Aus der Klinik für Diagnostische und Interventionelle Neuroradiologie des Universitätsklinikums Augsburg

# Die endovaskuläre Behandlung duraler Gefäße bei neurochirurgischen Krankheitsbildern:
## Präoperative, therapeutische und prophylaktische Ansätze

**Kumulative Dissertation**

zur Erlangung des akademischen Grades

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von

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Universität Augsburg University

## Eidesstattliche Versicherung und Erklärung

Hiermit versichere ich an Eides statt, dass die vorliegende Dissertation von mir selbständig und ohne unerlaubte Hilfe angefertigt wurde. Zudem wurden keine anderen als die angegebenen Quellen verwendet. Außerdem versichere ich, dass die Dissertation keiner anderen Prüfungskommission vorgelegt wurde und ich mich nicht anderweitig einer Doktorprüfung ohne Erfolg unterzogen habe.

## Statutory declaration and statement

I declare that I have authored this thesis independently, that I have not used other than the declared sources/resources. As well I declare that I have not submitted a dissertation without success and not passed the oral exam. The present dissertation (neither the entire dissertation nor parts) has not been presented to another examination board.

Dissertation eingereicht am: 07.01.2025

Erstgutachter (Hauptbetreuer): Herr Prof. Dr. med. A. Berlis

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Tag der mündlichen Prüfung: 05.08.2025

# Inhaltsverzeichnis

## 1. Abkürzungsverzeichnis

aPPT – aktivierte partielle Thromboplastinzeit

CSDH – Chronisches Subduralhämatom

CT – Computertomographie

dAVF – durale arteriovenöse Fistel

DSA – digitale Subtraktionsangiographie

KM – Kontrastmittel

MMA – Arteria meningea media

MVZ – medizinisches Versorgungszentrum

OP – Operation

PVA – Polyvinylalkohol

RCT – Randomisierte kontrollierte Studie

SD – Standardabweichung

WHO – World Health Organization

## 2. Publikationsliste

Publikation 1:

Onyinzo C, Berlis A, Abel M, Kudernatsch M, Maurer CJ. Efficacy and mid-term outcome of middle meningeal artery embolization with or without burr hole evacuation for chronic subdural hematoma compared with burr hole evacuation alone. J Neurointerv Surg. 2022 Mar;14(3):297-300. doi: 10.1136/neurintsurg-2021-017450. Epub 2021 Jun 29. PMID: 34187870.

Publikation 2:

Onyinzo C, Berlis A, Abel M, Kudernatsch M, Maurer C. Safety and Efficacy of Preoperative Embolization in Giant Intracranial Meningiomas Compared with Resection Surgery Alone. Arch Neurosci. 2024;11(1): e142629. https://doi.org/10.5812/ans-142629.

## 3. Erklärung zum Eigenanteil der Arbeiten

Bezüglich der ersten Publikation „Efficacy and mid-term outcome of middle meningeal artery embolization with or without burr hole evacuation for chronic subdural hematoma compared with burr hole evacuation alone“ habe ich zusammen mit den Co-Autoren das Studienprotokoll entwickelt. Anschließend habe ich das Protokoll zur ethischen Begutachtung bei der Beratungskommission für klinische Forschung in der Schön Klinik Vogtareuth eingereicht. Nach der positiven Beurteilung der Kommission habe ich die Patientenakten aller Patienten mit chronischen Subduralhämatomen gesucht und die zu verwendeten Daten anonymisiert und extrahiert. Danach habe ich die Daten in SPSS übertragen und die statistischen Analysen durchgeführt. Nach Abschluss der Analysen habe ich die Resultate mit den Co-Autoren besprochen und darauffolgend habe ich das Manuskript geschrieben. Das Manuskript wurde von den Co-Autoren überprüft und Anmerkungen wurden besprochen. Dann habe ich das Manuskript bei dem Journal of Neurointerventional Surgery eingereicht. Die Anmerkungen der Peer-Reviewer wurden wiederum mit allen Autoren besprochen und anschließend habe ich nach Vollendung der Anpassungen das Manuskript wieder eingereicht. Auch die zweite Runde der Reviewer- Anmerkungen wurden gemeinsam besprochen und nachdem ich auch diese in das Manuskript eingearbeitet habe, habe ich das Manuskript erneut eingereicht. Schlussendlich wurde dieser Artikel in dem Journal publiziert.

