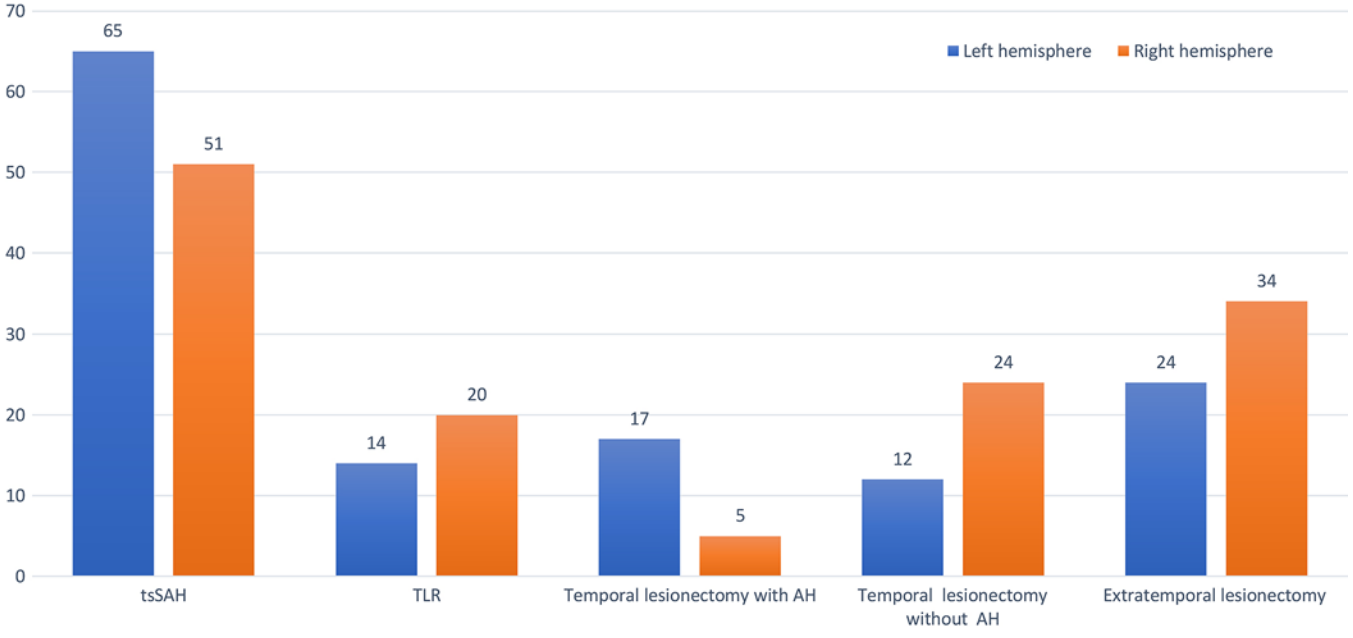

FIG. 1. Diagram showing procedure type and the site at which the procedure was performed. AH = amygdalohippocampectomy; TLR = temporal lobe resection; tsSAH = transsylvian selective amygdalohippocampectomy. Figure is available in color online only.

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TABLE 2. Postoperative adverse events requiring ICU care

Measured Outcome	No. of Cases (%)
IV insulin drip	2 (0.8)
IV hemodynamic medication	4 (1.5)
GCS score decrease ≥2 points	5 (1.9)
Ultra-early postop seizure	4 (1.5)
Ischemic stroke	2 (0.8)
Return to OR because of clinically relevant postop hematoma	5 (1.9)

IV = intravenous; OR = operating room.
Some patients experienced more than one significant event necessitating ICU care; therefore, the sum of all significant events is more than the number of the patients needing ICU care.

travenous insulin drip because of severe hyperglycemia (Table 2).

Among the whole cohort, none of the patients died in the hospital, none of them developed myocardial infarction, and none needed cardiopulmonary resuscitation or to be reintubated because of respiratory insufficiency.

Our analysis revealed that 12 (92.3%) of the 13 patients requiring a postoperative ICU setting developed the adverse event within the first 24 hours after surgery. There was only 1 patient (7.7%) out of 13 with a clinically relevant epidural hematoma who required an operative revision more than 24 hours after the initial surgery. For more details, see Fig. 2.

Patient-Related Factors Influencing Postoperative Adverse Events

We found a strong association between early postoperative complications and the patient's comorbidity burden: patients with DM experienced early postoperative adverse events significantly more often than the patients without DM (33.3% vs 4.2%, p = 0.03). In addition, patients with a BMI of more than 30 kg/m^2 were affected by early postoperative unfavorable events significantly more often than those with a BMI of 30 kg/m^2 or less (12.8% vs 3.2%, p = 0.014).

Surgery-Related Factors Influencing Postoperative Adverse Events

In terms of the intraoperative course, patients demonstrated a significant increase in the incidence of postoperative adverse events when the surgeon had reported an intraoperative increased bleeding tendency and vulnerable cortex tissue (p = 0.013). Furthermore, ROC analysis revealed a blood loss cutoff value of 325 ml in terms of the predictability of postoperative adverse events (AUC 0.766, p = 0.001, sensitivity 76.9%, specificity 77.7%). Subsequently, intraoperative blood loss ≥ 325 ml was significantly associated with the prevalence of postoperative adverse events (p < 0.001).

Multivariate Analysis

In order to preoperatively identify patients at high risk for early postoperative complications and therefore the need for postoperative ICU care, we additionally performed a multivariate logistic regression analysis. We found that DM (p = 0.029, OR 9.2, 95% CI 1.26–67.5) as well as intraoperative blood loss ≥ 325 ml (p = 0.012, OR 6.2, 95% CI 1.5–26) was a significant and independent predictor for an increased incidence of postoperative adverse events (Table 3).

Temporal Lobe Epilepsy and Postoperative Adverse Events

In a second step and in an effort to achieve more homogeneity in our cohort, we performed additional statistical analyses of the patients with temporal lobe epilepsy after excluding those with extratemporal lobe epilepsy to identify possible pre- and intraoperative risk factors for the development of postoperative adverse events requiring ICU interventions. The univariate analysis revealed that DM

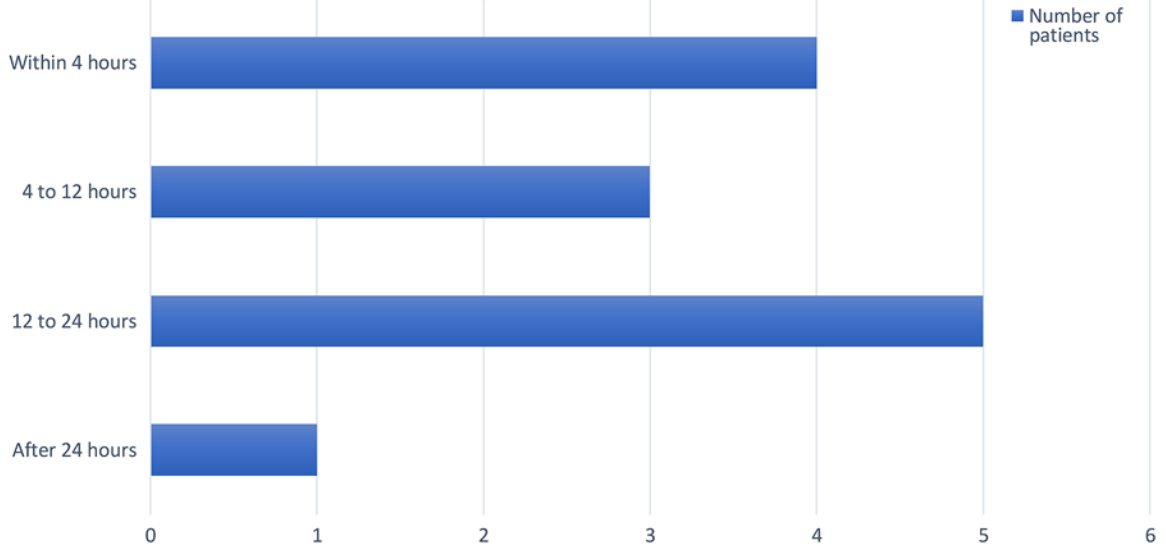

FIG. 2. Time interval between the operation and the adverse event. Figure is available in color online only.

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(40% vs 5.4%, p = 0.033) and a BMI of more than 30 kg/m^2 (15.4% vs 4.1%, p = 0.019) were significantly associated with early postoperative unfavorable events. Regarding the intraoperative course, the univariate analysis revealed a significant association between intraoperatively reported increased tissue vulnerability and postoperative unfavorable events requiring ICU intervention (p = 0.025) as well as a correlation between intraoperative blood loss and postoperative unfavorable events (p = 0.001). Furthermore, the multivariate logistic regression analysis identified DM (p = 0.018, OR 12.3, 95% CI 1.54–99) as well as intraoperative blood loss (p = 0.02, OR 5.6, 95% CI 1.35–23.2) as a significant and independent predictor of an increased incidence of postoperative adverse events requiring an ICU setting in patients undergoing temporal lobe epilepsy surgery.

TABLE 3. Multivariate logistic regression analysis of independent predictors of the need for postoperative ICU care

Factor	Adjusted OR	95% CI	p Value
Obesity	2.9	0.83–10.4	0.093
DM	9.2	1.26–67.5	**0.029**
Intraop surgical abnormalities & tissue vulnerability	2	0.3–12.8	0.48
Increased blood loss ≥325 ml	6.2	1.5–26	**0.012**

Boldface type indicates statistical significance (p < 0.05).

Discussion

ICU admission for neurosurgically treated patients is traditionally considered to be necessary at most neurosurgical centers. Along these lines, previous studies have shown that a neuroscience-based ICU may reduce in-hospital mortality in head-injured patients as well as mortality in patients with intracranial hemorrhage.[15,16] Indeed, in patients with good health conditions and fewer comorbidities who undergo elective neurosurgical treatment, recent studies have posited that these patients generally have a good outcome and only a small portion of them may require an ICU setting.[1,17] In line with the statements that elective epilepsy surgery is a low risk approach and that epilepsy patients generally have a good physical condition and fewer comorbidities,[18] our retrospective analysis revealed a 0% in-hospital mortality rate as well as only a 4.9% incidence rate of adverse events necessitating an ICU setting.

Among the 13 patients who required an ICU setting in our cohort, 5 (38.5%) developed an adverse event due to intracranial hematoma. In 4 of them, the symptoms occurred within the first 24 hours after surgery. In only 1 case, the patient developed a convulsive attack due to an epidural hematoma after more than 24 hours after surgery. Interestingly, Taylor et al.[19] could identify two varied intervals in which neurological deficits might occur due to intracranial hematoma after a neurosurgical intervention. The first period occurred within 6 hours and the second after 24 hours following surgery. Basali and colleagues[20] studied the correlation between hypertension and postoperative intracerebral hematoma. In their series, the median occurrence time of neurological deficits due to intracerebral hematoma was 21 hours after surgery. These authors also identified acute intraoperative and early postoperative increased BP values (systolic BP > 160 mm Hg or diastolic BP > 90 mm Hg) as significant risk factors for developing intracranial hematoma. In the series by Hanak et al.,[21] the application of continuous intravenous BP medications in patients with acute increased BP postoperatively was the most frequent ICU intervention (38.75% of their cohort). As the administration of continuous intravenous BP medications at our institution can be also implemented in the intermediate care unit, we did not define it as an ICU intervention in our study. Interestingly, only 21 (7.9%) of the 266 patients in our cohort required continuous intravenous BP medications postoperatively. Four patients (1.5%) required intravenous vasopressors to attain postoperative BP goals (mean arterial pressure ≥ 65 mm Hg). Note that the application of intravenous insulin drips and catecholamines with the necessary monitoring is permitted only in our ICU. In our cohort, only 2 patients needed intravenous insulin drip postoperatively because of postoperative hyperglycemia, defined as a blood glucose level higher than 160 mg/dl, and the consideration of the neuroprotective effect of normoglycemia in neurocritical care.[22,23] Both patients had preoperatively known DM.

In terms of pre- and intraoperative risk factors, Hanak et al.[21] assessed 400 patients who had undergone elective craniotomy with regard to postoperative ICU intervention and identified DM and older age as independent predictors of postoperative adverse events. In the current series, the multivariate analysis also yielded DM as an independent risk factor. In another study, older age was also a predictive risk factor for postoperative adverse events in a cohort of 343 patients undergoing elective craniotomy, as reported by Bui and colleagues.[1] However, older age as a risk factor seems to be controversial, as other studies have failed to find such a correlation.[24,25] In the current series, age at surgery did not correlate with a higher prevalence of postoperative adverse events. Moreover, the mean age of our cohort was 37.9 ± 13.4 years and is distinctly lower than the reported ages in the aforementioned studies. In terms of BMI, many studies have reported that obese patients have higher readmission rates as well as higher risks of reoperation for infection after elective craniotomy for tumor.[26,27] Likewise, Dasenbrock et al.,[28] in a National Surgical Quality Improvement Program analysis, reported increased odds for major perioperative complications in obese patients after craniotomy for tumor. The ASA classification scheme is used worldwide for preoperative patient assessments. Hanak et al.[21] described a significant increased prevalence of postoperative adverse events in patients with an ASA class ≥ III. Furthermore, in a multivariate analysis, they identified intraoperative blood products transfusion as a predictive risk factor (in addition to DM and higher age). However, in the current study, we could not confirm the higher ASA class, obesity, and intraoperative blood products transfusion as independent risk factors. Furthermore, and in line with their results, our analysis showed that the performed surgical procedure did not correlate with the prevalence of postoperative adverse events. Moreover, given the nature of our cohort, type of epilepsy (temporal lobe epilepsy vs extratemporal lobe epilepsy) was not associated with a higher prevalence of

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postoperative adverse events. Likewise, the second logistic regression analysis of patients with temporal lobe epilepsy yielded the same independent risk factors regarding early postoperative adverse events necessitating ICU settings.

Interestingly, our univariate analysis revealed intraoperatively reported increased tissue vulnerability as a possible risk factor for the need of an ICU setting postoperatively. This finding led us to further investigation; given the elective nature of the studied cases and considering the standardized surgical approaches implemented by several certified epilepsy neurosurgeons at our institution, all patients were routinely examined for coagulopathy (international normalized ratio, partial thromboplastin time, fibrinogen level in blood serum as well as fibrin stabilizing factor). Patients with known antiplatelet or anticoagulant medication were asked to discontinue the intake of these medications for an appropriate period preoperatively. After that, to rule out any residual effect of these medications, an appropriate preoperative laboratory study was performed. None of the reported cases of intraoperative bleeding abnormalities had perceptible preoperative coagulopathy. Furthermore, in all 21 cases, comprehensive intraoperative laboratory studies were performed to investigate for potential coagulopathy. According to the results, blood products and exhausted coagulation factors were substituted. Intriguingly, 15 (71.4%) of the 21 reported cases had a postoperative histologically confirmed diagnosis of hippocampal sclerosis. This aspect led us to search the literature for potential coherence; unfortunately, we could not find a distinct connection between the two points. However, according to our research, it can be assumed that the presumed immunological and inflammatory response in patients with mesial temporal lobe epilepsy with hippocampal sclerosis could play a role in modifying the cortex tissue, which seemed to be vulnerable intraoperatively.[29–31] However, an additional analysis of patients with histologically confirmed hippocampal sclerosis using Fisher's exact test did not reveal a significant correlation with an increased risk of developing a postoperative adverse event requiring an ICU setting ($p = 0.059$). Furthermore, the multivariate analysis did not reveal the intraoperatively described increased tissue vulnerability as an independent risk factor.

Our findings regarding elective craniotomy for epilepsy surgery are consistent with the practice of not routinely admitting to the ICU those patients undergoing elective supratentorial craniotomy unless certain preoperative and intraoperative conditions are present. In addition, considering the noted postoperative adverse events, we can state that the ICU setting in our cohort was required, in particular, for close neurological monitoring and intravenous medication drips. Therefore, we suggest that patients undergoing elective craniotomy for epilepsy surgery do not typically require the full capability of ICU resources and that a stepdown unit with a focus on neurological and physical surveillance and rapid response rates could be safe for monitoring these patients postoperatively. However, this conclusion is underpowered because of the study design and the fact that there are intangible factors of ICU settings that could not be quantified or assessed in this study. Hence, we recommend a multicenter prospective trial addressing the external validation of our results to establish a valid algorithm for admitting patients to the ICU after neurosurgical epilepsy treatment solely in cases of relevant comorbidities or intraoperative abnormalities.

Study Strengths and Limitations

Without doubt, the present study has certain limitations. As with all retrospective studies, the limitations of our study are inherent in its design and include retrospective data collection from a single center. Furthermore, we acknowledge that the variability in the surgical caseload, nursing staff numbers, and skill set between our institution and others will definitely have an impact on the applicability of these results to any particular institution. Therefore, external validation of our results is indispensable. Moreover, there was no quality of life assessment due to the overnight admission to the ICU to survey patient satisfaction, nor any cost-benefit analysis, which may exhibit a possible cost savings. An additional shortcoming due to the retrospective nature of our data without a control group was the inability to draw conclusions regarding whether adverse events could be detected early enough in a patient who had been admitted to a stepdown unit postoperatively. Therefore, we encourage further studies with a prospective and controlled design addressing this issue. Additionally, the reported risk factor of increased tissue vulnerability intraoperatively is rather an objective assessment and inherent in the experience of the neurosurgeon and should be interpreted with care.

On the other hand, the strengths of the present study are its narrowly defined cohort, which reduces the heterogeneity of the study population and may eliminate possible confounders. Moreover, the large sample size in relation to the number of studied potential risk factors is another particular strength, which may increase the reliability of our multifactorial logistic analysis. In addition, our standardized surgical approaches, implemented by only a few neurosurgeons, may reduce possible confounding factors caused by distinctions in surgical practice. All of these factors provide good warrants about the internal validity of our study.

Conclusions

The present study reveals routinely collectable factors that allow the identification of patients with an elevated risk of postsurgical complications requiring a postoperative ICU stay following epilepsy surgery. These findings may offer guidance for a stepdown unit admission policy following epilepsy surgical interventions. However, attention should be paid to patients with increased intraoperative blood loss (≥ 325 ml) and DM, who should be monitored postoperatively in the ICU. To confirm our results and to survey the external validation of how a selective postoperative ICU admission could be safe after elective surgical epilepsy treatment, further multicenter prospective studies must be performed.

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Disclosures

Dr. Rácz has received honoraria from UCB Pharma. Dr. Surges is part of the speakers bureaus for Arvelle, Bial, Desitin, Eisai, Livanova, Novartis, and UCB Pharma and is a consultant for Arvelle, Bial, Eisai, Livanova, UCB Pharma, and UNEEG.

Author Contributions

Conception and design: Bahna, Vatter, Borger. Acquisition of data: Bahna. Analysis and interpretation of data: Bahna, Borger. Drafting the article: Bahna. Critically revising the article: Bahna, Schneider, Borger. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Bahna. Statistical analysis: Bahna, Borger. Administrative/technical/material support: Bahna, Schneider, Borger. Study supervision: Vatter, Borger.

Supplemental Information

Previous Presentations

Parts of this work were presented as an oral presentation at the 72nd Annual Meeting of the German Society of Neurosurgery (DGNC) held in Erfurt, Germany, on June 6–9, 2021.