Bei der zweiten Publikation „Safety and Efficacy of Preoperative Embolization in Giant Intracranial Meningiomas Compared with Resection Surgery Alone” war meine Eigenarbeit gleich zur ersten Publikation. Zusammen mit den Co-Autoren habe ich das Studienprotokoll entwickelt, welches ich bei der Beratungskommission für klinische Forschung in der Schön Klinik Vogtareuth vorgelegt habe. Anschließend habe ich aus den Patientenakten aller Patienten mit Meningeomen die notwendigen Daten anonymisiert und extrahiert sowie in SPSS übertragen. Nachdem ich die statistischen Analysen abgeschlossen habe, habe ich die Ergebnisse mit den Co-Autoren besprochen und dann das Manuskript geschrieben. Das Manuskript wurde wiederum von den Co-Autoren geprüft und Anmerkungen wurden besprochen. Dann habe ich das Manuskript bei dem Journal Archives of Neuroscience eingereicht. Die Bemerkungen der Peer-Reviewer wurden zusammen mit allen Autoren besprochen und anschließend habe ich das Manuskript angepasst und erneut eingereicht. Daraufhin wurde der Artikel in dem Journal veröffentlicht.

# 4. Einleitung

## 4.1. Einführung in die Thematik

Die Arteria meningea media (MMA) ist eine relevante Struktur um verschiedene neurochirurgische Krankheitsbilder zu verstehen (1-3). Diese Arterie entspringt in der Regel der Pars mandibularis der Arteria maxillaris interna und ist der größte arterielle Ast, der die Dura mater und das Periost der inneren Lamina des Schädelknochens versorgt (3-5). Sie verläuft zunächst durch die Fossa infratemporalis nach cranial und zieht dann durch das Foramen spinosum im Os sphenoidale in die Schädelhöhle (1, 4). In der mittleren Schädelgrube folgt sie einer Vertiefung im Keilbeinflügel nach anterolateral und teilt sich als nächstes in die zwei Hauptäste, den Ramus anterior (frontaler Ast) und Ramus posterior (parietaler Ast), welche sich nachfolgend weiter verzweigen und die Dura und den inneren Schädelknochen versorgen (3-5). Abgesehen von diesen zwei Hauptästen, entspringen noch weitere Äste aus der MMA: Ramus petrosus superficialis, Ramus tympanica superior, Rami orbitalis und Rami temporalis (3, 5).

Aufgrund der komplexen Embryologie wurden bereits verschiedene Variationen und Abnormalitäten der MMA in der Literatur beschrieben (1, 4-6). Zu den seltenen Varianten der MMA zählt der Ursprung aus der Arteria cerebelli superior inferior und aus der Arteria basilaris oder aus einer ihrer Äste (7, 8). Eine häufigere Variante zeigt, dass die MMA der Arteria carotis interna im Bereich des Foramen lacerum entspringen kann (9). Andere Ursprungsvarianten aus der Arteria pharyngea ascendens oder aus der Arteria opthalmica werden ebenfalls in der Literatur genannt (10, 11). In den Fällen, in denen das Foramen spinosum nicht angelegt ist, tritt die MMA durch das Foramen ovale entlang des Nervus mandibularis in die mittlere Schädelgrube ein (12).

Das Bewusstsein über die Anatomie der MMA sowie ihrer Variationen ist essentiell bei der neurochirurgischen und neuroradiologischen Behandlung von verschiedenen Krankheitsbildern (13). Zu diesen Krankheitsbildern zählen chronische Subduralhämatome (CSDH), intrakranielle Meningeome, durale arteriovenöse Fisteln (dAVF), sowie auch epidurale Hämatome und (Pseudo-) Aneurysmen der MMA (4, 13). Diese kumulative Dissertation konzentriert sich auf die Behandlung der CSDH und intrakraniellen Meningeome.