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3.5 **Borger V**, Hamed M, Ilic I, Potthoff AL, Rácz A, Schafer N, Güresir E, Surges R, Herrlinger U, Vatter H, Schneider M, Schuss P. Seizure outcome in temporal glioblastoma surgery: lobectomy as a supratotal resection regime outclasses conventional gross-total resection. *J Neurooncol.* 2021;152(2):339-346.

Zielsetzung der Arbeit – Symptomatische Epilepsie ist eine häufige Form bzw. ein häufiges Symptom der Manifestation von malignen hirneigenen Tumoren wie z.B. des Glioblastoms. Durch institutseigene Arbeiten konnte gezeigt werden, dass bei temporalen Glioblastomen eine supramarginale Resektion im Sinne einer aus der Epilepsiechirurgie abgeleiteten anterioren temporalen Lobektomie sowohl das Gesamtüberleben als auch das progressionsfreie Überleben der Patienten signifikant verbessern konnte. Daten über den Einfluss einer solchen chirurgischen Herangehensweise auf das Anfallsoutcome von Patienten mit temporalen Glioblastomen sind bis dato in der Literatur nicht vorhanden. In dieser Studie soll diese klinische Translation einer aus der resektiven Epilepsiechirurgie am Temporallappen abgeleiteten Operationstechnik auf ihren Einfluss im Hinblick auf die Anfallskontrolle in der neurochirurgischen Therapie von neuroonkologischen Patienten erstmalig untersucht werden.
Methoden und Ergebnisse – in diese retrospektive Analyse wurden alle Patienten mit einem temporal gelegenen Glioblastom und preoperativ manifesten epileptischen Anfällen eingeschlossen, welche in dem Zeitraum von 2012 bis 2018 in unseren Klinik operativ mittels Tumorresektion behandelt wurden. Verglichen wurden die Patienten entsprechend dem postoperativen Anfallsoutcome gem. ILAE (ILAE 1 vs. ILAE 2-6). Die Gesamtkohorte beinhaltete eine Gruppe von Patienten, welche einer Tumorresektion nach epilepsiechirurgischen Gesichtspunkten im Sinne einer anterioren temporalen Lobektomie unterzogen wurden. Die andere Gruppe bestand aus Patienten, welche einer herkömmlichen Tumorresektion nach neuroonkologischen Kriterien im Sinne einer gross total resection (GTR) unterzogen wurden. Insgesamt wurden 33 Patieten in die Analyse eingeschlossen. Eine ATL wurde bei 13 Patienten (39%), eine GTR bei 20 Patienten (61%) durchgeführt (Details siehe Table 1, p. 342, Borger et al., JNO 2021). Betrachtet man die Patienten entsprechend dem post-op. Anfallsoutcome, so zeigt sich, dass alle –und somit signifikant häufiger- ATL-Patienten anfallsfrei waren, wohingegen nur 10 von

20 Patienten (50%) nach einer GTR eine Anfallsfreiheit erzielen konnten (siehe Table 2, p. 343, Borger et al., JNO 2021).

Schlussfolgerung – in der aktuellen Studie konnte aufgezeigt werden, dass eine ATL bei temporal lokalisierten Glioblastomen im Vergleich zu einer herkömmlichen GTR die Chancen auf eine post-op. Anfallskontrolle signifikant erhöhen kann. Im Kontext mit den Ergebnissen der Verbesserung der neuro-onkologischen Outcomes in weiteren hauseigenen Studien, hat die ATL das Potential, den herkömmlichen Ansatz der neurochirurgischen Therapie eines temporalen Glioblastoms als Modalität der Wahl abzulösen.

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CLINICAL STUDY

Seizure outcome in temporal glioblastoma surgery: lobectomy as a supratotal resection regime outclasses conventional gross-total resection

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Abstract

Introduction The postoperative seizure freedom represents an important secondary outcome measure in glioblastoma surgery. Recently, supra-total glioblastoma resection in terms of anterior temporal lobectomy (ATL) has gained growing attention with regard to superior long-term disease control for temporal-located glioblastoma compared to conventional gross-total resections (GTR). However, the impact of ATL on seizure outcome in these patients is unknown. We therefore analyzed ATL and GTR as differing extents of resection in regard of postoperative seizure control in patients with temporal glioblastoma and preoperative symptomatic seizures.

Methods Between 2012 and 2018, 33 patients with preoperative seizures underwent GTR or ATL for temporal glioblastoma at the authors' institution. Seizure outcome was assessed postoperatively and 6 months after tumor resection according to the International League Against Epilepsy (ILAE) classification and stratified into favorable (ILAE class 1) versus unfavorable (ILAE class 2–6).

Results Overall, 23 out of 33 patients (70%) with preoperative seizures achieved favorable seizure outcome following resection of temporal located glioblastoma. For the ATL group, postoperative seizure freedom was present in 13 out of 13 patients (100%). In comparison, respective rates for the GTR group were 10 out of 20 patients (50%) ($p = 0.002$; OR 27; 95% CI 1.4–515.9).

Conclusions ATL in terms of a supra-total resection strategy was associated with superior favorable seizure outcome following temporal glioblastoma resection compared to GTR. Regarding above mentioned survival benefit following ATL compared to GTR, ATL as an aggressive supra-total resection regime might constitute the surgical modality of choice for temporal-located glioblastoma.

Keywords Glioblastoma · Seizure outcome · Supra-marginal resection

Introduction

Seizures are the most common symptoms in patients with malignant brain tumors and often constitute the first clinical manifestation of an intracranial lesion. Tumor location and histopathological classification are decisive for the frequency of seizures. Supratentorial tumors, especially those with superficial and/or temporal localization, are more epileptogenic. However, the incidence of seizures inversely correlate with the degree of malignancy with seizures occurring more frequently in low-grade tumors.

Nevertheless, as neurosurgical, radiological, chemotherapeutic and supportive therapies for glioblastoma have been improved over the last decades [1–5] and overall survival is

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prolonged, appropriate symptom management is becoming increasingly important in this patient population to avoid negative consequences for the patients' quality of life.

Previous study results indicated that a larger extent of resection might improve the survival of glioblastoma patients [6–8]. In the case of temporally located glioblastomas, it was previously demonstrated that such supramarginal resection—here in the sense of an anterior temporal lobectomy (ATL) as an epilepsy-surgical therapeutic approach—improves both progression-free and overall survival [9]. Due to the scarcity of data, it remains uncertain to what extent this therapeutic approach has an impact on tumor-related epilepsy (TRE).

Here, we present for the first time data on the influence of this aggressive onco-surgical therapy approach on the outcome of seizures after surgical treatment of temporally located glioblastomas.

Methods

Patients

Between 2012 and 2018, all patients with temporal glioblastoma and preoperative seizures aged 18 years or older were included in further analysis. All patients who underwent only biopsy were excluded. After approval by the institutional ethics committee, the medical records were retrospectively reviewed and relevant clinical information were collected and entered into a computerized database (SPSS Version 25, IBM Corp.). These information included patient age, gender, Karnofsky Performance Score (KPS), tumor size and extent, seizure status and semiology (focal vs. generalized) according to the International League Against Epilepsy (ILAE), molecular histopathological parameters and postoperative seizure outcome.

Using the KPS, patients were categorized according to their neurological functional status both preoperatively and in the further postoperative course. KPS $\geq$ 70 was defined as a favourable outcome during postoperative follow-up immediately after surgery and 3 and 12 months postoperatively.

Treatment decision

The institutional interdisciplinary central nervous system (CNS) tumor board made the decision on treatment modality on a case-by-case basis at the initial presentation of the patient and during postoperative follow-up. Within the framework of the weekly CNS tumor board, a consensus treatment algorithm is determined for each patient by specialists in neuro-oncology from the fields of neurology, neurosurgery, neuroradiology, neuropathology and radio-oncology. The specification of neurosurgical procedures is primarily based on the individual assessment of the neurosurgeons participating in the CNS tumor board meeting. The decision whether the patient was assigned to ATL or conventional tumor resection was primarily based upon the prevalence of the responsible treating neurosurgeon. Given by the fact, that authors' institution have a long tradition of epilepsy surgery, those neurosurgeons with epilepsy surgery skills performed more likely ATL. All leading neurosurgeons involved in the surgical treatment of neuro-oncological patients fulfilled the requirements for Neuro-Oncology Centers certificated by the German Cancer Society. Patients with temporal glioblastoma were only selected in this series if the temporal tumor manifestation was within the margin of 4–5 cm in the dominant and 5–6 cm in the non-dominant hemisphere from the temporal pole. Patients with additional infiltration of the mesial temporal lobe structures (amygdala, hippocampus, parahippocampal gyrus and / or entorhinal cortex) in preoperative gadolinium enhanced MR-imaging were also included in the current series. As known from reports on patients with low-grade glioma, the resection of mesial temporal lobe structures is more likely to achieve a better post-operative seizure control [10]. Thus, patients with temporal glioblastoma and evidence of contrast enhancement in mesial temporal lobe on pre-operative MRI underwent additional amygdalohippocampectomy. In patients who had a FLAIR component without any contrast enhancement in the temporo-mesial structures, the removal of these structures was at the discretion of the surgeon and was usually not carried out for epileptological considerations, but rather for neuro-oncological considerations regarding a reduction of the local mass in view of an imminent further therapy such as radiation with the potential danger of subsequent reactive tissue swelling.