### 4.1.1. Chronische Subduralhämatome

Das CSDH ist eine häufige und herausfordernde neurochirurgische Erkrankung mit einer Prävalenz von ungefähr 14 Patienten/ 100.000 (14, 15). Es wird erwartet, dass sich die Inzidenz des CSDH in den nächsten 25 Jahren durch das Älterwerden der Gesellschaft verdoppelt (14, 16). Die Pathophysiologie hinter der Formation und dem Wachstum von CSDH ist wesentlich komplexer als die ursprüngliche Theorie vermutete, nämlich, dass die Ruptur von Brückenvenen durch ein Schädel-Hirn-Trauma verursacht wird und so zur Entstehung des CSDH führt (15, 17). Die Entstehung des CSDH beginnt mit der Trennung der duralen Grenzschichten, was zu einer Proliferation der duralen Grenzzellen führt (15, 18). Die inflammatorische Reaktion der Dura mater involviert die Formation von Granulationsgewebe, Disposition von Makrophagen und resultiert folglich in die Angiogenese und Fibrinolyse von fragilen Kapillären und Bildung von inflammatorischen Membranen, die verantwortlich sind für die Akkumulation und Persistenz des CSDH (19, 20). Die Hauptblutversorgung dieser Membranen erfolgt durch die MMA (21, 22).

Der Goldstandard in der Behandlung des CSDH verbleibt weiterhin die traditionelle Bohrlochtrepanation zur Entlastung der Raumforderung, obwohl dadurch die grundliegenden pathophysiologischen Mechanismen nicht ausgeschalten werden und die Rezidive mit bis zu 30% weiterhin häufig vorkommen (23-27). In jüngster Vergangenheit hat sich die endovaskuläre Embolisation der MMA als vielversprechende zusätzliche oder alternative Behandlung bei CSDH gezeigt (28). Positive Resultate der Embolisation der MMA wurden bereits in einigen Fallstudien und auch in einer Multicenter-Studie demonstriert (29-38).

Die ersten randomisierten kontrollierten Studien (RCT) wurden kürzlich veröffentlicht, welche gezeigt haben, dass die MMA Embolisation als adjuvante Behandlungsmethode mit weniger Rezidiv-Hämatomen und somit mit weniger Revisionsoperationen assoziiert wurde und auch mit weniger gravierenden Komplikationen einherging (39-41). Dennoch verbleibt der Stellenwert der MMA Embolisation in der Behandlung von CSDH noch unklar, insbesondere was die Langzeitergebnisse betrifft.

### 4.1.2. Intrakranielle Meningeome

Intrakranielle Meningeome gehören zu den häufigsten primären intrakraniellen Tumoren, die regelmäßig, aufgrund ihrer vaskulären Natur, eine Herausforderung in der neurochirurgischen Behandlung darstellen (42-44). Die Blutversorgung dieser Tumore geht von der Dura mater und den benachbarten pialen Gefäßen aus (45-52). Die chirurgische Resektion des Tumors sowie der Dura mater und, wenn nötig, auch des betroffenen Schädelknochens, verbleibt die primäre Behandlung der Meningeome, auch wenn ihre Hypervaskularisation die Resektion häufig erschwert und Bluttransfusionen oft erforderlich sind (48, 51).

In den letzten Jahrzehnten wurde bereits vermutet, dass die präoperative Embolisation von Meningeomen zu geringerem intraoperativem Blutverlust, sicherer Resektion und weniger Komplikationen führen kann (53, 54). Dennoch sind die Vorteile der präoperativen Embolisation von intrakraniellen Meningeomen noch stets nicht vollkommen verstanden, da diese Intervention auch potentielle Risiken, besonders bei großen Meningeomen („Giant Meningiomas"), mit sich bringen kann. Diese Risiken beinhalten ischämische Schlaganfälle, postinterventionelles Hirnödem, Einblutungen in den Tumor und Paresen von Hirnnerven (54-61).

Obwohl es in der Literatur noch keine präzise Definition für „Giant Meningiomas" gibt, werden diese normalerweise klassifiziert als Meningeome mit einem Diameter größer als 5cm (62, 63). Diese seltene Subgruppe der Meningeome stellt aufgrund ihrer Größe, meist tieferer Lokalisation und vaskulären Blutversorgung des Tumors eine besondere Herausforderung für Neurochirurgen da. Außerdem werden diese Tumore assoziiert mit längerer Operationsdauer, erhöhtem Blutverlust und erschwerter Tumorpräperation infolge der umgebenden Arterien und Brückenvenen (60, 63). Daher wird vermutet, dass die präoperative Angiographie und Embolisation der tumorversorgenden Gefäße sowohl ausschlaggebende Informationen über die Blutversorgung des Tumors bieten als auch zu einer Verringerung der Operationsdauer und des intraoperativen Blutverlustes führen kann (64).

## 4.2. Ziele der Publikationen

Das übergeordnete Ziel beider Publikationen ist es zu zeigen, dass die endovaskuläre Embolisation duraler Gefäße, insbesondere der MMA, bei CSDH und Meningeomen eine sichere und effiziente Intervention in der Behandlung dieser Krankheitsbilder darstellt. Dafür wurde jeweils eine retrospektive Kohortenstudie durchgeführt.

Die erste retrospektive Studie inkludierte Patienten, die sich in der Schön Klinik Vogtareuth zwischen Januar 2018 und Dezember 2020 vorstellten und mit CSDH diagnostiziert wurden. Die Patienten wurden je nach der durchgeführten Behandlung in einer der drei Subgruppen unterteilt, nämlich Operation, Operation und MMA Embolisation oder MMA Embolisation allein. Es wurde die Hypothese aufgestellt, dass die MMA Embolisation sich effektiv in der Behandlung von CSDH hinsichtlich der Komplikations- und Rezidivraten zeigt, ob in Kombination mit einer chirurgischen Behandlung oder nicht. Hierfür wurden die Patientenakten, radiologischen Befunde sowie Operations- und Angiographieberichte, und die Nachsorge- Berichte evaluiert. Außerdem wurde ein Hauptaugenmerk auf Patienten gerichtet, die in ihrer Dauermedikation Thrombozytenaggregationshemmer oder antikoagulierende Medikamente aufwiesen. Die primären Endpunkte wurden definiert als Komplikationen der Behandlung, klinischer Befund bei Entlassung des Patienten und die Rate der Revisionsoperation und Rezidive. Als sekundärer Endpunkt wurden die Befunde der Computertomographie (CT) in der Nachsorge ausgewertet.

Die zweite retrospektive Kohortenstudie schloss Patienten mit intrakraniellen Meningeomen ein, die in der Schön Klinik Vogtareuth zwischen Januar 2012 und Dezember 2022 diagnostiziert und behandelt wurden. Die Patienten wurden je nach Behandlung in die Gruppe Operation oder präoperative Embolisation und Operation eingeteilt. Eine Subgruppe wurde bezüglich Patienten mit „Giant Meningiomas“ erstellt. Es wurde die Hypothese aufgestellt, dass die präoperative Embolisation von Meningeomen, und besonders von „Giant Meningeomas“, eine risikoarme und effektive Behandlung ist, welche zu weniger intraoperativen Blutverlust und einer kürzeren Operationsdauer führt. Die Endpunkte dieser Studie wurden definiert als Grad der Devaskularisierung, intrainterventionelle und intraoperative Komplikationen, intraoperativer Blutverlust, postoperative Komplikationen und ob Bluttransfusionen gegeben werden mussten.

# 5. Darstellung der Ergebnisse

## 5.1. Publikation 1

Insgesamt wurden 132 Patienten mit CSDH in diese retrospektive Kohortenstudie eingeschlossen. Die MMA Embolisation in Kombination mit einer Operation im Sinne einer Bohrlochtrepanation wurde bei 31 Patienten (23,5%) durchgeführt. Die alleinige Bohrlochtrepanation erfolgte bei 82 Patienten (62,1%) und die alleinige MMA Embolisation bei 19 Patienten (14,4%).

Die zugrundeliegenden Patientencharakteristika wie Alter, Geschlecht, laborchemische Blutgerinnungsparameter (aktivierte partielle Thromboplastinzeit (aPPT), Prothrombinzeit und Thrombozytenzahl) und Größe des Hämatoms zeigten keine signifikanten Unterschiede zwischen den Gruppen. Dennoch wurde ein signifikanter Unterschied zwischen den Gruppen bezüglich der Einnahme von Antikoagulantien und Thrombozytenaggregationshemmer gefunden ($p<0.001$), welche höher war in der Embolisationsgruppe (84,2%) und in der kombinierten Behandlungsgruppe (61,1%) verglichen mit der Patientengruppe, die nur operiert wurden (36,6%). Außerdem erfolgte die Bohrlochtrepanation in 92,7% der Fälle in Intubationsnarkose, wohingegen die MMA Embolisation in 84,2% der Fälle in Lokalanästhesie durchgeführt wurde ($p<0.001$).