Surgical procedures

For further analysis the patients were divided into two groups: (1) patients undergoing gross-total resection (GTR) of the temporal contrast-enhancing tumor, and (2) those patients who underwent temporal tumor removal by means of additional anterior temporal lobectomy (ATL). ATL was performed with the inclusion of the contrast-enhanced tumor portion as well as unaffected brain parenchyma as indicated by the preoperatively performed magnetic resonance imaging (MRI). Furthermore, in selected cases resection of the temporal glioblastoma with additional amygdalohippocampectomy was performed. In these cases, however, an oncosurgical rather than an epilepsy-surgical therapeutic approach was pursued, which was derived from the accompanying tumor infiltration of the temporo-mesial structures. All surgical procedures were performed using intraoperative neuronavigation, 5-aminolevulinic acid (5-ALA) fluorescence, and if indicated intraoperative neurophysiological

monitoring with motor evoked and somatosensory evoked potentials. When performing ATL, the temporal lobe was removed until the margin of maximum 4.5 cm from temporal pole in dominant and 6.5 cm in non-dominant hemisphere [11]. The resection of uncus and amygdala was performed using ultrasound suction system (CUSA) or Penfield dissector, until the pial and arachnoid membranes, adjacent to the crural and ambient cisterns, was reached. The temporal horn was opened using a Penfield dissector followed by entering the ventricle and resection of the anterior part of the hippocampus. Then the en bloc resection of the hippocampus body was performed with the posterior margin at the level of the tectum. The conventional GTR was performed by surgical removing of gadolinium enhanced tumor tissue guided by 5-ALA fluorescence.

Postoperative care

The extent of resection was evaluated according to the early post-operative MRI within 72 h after surgery. The GTR was defined as complete resection of gadolinium enhancing tissue. In addition, the result of the neuroradiological report of the post-operative MRI examination was taken into account. For this purpose, two independent neuroradiologists, without any knowledge of the clinical course, assessed the neuroimaging. The required information was available for all included patients, extracted from these reports, and categorized according to the above definition. Only patients with GTR were included in the further analysis.

Peri- and postoperative complications were defined as any unfavorable event that occurred within 30 days following initial temporal glioblastoma resection [12].

After histopathological confirmation of glioblastoma, the methylation status of the MGMT promoter was analyzed by pyrosequencing and combined bisulfite restriction analysis.

After surgical removal of the tumor, all patients received adjuvant treatment consisting of radiotherapy, chemotherapy or combined radiochemotherapy, as recommended by the institutional interdisciplinary tumor board.

Tumor-related seizures

According to ILAE, tumor-associated epilepsy was defined as (1) at least two unprovoked seizures occurring at intervals of > 24 h or (2) one unprovoked seizure with an increased probability of further seizures similar to the general risk after two unprovoked seizures. Therefore, glioblastoma patients with both 1 and > 1 symptomatic seizure were included for further analysis. According to the semiology, the seizures were distinguished into focal aware seizures, focal impaired awareness seizures and focal to bilateral tonic–clonic seizures.

Full seizure control as defined by ILAE Class 1 was determined after 6 months of follow-up instead of the recommended 12 months in the investigated glioblastoma patients and was considered favorable. An unfavorable outcome was defined as ILAE classes 2–6, i.e. pure auras, rare to no improvement and worsening of seizure frequency and/or seizure disabling quality. Detailed information on the ILAE classification system can be found in Fig. 1.

Statistics

Data analysis was performed using the SPSS (Version 25, IBM Corp.) computer software package. An unpaired t-test was used for parametric statistics. Categorical variables were analyzed in contingency tables using the exact Fisher test. Results with p values < 0.05 were considered statistically significant.

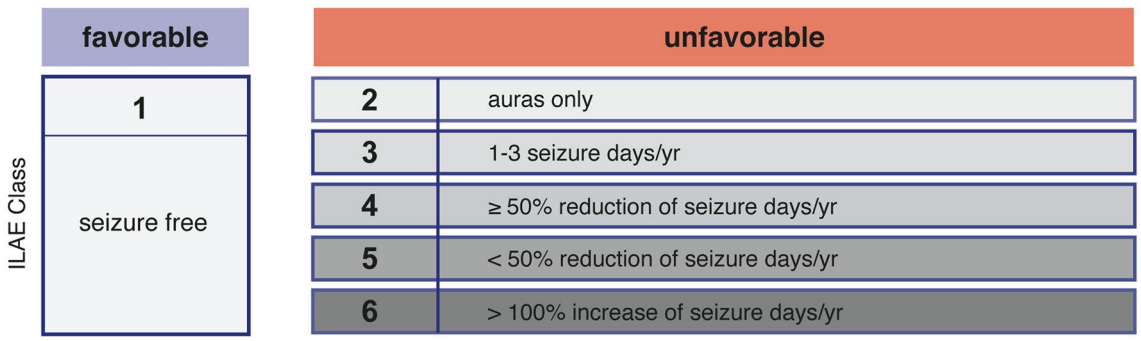

Fig. 1 Schematic illustration of the ILAE classification system. Scheme modified from Schneider et al. [31]. ILAE international league against epilepsy

Results

Patient characteristics

Between 2012 and 2018, a total of 33 patients with temporally located glioblastoma and preoperative seizures were treated at the authors' institution. The patients ' mean age was 59 ± 14 years. The median KPS score at presentation was 90 (range 60–100). Anterior temporal lobectomy (ATL) was performed in 13 patients (39%), whereas the temporal GTR was performed in 20 patients (61%). The median overall survival (OS) was 22 months (95% CI 11.3–32.7). Further details on patient and tumor characteristics are given in Table 1.

Surgery-related unfavorable events were present in 4 out of 33 patients (12%). Thereby, postoperative hemorrhage was found in 2 patients (6%) and postoperative meningitis and wound dehiscence in 1 patient, respectively (3%). Among the patients with postoperative hemorrhage, revision surgery was required in one case. Analysis of peri- and postoperative complications did not reveal any profound new language deficit.

Table 1 Patient characteristics

No. of patients	33
Sex	
Male	19 (58)
Female	14 (42)
Mean age (±SD) (in yrs)	59 ± 14
Tumor location	
Dominant hemisphere	19 (58)
Temporomesial infiltration (+)	17 (52)
Semiology	
Focal aware seizures	12 (36)
Focal impaired-awareness seizures	3 (9)
Focal to bilateral tonic–clonic seizures	18 (55)
Preoperative KPS	
≥ 70	32 (97)
< 70	1 (3)
Surgical modality	
ATL	13 (39)
GTR	20 (61)
MGMT promotor methylation status	
Methylated	16 (48)
Unmethylated	17 (52)
Favorable seizure outcome (ILAE 1)	23 (70)

ATL anterior temporal lobectomy, *GTR* gross total resection, *ILAE* International League Against Epilepsy, *KPS* Karnofsky Performance Score, *yrs* years

Values represent number of patients unless otherwise indicated (%)

Seizure semiology

As shown in Table 1, the preoperative evaluation revealed focal to bilateral tonic–clonic seizures as a predominantly seizure semiology (18 out of 33 patients (55%)). Most frequently observed were focal aware seizures in 12 out of 33 patients (36%) followed by focal impaired-awareness seizures (3 out of 33 patients (9%)). At admission, all the glioblastoma patients in this series were under antiepileptic drug medication, whereby Levetiracetam was present in 31 patients (94%) and Carbamazepine in 2 patients (6%).

Seizure outcome

Overall, favorable postoperative seizure outcome in terms of ILAE class 1 was achieved in 23 patients (70%) with temporal glioblastoma and preoperative TRE. There was no statistically significant difference between seizure free patients and patients with continuous seizures according to the preoperative seizure semiology. The analysis of the correlation between seizure control and overall survival (OS) revealed a median OS of 23 months (IQR 13–33.5) in seizure free patients (ILAE 1) vs. 26 months (IQR 3–33.5) in patients with postoperatively persistent seizures ($p = 0.34$). From the total of 33 patients, adjuvant treatment according to the Stupp protocol was performed in 26 patients (80%), 4 patients (12%) received adjuvant treatment according to the protocol of the CeTeG-trial [13], and 3 patients (9%) received individual adjuvant treatment according to the recommendation of the institutional interdisciplinary tumor board. The comparison of the both outcome groups did not reveal a statistically significant difference. The IDH1 status was available in 22 of 33 patients (66.7%) in this series. From the patients with known IDH1 mutation status, 21 patients (95.5%) were IDH1-wildtype and only 1 patient (4.5%) has an IDH1 mutation. This particulary patient underwent GTR and had persisting seizures (ILAE 2–5) after the surgery. From the total of 21 patients with IDH1-wildtype status, in 9 patients (43%) ATL was performed with a favorable seizure outcome in 15 patients (71.4%). Further details are given in Table 2.

Influence of additional amygdalohippocampectomy on seizure outcome

A total of 17 patients (52%) suffering from temporally located glioblastoma and preoperative TRE had additional temporo-mesial tumorous infiltration. In detail, 3 of the 17 patients exhibited a contrast-absorbing infiltration of the temporo-mesial structures, whereas 14 of the 17 patients had a FLAIR-correlate in the area of the temporo-mesial structures. In selected patients, additional amygdalohippocampectomy was performed in order to achieve GTR, better relief

Table 2 Seizure outcome

	Favorable seizure outcome (ILAE 1)	Unfavorable seizure outcome (ILAE 2–6)	p value
No. of patients	23 (70)	10 (30)	
Mean age (± SD) (in years)	59 ± 14	60 ± 16	0.96
Female sex	11 (48)	3 (30)	0.46
Tumor location			
Dominant hemisphere	14 (61)	5 (50)	0.71
Temporomesial infiltration (+)	12 (52)	5 (50)	1.0
Preoperative KPS ≥ 70	22 (96)	10 (100)	1.0
Semiology			0.49
Focal aware seizures	8 (35)	4 (40)	
Focal impaired-awareness seizures	3 (13)	0 (0)	
Focal to bilateral tonic–clonic seizures	12 (52)	6 (60)	
Surgical modality			0.002
ATL	13 (56)	0 (0)	
GTR	10 (44)	10 (100)	
Additonal amygdalo-hippocampectomy	12 (52)	1 (10)	0.05
Unmethylated MGMT promotor status	16 (70)	6 (60)	0.69
Postoperative adjuvant treatment			
Stupp	19 (83)	7 (70)	0.64
CeTeG	3 (13)	1 (10)	1.0
Individual	1 (4)	2 (20)	0.21
Mean hospital stay (± SD) (ds)	16 ± 10	11 ± 7	0.13
mOS (IQR)	22 (13–34)	26 (3–34)	0.34

ATL anterior temporal lobectomy, *ds* days, *GTR* gross total resection, *ILAE* International League Against Epilepsy, *IQR interquartile range, KPS* Karnofsky Performance Scale, *mOS* median overall survival, *yrs* years

Values are presented as the number of patients (%) unless stated otherwise

of space-occupying effect and/or a more favorable seizure outcome. Therefore, 12 of 13 patients (92%) with additional amygdalohippocampectomy achieved favorable seizure outcome compared to 12 of 20 patients (60%) without additional amygdalohippocampectomy (p = 0.06).