Tabelle 1 zeigt die Unterschiede der Komplikationen und der klinischen Entlassbefunde zwischen den Patientengruppen, bei denen entweder die alleinige Bohrlochtrepanation oder in Kombination mit der MMA Embolisation durchgeführt wurde. Es wurde eine Tendenz gefunden, dass weniger Revisionsoperationen in der kombinierten Behandlungsgruppe erfolgten ($p=0.083$). Es gab keinen statistischen Unterschied in den Gruppen in Bezug auf die Komplikationen und den klinischen Entlassbefund ($p=0.456$ und $p=0.516$). In der Embolisationsgruppe wurde keine akute Nachblutung oder Hirnnervenparese gefunden. Ebenso wurden keine vaskulären Komplikationen wie ischämische Schlaganfälle oder kardiovaskuläre Komplikationen gefunden. In der Patientengruppe, bei denen nur die Bohrlochtrepanation als Behandlung durchgeführt wurde, brauchten elf Patienten (13,1%) eine Revisionsoperation, fünf von ihnen zeigten eine akute Nachblutung und bei wiederum drei von diesen Patienten musste eine Notfall-Kraniotomie durchgeführt werden. Ein Patient verstarb während des stationären Aufenthaltes, jedoch nicht aufgrund Komplikationen, die mit der Operation in Zusammenhang standen. In der Patientengruppe, die nur die MMA Embolisation erhalten haben, gab es keine Revisionsoperationen und auch keine Komplikationen, die durch die Intervention verursacht wurden.

*Tabelle 1: Vergleich von Komplikationen und Behandlungsergebnisse zwischen der Operationsgruppe und der kombinierten Behandlungsgruppe*

| ***Gruppen*** **Parameter** | **Operation + Embolisation (n=31, 27,4%)** | **Operation (n=82, 72,5%)** | **p-Wert** |
|---|---|---|---|
| **Komplikationen** | | | 0.456 |
| Keine Komplikation | 30 (96,8%) | 72 (87,8%) | |
| Rezidiv- Hämatom | 1 (3,2%) | 4 (4,9%) | |
| Akute Nachblutung | 0 | 5 (6,1%) | |
| Liquorfistel | 0 | 1 (1,2%) | |
| **Klinischer Entlassbefund** | | | 0.516 |
| Kein Defizit | 29 (93,5%) | 69 (84,1%) | |
| Aphasie | 2 (6,5%) | 5 (6,1%) | |
| Hemiparese | 0 | 5 (6,1%) | |
| Dysphagie | 0 | 2 (2,4%) | |
| Exitus lethalis | 0 | 1 (1,2%) | |
| **Notoperation** | 1 (3,2%) | 11 (13,4%) | 0.083 |

Insgesamt wurden 73 von den initial einbezogenen 132 Patienten (55,3%) in unserem medizinischen Versorgungszentrum (MVZ) zur Nachsorge gesichtet. Der Mittelwert ± Standartabweichung (SD) der Nachsorge-Periode betrug 3,4 ± 2,2 Monate. Sechs Patienten (8,2%) erhielten die MMA Embolisation als alleinige Behandlung, 16 Patienten (21,9%) in Kombination mit der Bohrlochtrepanation und 51 Patienten (69,9%) die alleinige Bohrlochtrepanation (Tabelle 2).

Ein Patient mit Antikoagulantien in der Dauermedikation, der die kombinierte Behandlung erhalten hat, zeigte ein raumforderndes Rezidiv-CSDH. Dieser Patient brauchte eine Revisionsoperation über das bereits vorbestehende Bohrloch zehn Tage nach der stationären Entlassung. In der Patientengruppe, die nur chirurgisch behandelt wurden, zeigten acht Patienten (15,7%) ein Rezidiv-CSDH. Bei diesen acht Patienten war eine Revisionsoperation notwendig, zwei von ihnen brauchten sogar eine Kraniotomie. Sechs von diesen acht Patienten hatten Antikoagulantien oder Thrombozytenaggregationshemmer in ihrer Dauermedikation präoperativ. Alle Patienten, die nur mit der MMA Embolisation behandelt wurden, zeigten eine komplette Resorption des CSDH bei der Nachsorge. Interessanterweise hatten 83,3% dieser Patienten Antikoagulantien oder Thrombozytenaggregationshemmer in ihrer Vormedikation.