Influence of extent of resection on seizure outcome

The groups of ATL and temporal GTR did not significantly differ in regard of age, sex, tumor localization and MGMT promoter methylation status (Table 3).

20 patients (61%) with temporal glioblastoma and preoperative TRE underwent GTR, whilst ATL was performed in 13 patients (39%). Patients who underwent ATL for temporal glioblastoma achieved significantly more often favorable seizure outcome (ILAE 1) compared to patients with temporal GTR (13 vs. 10; p = 0.002; OR 27; 95% CI 1.4–515.9).

Table 3 Comparison of ATL and temporal GTR as differing oncosurgical resection modalities

	ATL	Temporal GTR	p value
No. of patients	13 (39)	20 (61)	
Mean age (± SD) (in yrs)	62 ± 13	55 ± 16	0.17
Female sex	5 (38)	9 (45)	1.0
Tumor location			
Dominant hemisphere	8 (62)	11 (55)	1.0
Unmethylated MGMT promotor status	9 (69)	13 (65)	0.7

ATL anterior temporal lobectomy, *GTR* gross total resection, *ILAE* International League Against Epilepsy, *MGMT O-6-methylguanine-DNA methyltransferase, SD standard deviation, yrs* years

Values are presented as the number of patients (%) unless stated otherwise

Discussion

The concept of supra-total resection strategies extending considerably beyond tumor-enhancing MRI lesions is gaining a growing evidence base in neurosurgical oncology for the surgical treatment of malignant primary brain tumors. In addition to improved overall survival and prolonged progression-free survival interval in previous studies, the present case study also indicates an advantage of a supra-marginal resection strategy with regard to seizure outcome in temporally localized glioblastoma associated with tumor-related epilepsy.

In brain tumors, epilepsy often represents the first symptom and is considered to be a favorable prognostic factor with regard to survival in both low and high-grade gliomas [14–16]. However, TRE leads to a reduced quality of life and can additionally aggravate the burden of living with a brain tumor [17]. To ensure adequate symptomatic therapy of TRE throughout the treatment of these patients, several factors must be considered at different stages. Since tumor related epilepsy is usually based on a local focus, levetiracetam, carbamazepine or phenytoin are often used in the antiepileptic treatment of tumor-related seizures. In some studies, the use of valproic acid (VPA) has often been associated with better overall survival [18–22]. In the context of preoperative treatment of tumor seizures in particular, VPA can be avoided due to the possibility of inducing or aggravating thrombocytopenia.

Nevertheless, in addition to pharmacological therapy, surgical treatment—as evidenced by epilepsy surgery and experiences with low-grade glioma surgery—can also make a decisive contribution to seizure outcome [10, 23, 24]. In a preceding study, we were able to illustrate that a supra-marginal resection strategy in temporal glioblastoma may lead to a significantly prolonged overall survival. In addition to this merely oncological aspect concerning overall survival, we therefore have investigated whether the same procedure might also contribute to seizure outcome in patients with temporal glioblastoma and TRE. Postoperative favorable seizure outcome after initial resection of glioblastomas was previously reported with up to 77% of patients [14]. The results of the present study describing a postoperative seizures freedom in 70% of patients with temporal glioblastomas support these findings.

Anterior temporal lobectomy has already been established in epilepsy surgical research as a useful surgical strategy for alleviating seizures in patients with an epileptogenic focus in the temporal lobe area [25, 26]. In the present study, the performance of ATL for treatment of temporal glioblastoma with TRE was observed to have a significant impact on a favorable seizure outcome in impaired patients ($p = 0.002$).

Infiltration of the temporo-mesial structures seems to make a significant contribution to the postoperative seizure outcome. In this context, an additional amygdalohippocampectomy was performed in patients with preoperatively proven contrast agent enriching lesions in the area of the temporo-mesial structures. In patients who had a FLAIR component without any contrast enhancement in the temporo-mesial structures, the removal of these structures was at the discretion of the surgeon and was usually not carried out for epileptological considerations, but rather for neuro-oncological considerations regarding a reduction of the local mass in view of an imminent further therapy such as radiation with the potential danger of subsequent reactive tissue swelling. In the literature, especially in the case of low-grade gliomas with accompanying epilepsy, surgical resection of the temporo-mesial structures is associated with an improved seizure outcome [10, 27]. Besides, supramarginal resection might be accompanied by elevated levels of postoperative complications with regard to potentially increased vasculature and eloquent areas at risk which in turn might lead to impaired patients quality of life and worsened OS. In accordance to our previous study on the complication rate in temporal glioblastoma surgery dependent on the extent of temporal glioblastoma resection [12], the present findings do not provide any indication for elevated levels of unfavorable postoperative events in the lobectomy group. This might be reasoned in a reduced risk for postoperative hemorrhage from partially-resected glioblastoma remnants or a potentially reduced occurrence of postoperative increasing reactive peritumoral edema [12, 28, 29]. Nevertheless, surgical interventions in the area of the temporo-mesial structures invariably carry the risk of postoperative neuropsychological impairment. In addition to the tumor burden itself, patients have to deal with eventual side effects of adjuvant therapy and the recurrence therapy that may be necessary during the course of the treatment. Extensive neuropsychological examinations are often not planned in the preoperative evaluation of patients with glioblastomas and often these examinations cannot be undertaken by the patients themselves to the extent practiced in epilepsy/low-grade-glioma surgery due to the often existing tumor-related cognitive limitations. Nevertheless, this aspect is an intriguing perspective for future studies on the neuropsychological assessment of glioblastoma patients, which are intended to undergo supra-marginal resection [30]. The present study endorses the ATL in addition to its known benefit regarding overall survival as the method of choice for surgical control of potential tumor-related seizures in patients with temporal glioblastoma.

Limitations

The present study has several limitations. The main limitations of this study are the small sample size and the retrospective study design. The surgical procedure of ATL as a paradigm for supratotal resection regimes entails a highly selected cohort of glioblastoma patients with a tumor manifestation within 4 to 5 cm from the temporal pole on the dominant hemisphere and 5 to 6 cm on the non dominant hemisphere. Therefore, a greater sample size is instantly needed in order to increase the validity of our findings. For this purpose, rather multicenter prospective studies will be capable to cope with the restriction of a low incidence of precisely temporal located glioblastoma and thus might create a safe prerequisite to sufficiently assess ATL as a supramarginal resection strategy in temporal glioblastoma disease. Furthermore, estimating the potential effects of radiation and chemotherapy on seizure outcome is complex. However, there are only a few studies assessing the outcome of seizures in patients undergoing glioblastoma resection. The vast majority of studies on glioblastoma resection focus on factors that influence survival or recurrence. Seizure control represents an aspect that has not yet been studied in depth, and has so far been limited to patients with low-grade gliomas. Therefore, the homogeneity of patient/tumor characteristics, methods and results provide an encouraging clinical background for future studies focusing on the influence of the extent of resection on the control of preoperative tumor-related epilepsy in patients suffering from glioblastoma.

Conclusions

The present study indicates that anterior temporal lobectomy might be associated with a more favorable seizure outcome after temporal glioblastoma resection in terms of a supramarginal resection strategy compared to GTR. In addition to the described survival advantage, ATL for surgical treatment of temporally localized glioblastoma henceforth seems to be the therapy of first choice given the potential increased seizure freedom.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The present study was approved by the local ethics committee of the University of Bonn.

Informed consent Informed consent was not sought as a retrospective design was used.