*Tabelle 2: Vergleich der CT-Befunde bei der Nachsorge der CSDH-Patienten*

| **Gruppen** / ***CT-Befund*** | **Operation + Embolisation (n=16, 21,9%)** | **Operation (n=51, 69,9%)** | **Embolisation (n=6, 8,2%)** | **p-Wert** |
|---|---|---|---|---|
| Komplette Hämatomresorption | 7 (55,8%) | 21 (43,1%) | 6 (100%) | 0.074 |
| Resterguss <10mm | 8 (40,0%) | 22 (42,1%) | 0 | |
| Revisions-OP | 1 (5,0%) | 8 (15,7%) | 0 | |

## 5.2. Publikation 2

Insgesamt wurden 189 Patienten mit Meningeomen in der Schön Klinik Vogtareuth zwischen Januar 2012 und Dezember 2022 zur Resekionsoperation stationär aufgenommen. Die präoperative Tumorembolisation wurde in 22 Fällen (11,6%) durchgeführt. Neun dieser embolisierten Patienten (40,1%) haben noch am gleichen Tag in derselben Vollnarkose die Resektionsoperation erhalten. In den restlichen 59,9% der Patienten wurde die Operation für den nächsten Tag geplant und in sieben von diesen Patienten konnte die Embolisation in Lokalanästhesie durchgeführt werden. Abbildung 1 zeigt ein Beispiel für die angiographische Darstellung eines rechtsseitigen, großen Keilbeinflügelmeningeoms vor und nach der Tumorembolisation.