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4. Diskussion

Die resektive Epilepsiechirurgie ist eine etablierte Behandlungsoption für Patienten mit einer fokalen refraktären Epilepsie, insbesondere der Temporallappenepilepsie. Obwohl eine epilepsiechirurgische Behandlung wirksam ist, hat sich jedoch gezeigt, dass die Anfallsfreiheit nach der Operation mit der Zeit abnimmt. Die Berichte in der Literatur zeigen, dass trotz der chirurgischen Behandlung von TLE bei 20-30% der Betroffenen keine Anfallsfreiheit erreicht wird (Jeha et al., 2006; McIntosh et al., 2004). Die Gründe für das Scheitern der chirurgischen Behandlung sind vielfältig und ein Vergleich mit vorhandenen Daten ist aufgrund methodischer Probleme zuweilen nicht ganz einfach. In unserer ersten hier aufgeführten Arbeit haben wir versucht, Faktoren zu identifizieren, die mit einem ungünstigen Anfallsergebnis bei Patienten mit TLE, die sich einer epilepsiechirurgischen Behandlung unterzogen haben, assoziiert sind. In der vorliegenden Studie, wurde ein günstiger Anfallsverlauf (ILAE-Klasse 1) ein Jahr nach der OP bei 75 % der Patienten berichtet, was mit in der Literatur publizierten Daten übereinstimmt. Die Patienten in unserem Kollektiv wurden vermehrt mittels einer selektiven Amygdalohippokampektomie (tsSAHE) behandelt (Borger et al., 2021a). Die Daten in der Literatur zeigen in etwa vergleichbare Ergebnisse hinsichtlich des Anfallsoutcomes zwischen der Standard-Temporal-Lobektomie (ATL) und der tsSAHE. Das systematische Review und Meta-Analyse von Josephson et al. zeigt, dass die ATL hinsichtlich der Anfallsfreiheit etwas wirksamer ist als die tsSAHE (Josephson et al., 2013). Die Daten der vorliegenden Serie zeigen, dass die chirurgische Modalität keinen Einfluss auf das Anfallsgeschehen hatte. Der aufgrund der Datenlage in der veröffentlichen Literatur bewiesene Vorteil der selektiven Resektionen ist die Schonung der neurokognitiven Funktionen. Dies ist der Grund für überwiegend selektive Resektionen an unserem Epilepsiezentrum. In einer von Tonini et al. durchgeführten Meta-Analyse fanden die Autoren heraus, dass ein invasives intrakranielles Anfallsmonitoring ein Prädiktor für ein ungünstiges Anfallsoutcome war (Tonini et al., 2004). In Übereinstimmung mit diesen Ergebnissen fanden wir in unserer Serie signifikant mehr Patienten in der Gruppe mit der ungünstigen Anfallskontrolle, die einer invasiven prächirurgischen Evaluation mittels Tiefenelektroden unterzogen wurden. Interessanterweise zeigte sich in unserer Arbeit in der multivariaten logistischen Regressionsanalyse dieser Umstand nicht als unabhängiger Prädiktor für ein ungünstiges Anfallsoutcome.

Gemäß den veröffentlichten Daten, haben etwa 20-30% der Patienten mit TLE eine normale MRT ohne Nachweis einer epileptogenen Läsion. Die berichteten Raten der Anfallsfreiheit nach resektiven Temporallappeneingriffen bei diesen Patienten liegen zwischen 20% und 80%. In der von uns untersuchten Population, lag die Gesamtrate der Patienten mit MRT negativer TLE bei 8,7%. In der Gruppe mit negativer MRT gab es signifikant mehr Patienten (20%) mit ungünstigem Anfallsoutcome. Im Gegensatz zu den Daten von Tonini et al. erwies sich eine negative MRT ebenfalls nicht als ein unabhängiger prognostischer Faktor für einen ungünstigen postoperativen Anfallsverlauf in der multivariaten logistischen Regressionsanalyse. Diese Ergebnisse legen nahe, dass ein normales MRT und die Notwendigkeit einer invasiven präoperativen Untersuchung nicht immer mit einem schlechteren postoperativen Anfallsergebnis verbunden sind. Diese Vermutung wird durch die Daten von Sotero de Menezes et al. und Roberts et al., die zeigen, dass die Anfallsergebnisse bei Patienten mit normaler MRT vergleichbar sind mit Patienten mit abnormalem MRT, gestützt (Roberts et al., 2001; Sotero de Menezes et al., 2001). Ivanovic et al. zeigten in ihrer Analyse ähnliche Ergebnisse. Hinsichtlich der histopathologischen Befunde gibt es mehrere Studien, die darauf hindeuten, dass eine HS mit einem ausgeprägten Muster das chirurgische Ergebnis bei Patienten mit TLE vorhersagen können (Ivanovic et al., 2017). Histopathologisch von der klassischen HS zu differenzieren ist die hippocampale Astrogliose ohne Neuronenverlust. In der aktuellen ILAE Nomenklatur wird dieses als „keine Hippocampussklerose, nur Gliose" bezeichnet. Es ist jedoch unklar, ob eine Hippocampusgliose dem neuronalen Verlust vorausgeht, der zu HS führt, oder ob es sich um eine eigenständige Entität handelt. Die Daten zur Bewertung der Auswirkungen von HG auf das Anfallsoutcome bei Patienten mit TLE nach einem resektiven Eingriff sind kaum vorhanden. Der Großteil der Literatur befasst sich mit der Bewertung der Auswirkungen von HS auf das postoperative Anfallsgeschehen (de Lanerolle et al., 2003; Thom et al., 2010). So ist die Identifizierung von HG als ein unabhängiger Prädiktor für fehlende Anfallsfreiheit in unserer Serie ein Aspekt, der in der Literatur relativ unterrepräsentiert ist. Seit die ILAE eine Klassifikation von HS entwickelt hat, wurden mehrere Berichte veröffentlicht, die den Einfluss von Subtypen von HS auf das postoperative Anfallsergebnis beschreiben. In der kürzlich veröffentlichten Serie fanden Hattingen et al. heraus, dass Patienten mit alleiniger hippocampaler Gliose gem. der ILAE-Klassifikation unterschiedliche histopatho-

logische und MRT-Muster aufweisen im Vergleich zu Patienten mit einer HS. In der aktuellen Serie haben wir nicht zwischen den Subtypen der HS-Patienten und deren Auswirkungen auf die postoperative Anfallsfreiheit unterscheiden (Hattingen et al., 2018). Allerdings zeigen unsere Ergebnisse signifikant mehr Patienten mit HS in der Gruppe mit günstigem Anfallsoutcome. Im Gegensatz dazu wurde die HG signifikant häufiger bei Patienten mit ungünstigem Anfallsoutcome diagnostiziert und auch als ein unabhängiger Prädiktor für ein ungünstiges Anfallsoutcome in der multivariaten logistischen Regressionsanalyse identifiziert. Diese Ergebnisse unterstützen möglicherweise die Vermutung von Hattingen et al., die HG als eine eigenständige Entität bei Patienten mit TLE identifizierten. Dieser Befund ist insoweit wichtig als kürzlich mehrere Berichte veröffentlicht wurden, die unter Verwendung neuer Methoden der Neurobildgebung das Potenzial haben, bereits in präoperativen MRT zwischen HG und HS zu unterscheiden (Bernhardt et al., 2019). Somit ist die von uns herausgearbeitete Tatsache, dass HG unabhängig das postoperative Anfallsoutcome vorherzusagen vermag, in Bezug auf frühere Veröffentlichungen als eine neue Erkenntnis zu werten. Ein weiterer offensichtlicher Grund für postoperativ anhaltende Anfälle ist eine unzureichende Resektion der epileptogenen Strukturen. Mehrere Arbeiten, die berichten, dass eine weitere Resektion der verbliebenen epileptogenen Strukturen zu einem anfallsfreien Ergebnis führen kann, stützen die Hypothese, dass bei einer Subgruppe von Patienten mit TLE eine unvollständige Resektion der temporomesialen Strukturen zum Scheitern der epilepsiechirurgischen Behandlung führen könnte (Paolicchi et al., 2000; Tonini et al., 2004). In Übereinstimmung mit diesen Ergebnissen konnte in unserer Serie eine unvollständige Resektion der epileptogenen Läsion als unabhängiger Prädiktor für ein ungünstiges postoperativen Anfallsoutcome identifiziert werden.

Dieses Ergebnis war der Anlass für nachfolgende Untersuchungen. Wir konnten zum ersten Mal zeigen, dass das Ausmaß der Resektion des piriformen Kortex die Anfallsfreiheit nach tsSAHE bei Patienten mit mTLE vorhersagt (Borger et al., 2021b). Kürzlich veröffentlichte Daten von Galovic et al. zeigen den Zusammenhang zwischen dem volumetrisch berechneten Ausmaß der Resektion im Rahmen der Standard-ATL und dem Anfallsoutcome bei TLE-Patienten (Galovic et al., 2019). Die Ergebnisse legen nahe, dass Anfallsfreiheit bei 60% der Patienten erreicht werden konnte, wenn mindestens 50% des piriformen Kortex reseziert worden waren. Im Gegensatz zu diesen Ergebnissen konnten wir in unseren Serie zeigen, dass bereits

die Resektion von mindestens 26,4% des piriformen Kortex ausreichte, um bei 96% der Patienten nach der tsSAHE eine Anfallsfreiheit zu erreichen. Die Ergebnisse unserer Studie stützen somit stark die Annahme, dass eine umfangreichere Resektion des piriformen Kortex mit einer signifikant höheren Chance auf Anfallsfreiheit nach tsSAHE bei mTLE verbunden ist. Interessanterweise konnte in einer aktuellen Studie von Wu et al. gezeigt werden, dass bei der Behandlung von Patienten mit mTLE mittels LITT eine umso höhere Rate an Anfallsfreiheit erzielt werden konnte je mehr mesial und anterior gelegenen Zielstrukturen ablatiert wurden (Wu et al., 2019). Ungeachtet der Tatsache, dass die berichteten Daten keine eindeutige topographische Analyse der Ablationsvolumina des piriformen Kortex liefern, könnten die Ergebnisse von Wu et al. die Hypothese stärken, dass die „Ausschaltung“ streng temporomesial gelegener Zielvolumina eine signifikant höhere Rate an postoperativen Anfallsfreiheit zu Folge haben könnte. Durch unsere Untersuchungen konnte auch gezeigt werden, dass das ausgedehnte Resektionsausmaß des PiC sowohl mit keinem signifikant höheren Risiko für perioperative Komplikationen als auch mit keiner Verschlechterung der neuro-psychologischen Ergebnisse vergesellschaftet war. Obwohl die Rolle des PiC bei der Auslösung und Ausbreitung von Anfällen in Tiermodellen gut beschrieben ist, gibt es nur wenige Hinweise über die genaue Funktion des PiC beim Menschen (Koepp and Galovic, 2020; Stettler and Axel, 2009). Daher sind weitere Forschungen erforderlich, um das Ausmaß der Resektion sowohl mit dem Anfallsgeschehen als auch mit den neurokognitiven Ergebnissen zu korrelieren. Erwähnenswert ist, dass die Resektion des PiC bei einem transsylvischen Zugang für eine sAHE für den Neurochirurgen aufgrund mehrerer Aspekte anspruchsvoll ist. Eine ausgedehntere Resektion könnte riskant sein, da Teile der Basalganglien, des M1-Segments der MCA und anderer Gefäße, die die vordere perforierte Substanz durchqueren, verletzt werden könnten. Trotz dieses potenziellen Risikos deuten unsere Daten stark darauf hin, dass ein Versuch, den temporalen Anteil des PiC möglichst weit zu entfernen, während der tsSAHE unternommen werden sollte. Insgesamt liefert diese Arbeit starke Evidenz dafür, dass das Resektionsausmaß des PiC bei Patienten mit TLE signifikant mit der post-operativen Anfallskontrolle assoziiert ist. Zusätzlich stütze die Ergebnisse auch die Hypothese über eine mögliche Beteiligung des PiC als eine Art Hub-Station an der Entstehung und der Propagation von Anfällen im humanen Temporallappen.

Über die Auswirkungen der Resektion des PiC auf das langfristige Anfallsgeschehen nach einer tsSAHE existieren bisher keine Daten in der veröffentlichten Literatur. Basierend auf unseren Erkenntnissen aus der o.g. Publikation erfolgte in der folgenden klinischen Arbeit nun erstmalig die Evaluation des Einflusses des Resektionsausmaßes des PiC auf das Langzeit-Anfallsoutcome in dieser Patientenpopulation. Unsere Untersuchungen zeigten ein signifikant höheres Resektionsausmaß von PiC bei Patienten mit günstigem Langzeit-Anfallsoutcome. Außerdem war die Resektion von mindestens 27% des PiC mit einer hohen Rate (79%) an Anfallsfreiheit in der Langzeit-Beobachtung vergesellschaftet. Darüber hinaus konnten wir in der vorliegenden Arbeit zum ersten Mal das Ausmaß der PiC-Resektion von über 27% des Volumens als einzige unabhängigen und signifikanten Prädiktor für die Reduktion oder das Absetzen von AEDs während des langfristigen klinischen Verlaufs nach tsSAHE identifizieren. In der nun anbrechenden Ära, in der die minimalinvasiven Verfahren wie die LITT zunehmend an Interesse gewinnen, rückt auch hier der möglichst selektive Zugang zu den neuen Ablations-Zielvolumina im mesialen Temporallappen zunehmend in den Fokus. In der kürzlich veröffentlichten Studie zeigten Liu et al., dass eine Ablation mittels LITT mit einer zusätzlichen zweiten Trajektorie mit dem Ziel eine umfangreichere Ablation des Hippocampus, der Amygdala und des PiC zu erreichen, mit einer höheren Chance für Anfallsfreiheit vergesellschaftet ist, verglichen mit der herkömmlichen Trajektorie alleine (Liu et al., 2021).

Auch im Bereich des perioperativen und postoperativen Managements der Patienten findet in vielen neurochirurgischen Zentren gerade ein Umdenken statt mit dem Ziel dieses möglichst ressourcenschonend und individualisiert zu gestalten. Dies betrifft z.B. auch die Frage der Notwendigkeit einer intensivmedizinischen post-operativen Überwachung von neurochirurgischen Patienten nach stattgehabten elektiven Eingriffen über eine Kraniotomie (Bui et al., 2011; Terada et al., 2010). Dieser Fragestellung sind wir beim Management von epilepsiechirurgischen Patienten nachgegangen. Innerhalb des neuro-chirurgischen Patientenkollektives, stellen die epilepsiechirurgischen Patienten eine relativ homogene Gruppe dar. Sie sind häufig nicht besonders vorerkrankt und verhältnismäßig jung. So zeigte unsere Analyse, dass die elektive Epilepsiechirurgie wenig risikobehaftet ist und die Inzidenz von Ereignisse, die eine Überwachung auf einer Intensivstation erforderlich machten, lediglich bei 4,9% liegt bei einer Mortalität von 0%. Das häufigste Ereignis, welches

ein ICU-Setting erforderte, war eine frühe post-op. Nachblutung im Resektionsgebiet. Bis auf einen Patienten, traten die Ereignisse innerhalb der ersten 24 Std. post-operativ auf. Interessanterweise konnten Taylor et al. zwei unterschiedliche Intervalle identifizieren, in welchen neurologische Defizite aufgrund eines intrakraniellem Hämatoms nach einem neurochirurgischen Eingriff auftreten können (Taylor et al., 1995). Basali und Kollegen untersuchten die Korrelation zwischen Bluthochdruck und postoperativen intrazerebralen Hämatomen. Die Autoren identifizierten akute intraoperative und früh postoperativ erhöhte Blutdruckwerte als signifikante Risikofaktoren für die Entwicklung von intrakraniellen Hämatomen (Basali et al., 2000). In der Serie von Hanak et al., wurde die kontinuierliche intravenöse Applikation von Blutdruckmedikamenten bei Patienten mit akut erhöhtem Blutdruck postoperativ als häufigste Intervention auf der Intensivstation angegeben (Hanak et al., 2014). Interessanterweise benötigte in unserer Kohorte nur ein geringer Anteil der Patienten eine kontinuierliche intravenöse blutdruckwirksame Medikation. Weiter konnten Hanak et al. in ihrer Serie DM und höheres Alter als unabhängige Prädiktoren von postoperativen ICU pflichtigen Ereignissen identifizieren. Allerdings scheint das höhere Alter als Risikofaktor jedoch umstritten zu sein, da andere Studien eine solche Korrelation nicht gefunden haben (Layon et al., 1995; Ziai et al., 2003). In der vorliegenden Serie korrelierte das Alter bei der Operation nicht mit einer höheren Prävalenz postoperativer Ereignisse mit ICU-Bedarf. Außerdem lag das Durchschnittsalter unserer Kohorte bei 37,9 ± 13,4 Jahren und damit deutlich unter den Altersangaben in den oben genannten Studien. Die multivariate Analyse identifizierte in unserer Serien DM ebenfalls als einen unabhängigen Risikofaktor. Weitere Faktoren, die häufig als relevant für die Notwendigkeit einer ICU-Überwachung berichtet werden, wie z.B. höhere ASA-Klasse, Adipositas und die intraoperative Transfusion von Blutprodukten konnten in unserer Kohorte nicht als solche bestätigt werden. Darüber hinaus war auch die Lokalisation des zur epilepsiechirurgischen Behandlung führenden Fokus der vorliegenden Epilepsie (Temporallappenepilepsie vs. extratemporallappen Epilepsie) nicht mit einer höheren Prävalenz von ICU-pflichtigen Ereignissen einhergehend. Neben DM wurde in unserem Kollektiv ein intraoperativer Blutverlust über 325ml als weiterer prädiktiver Risikofaktor ermittelt. Die Ergebnisse dieser Arbeit zeigten auf, dass eine routinemäßige postoperative Überwachung von epilepsiechirurgischen Patienten auf einer ICU in erster Linie für Patienten mit entsprechend ermittelten Risikofaktoren

erforderlich ist. Insgesamt wäre eine postoperative Überwachung bei Abwesenheit dieser Risikofaktoren auch auf einer entsprechend ausgelegten IMC-Station vertretbar. Einschränkend muss jedoch erwähnt werden, dass es sich hierbei um eine single center Studie handelt und eine externe Validierung der Daten an anderen epilepsiechirurgischen Zentren helfen könnten, einen validen Algorithmus oder allgemeingültige Empfehlung in dieser Frage zu erarbeiten und zu etablieren.

Eine Möglichkeit der innerklinischen Translation der in der Epilepsiechirurgie angewandten Operationstechniken auf andere Bereiche der resektiven Neurochirurgie, wie z.B. neurochirurgische Behandlung von Hirntumoren, stellt das an unserer Klinik implementierte Ansatz der Behandlung von temporalen malignen Gliomen dar. Das Konzept der sog. supra-marginalen Resektionsstrategien, die über KM-verstärkende Grenzen der MRT-Läsionen hinausgeht, gewinnt eine wachsende Evidenzbasis für die chirurgische Behandlung von bösartigen primären Hirntumoren. Neben dem verbesserten Gesamtüberleben und dem verlängerten progressions-freien Überlebensintervalls in früheren hauseigenen Studien, weist die vorliegende Fallstudie auch auf einen Vorteil der supra-marginalen Resektion in Bezug auf die Ergebnisse der Anfallskontrolle bei Patienten mit temporalem Glioblastom und tumorbedingter Epilepsie hin. Bei Hirntumoren ist die Epilepsie häufig das erste Symptom (Chaichana et al., 2009; van Breemen et al., 2007; Vecht et al., 2014) und geht mit verminderten Lebensqualität einher (Shin et al., 2016). Neben der pharmakologischen Therapie kann die chirurgische Behandlung - wie die Epilepsiechirurgie und Erfahrungen mit der Operation niedriggradiger Gliome - einen entscheidenden Beitrag zur Anfallskontrolle leisten (Englot et al., 2012; Pallud et al., 2014; Yordanova et al., 2011). Postoperativ günstige Anfallsergebnisse nach der ersten Resektion von Glioblastomen wurden bei bis zu 77 % der Patienten berichtet (Chaichana et al., 2009). Die Ergebnisse der vorliegenden Studie beschreiben eine postoperative Anfallsfreiheit bei 70 % der Patienten mit temporalen Glioblastomen und liegen im in der Literatur beschriebenen Bereich. Die anteriore temporale Lobektomie hat sich in der epilepsiechirurgischen Behandlung bereits als eine valide chirurgische Option zur Anfallskontrolle bei Patienten mit einem epileptogenen Fokus im Bereich des Temporallappens etabliert (Bate et al., 2007; Duncan and Sagar, 1987). In der vorliegenden Studie konnte für die ATL als chirurgischer Behandlungsansatz in der Therapie des temporalen Glioblastoms mit TRE ein signifikanter Einfluss auf das günstige Anfallsoutcome gezeigt ($p = 0,002$) werden.

Aus der Literatur ist bekannt, dass insbesondere bei niedriggradigen Gliomen mit begleitender Epilepsie, die Resektion der temporomesialen Strukturen mit einem verbesserten Anfallsergebnis assoziiert ist (Englot et al., 2012; Xu et al., 2018). Die Ergebnisse unserer Arbeit scheinen in der Analogie dazu diese Hypothese zu bestätigen und stellen in der Form ein Novum in der neurochirurgischen Therapie von hochgradigen Gliomen dar. Es wird auch diskutiert, dass die supra-marginale Resektion mit einer höheren Rate an postoperativen Komplikationen einhergehen könnte. Die Ergebnisse dieser Arbeit liefern keinen Hinweis auf für ein erhöhtes Maß an ungünstigen postoperativen Ereignissen in der Lobektomie-Gruppe. Resektionen im Bereich der temporomesialen Strukturen bergen immer das Risiko einer postoperativen neuropsychologischen Beeinträchtigungen. Ausführliche neuro-psychologische Untersuchungen von Glioblastom-Patienten sind im Rahmen der präoperativen Vorbereitungen oft nicht vorgesehen und oftmals können diese Untersuchungen von den Patienten selbst nicht in dem Maße durchgeführt werden, wie es beispielsweise in der Epilepsiechirurgie der Fall ist. Dennoch ist dieser Aspekt eine interessante Perspektive für zukünftige Studien zur neuropsychologischen Beurteilung von Glioblastom-Patienten, die sich einer supra-marginalen Resektion unterziehen sollen (Zigiotto et al., 2020). Die vorliegende Studie bestätigt die ATL zusätzlich zu ihrem bekannten Nutzen hinsichtlich des Gesamtüberlebens als Methode der Wahl für die chirurgische Kontrolle von potenziellen tumorbedingten Anfällen bei Patienten mit temporalem Glioblastom.

5. Zusammenfassung

Die Temporallappenepilepsie ist nach wie vor die häufigste Form der fokalen Epilepsien. Die resektive Epilepsiechirurgie des Temporallappens in allen ihren Facetten hat sich über die Jahre und Jahrzehnte zur einen wichtigen und etablierten Säule der Behandlung von pharmakorefraktären TLE entwickelt. Dank des hochstandardisierten Vorgehens sowohl in der prächirurgischen Diagnostik als auch bei den operativen Eingriffen, ist es möglich, vergleichsweise hohe Raten an Anfallsfreiheit bei gleichzeitig geringen oder gut kontrollierbaren Risiken für Beeinträchtigungen zu erzielen. Auch die Epilepsiechirurgie selbst unterliegt einem stetigen Wandel. Insbesondere die Fortschritte in der modernen Bildgebung, der experimentellen Forschung aber auch der Technologien zur Detektion von Anfällen führen dazu, dass die Epilepsie zunehmend als eine Netzwerkerkrankung verstanden wird bei gleichzeitig immer präziserem Nachweis der Lokalisation des möglichen Anfallsgenerators. Dies ermöglicht zunehmend auch möglichst individualisierte Behandlungsansätze für die betroffenen Patienten zu entwickeln. Trotz dieser Entwicklungen bleibt auch nach einer an sich erfolgreichen epilepsiechirurgischen Behandlung in etwa bei einem Drittel der Patienten die angestrebte Anfallskontrolle aus. Die erste der hier vorgelegten Arbeiten fokussiert sich auf die Identifikation von Faktoren bei Patienten mit TLE, die mit einem ungünstigen postoperativen Anfallsoutcome einhergehen. Hier konnte zum einen die Hippocampusgliose erstmalig als eine eigenständige histologische Entität als ein negativer Prädiktor identifiziert werden. Zum anderen korrelierte eine nicht vollständige Resektion von temporo-mesialen Strukturen ebenfalls signifikant mit einem ungünstigen Anfallsoutcome. In den dann folgenden Arbeiten konnte ebenfalls zum ersten Mal gezeigt werden, dass das Resektionsausmaß des piriformen Kortex, eine in der Literatur zum humanen Temporallappen unterrepräsentierte Struktur des mesialen Temporallappens, im Vergleich zu den bekannten im Rahmen von tsSAHE zu resezierenden mesialen Strukturen alleinig mit der Rate an postoperativer Anfallsfreiheit korreliert. Dies konnte ebenfalls für die Anfallskontrolle sowie die Wahrscheinlichkeit der Reduktion oder Absetzen der antikonvulsiven Medikation im post-operativen Langzeitverlauf von Patienten mit TLE nach einer stattgehabten tsSAHE gezeigt werden. Im klinischen Alltag unseres Epilepsiezentrums haben die Ergebnisse dieser Arbeit bereits zur Änderung des Managements von

epilepsiechirurgischen Patienten geführt. So wird bei Resektionen im Rahmen von ATL oder tsSAHE der temporale Anteil des PiC möglichst weit reseziert. Zum anderen erfolgt im Rahmen der Implantation von Tiefenelektroden zwecks SEEG bei TLE das Einbringen von Tiefenelektroden in der temporalen PiC. Die Untersuchungen zum post-operativen Management von epilepsiechirurgischen Patienten, welche in der Form in dieser hochselektierten und homogenen Patientenpopulation bis dato in der Literatur nicht verfügbar waren, zeigen, dass in unserem Patientenkollektiv die Rate an Ereignissen im postoperativen Verlauf, welche das Setting und die Ressourcen einer ICU benötigen, niedrig ist. Auf der anderen Seiten konnten wir zeigen, dass sich perioperativ patientenbezogene und prozedurbezogene Faktoren identifizieren lassen, welche eine Estimation der Notwendigkeit einer postoperativen ICU-Überwachung durchaus ermöglichen. Vor diesem Hintergrund haben wir klinikintern unsere Strategie der postoperativen Überwachung von epilepsiechirurgischen Patienten dahingehend geändert und angepasst, dass in Abwesenheit der o.g. Faktoren eine postoperative Überwachung nicht zwingend und routinemäßig auf einer ICU stattfindet. Die letzte Arbeit rundet das Spektrum dahingehend ab, als ein Weg einer möglichen innerklinischen Translation von Epilepsiechirurgie zur onkologischen Neurochirurgie hin aufgezeigt werden konnte. Hier konnten wir an Patienten mit temporal lokalisierten Glioblastomen und Vorliegen einer Tumor assoziierten Epilepsie ebenfalls erstmalig nachweisen, dass das aus der Epilepsiechirurgie abgeleitete chirurgische Vorgehen im Sinne einer anterioren temporalen Lobektomie mit einer über die eigentlichen radiologisch definierte Tumorgrenzen hinweg reichender sog. supra-marginaler Resektion unter Mitnahme der temporo-mesilaer Strukturen einer klassischen onkologischen Strategie der gross total resection im Bezug auf die Anfallskontrolle signifikant überlegen ist. In der Zusammenschau zeigen die vorgelegten Arbeiten durch den Gewinn an neuen Erkenntnissen neue wesentlichen Aspekte im Bezug auf das Management von epilepsiechirurgischen Patienten mit pharmakoresistenten TLE auf. Darüber hinaus tragen die gezeigten Ergebnisse zur Optimierung und der Möglichkeit einer besseren Individualisierung sowie dem Erreichen und Sichern weiterhin sehr guter Resultate der resektiven Epilepsiechirurgie bei TLE bei. Dieser Umstand ist insbesondere vor dem Hintergrund eines sich fortentwickelnden Trends hin zu den minimalinvasiven chirurgischen Techniken zur Behandlung von TLE wie z.B. LITT hervorzuheben. Denn den traditionellen resektiven und selektiven

epilepsiechirurgischen Verfahren einschließlich der ATL und der tsSAHE bleibt aufgrund ihrer Wirksamkeit und Sicherheit auch im Langzeitverlauf in der Behandlung der TLE eine wichtige Rolle erhalten, nicht zuletzt auch als Rescue-Strategie bei Versagen der minimalinvasiven Behandlungsmethoden.

6. Überlappung durch geteilte Autorenschaften

Beispiel Text:

Die vorliegende Habilitationsschrift hat fünf publizierte Originalarbeiten zur Grundlage. Vier der Arbeiten habe ich als Erstautor (Borger et al., JNS 2021; Borger und Schneider et al., ACTN 2020; Borger et al. ACTN 2022; Borger et al. JNO 2021) und eine der Arbeiten als Letztautor veröffentlicht (Bahna et al., JNS 2022). Eine Arbeit habe ich mit Herrn Matthias Schneider als geteilter Erstautor zusammen veröffentlicht. Herr Matthias Schneider ist ein wissenschaftlich sehr engagierter Kollege und Leiter der neuro-onkologischen Forschung der Klinik für Neurochirurgie. Es besteht eine enge Kooperation zwischen der epilepsiechirurgischen und neuro-onkologischen Arbeitsgruppe. Mit Herrn Schneider habe ich die Daten der Arbeit akquiriert, analysiert sowie interpretiert. Die Arbeit wurde durch mich initiiert und konzipiert. Entsprechend seines Engagements wurde die Autorenschaft geteilt.

Eine Überlappung mit anderen Habilitationsschriften ist nicht gegeben.

Hier müssen Sie ganz klar Ihren eigenen Anteil an den geteilten Erst/ Letztautorenschaften die Sie für die Kumulation verwendet haben darlegen. Dadurch ist gewährleistet, dass die gemeinsam Publizierten Paper auch vom anderen Autor für eine zukünftige Habilitationsschrift genutzt werden darf.

7. Bibliographie

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8. Danksagung

Hier können Sie einen Danksagungstext einfügen.

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Fügen Sie hier bitte Ihren Lebenslauf samt Unterschrift ein.

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