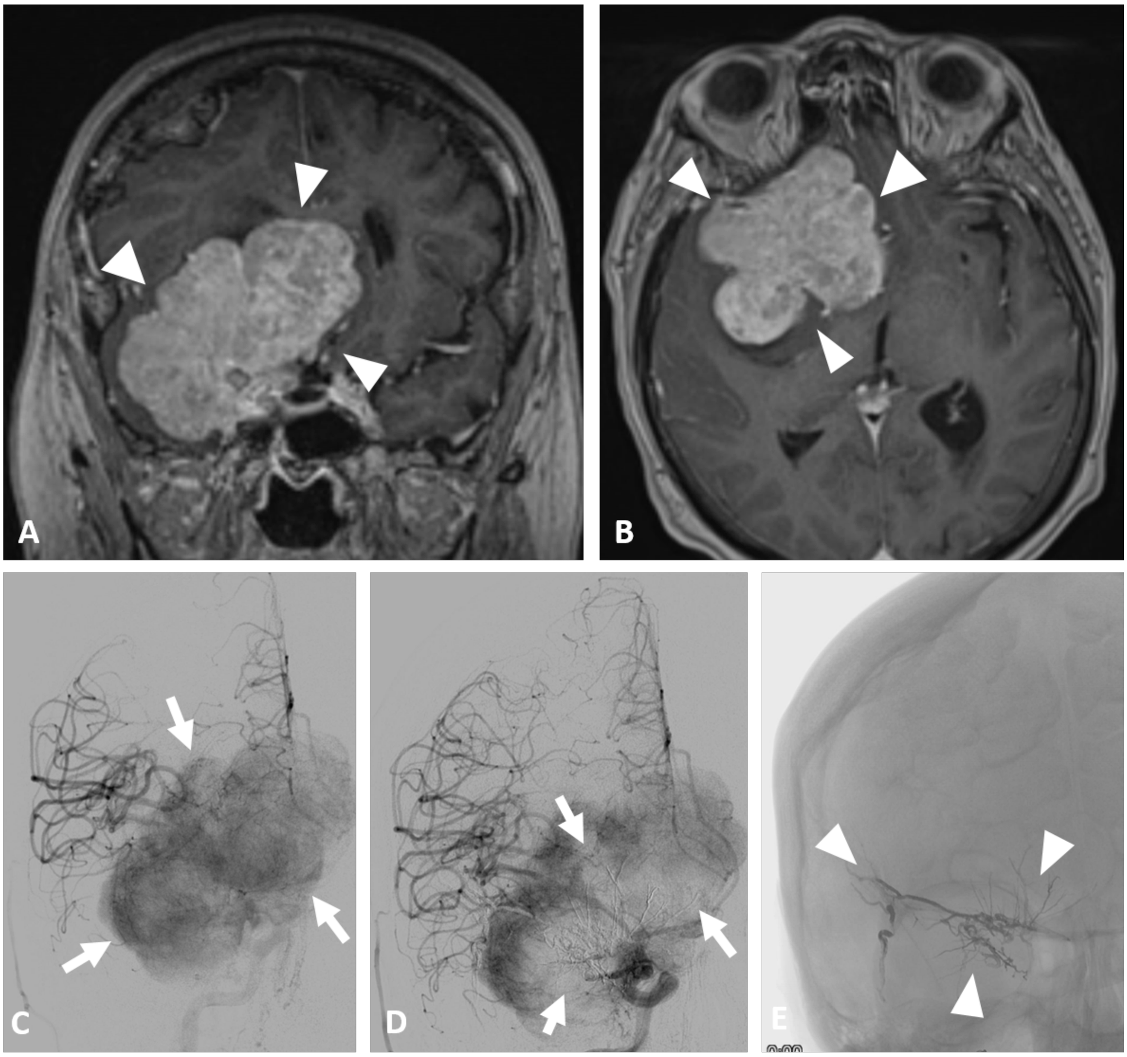


*Abbildung 1: A und B, Ein Patient mit einem „Giant Meningioma" lokalisiert am rechten Keilbeinflügel (Pfeilspitzen), coronare und transversale T1-Sequenz nach Kontrastmittelgabe (KM); C, digitale Subtraktionsangiographie (DSA) mit Injektion in die rechte Arteria carotis*

*communis und einer signifikanten Tumoranfärbung in der späten arteriellen Phase (Pfeile); D, DSA wieder mit Injektion in die Arteria carotis communis nach Embolisation und einer signifikanten Abnahme der Tumoranfärbung im Zentrum des Meningeoms (Pfeile); E, Durchleuchtung ohne KM-Gabe, die das Flüssigembolisat im Zentrum des Tumors zeigt (Pfeilspitzen).(64)*

In Bezug auf die Patientencharakteristika wie Alter und Geschlecht, aber auch WHO-Grad des Meningeoms wurden keine signifikanten Unterschiede zwischen den Behandlungsgruppen gefunden. Dahingegen wurde ein signifikanter Unterschied des Tumorvolumens zwischen den Gruppen gefunden ($p<0.001$). Das Tumorvolumen mit durchschnittlich 59,2 $cm^3$ zeigte sich in der kombinierten Behandlungsgruppe signifikant größer in Vergleich mit der Operationsgruppe, die ein durchschnittliches Tumorvolumen von 15,7 $cm^3$ aufwies (siehe Tabelle 3). Ebenfalls wurde auch ein signifikanter Unterschied zwischen den Gruppen hinsichtlich der Lokalisation des Tumors und der initialen Symptome gefunden ($p<0.001$ und $p=0.004$). In der Gruppe Patienten, die die präoperative Embolisation erhalten haben zeigten sich mehr tiefer lokalisierte Tumore wie Keilbeinflügelmeningeome (36,4%) verglichen mit der Operationsgruppe, die beinahe zur Hälfte Konvexitätsmeningeomen aufwiesen.

*Tabelle 3: Die Tumorcharakteristika der kombinierten Behandlungsgruppe verglichen mit der Operationsgruppe*

| ***Gruppen*** / **Parameter** | **Embolisation + Operation (N=22)** | **Operation (N=167)** | **p-Wert** |
|---|---|---|---|
| **Tumorlokalisation** | | | <0.001 |
| Sulcus olfactorius | 4 (18,1%) | 7 (4,2%) | |
| Keilbeinflügel | 8 (36,4%) | 11 (6,6%) | |
| Parasagittal | 4 (18,1%) | 17 (10,2%) | |
| Falx | 3 (13,6%) | 34 (20,4%) | |
| Tentorium | 1 (4,5%) | 14 (8,4%) | |
| Intraventrikulär | 1 (4,5%) | 2 (1,2%) | |
| Konvexität | 1 (4,5%) | 82 (49,1%) | |
| **Tumorvolumen ($cm^3$± SD)** | 59,2 ± 23,7 | 15,7 ± 20,8 | 0.002 |
| **WHO-Grad** | | | 0.789 |
| I | 19 (86,4%) | 138 (82,6%) | |
| II | 3 (13,6%) | 26 (15,6%) | |
| III | 0 | 3 (1,8%) | |

Hinsichtlich der angiographischen Charakteristika der kombinierten Behandlungsgruppe wurden im Durchschnitt 2,1 tumorversorgende Gefäße gefunden und durchschnittlich wurden 1,5 von diesen embolisiert. In 81,8% der Fälle wurde die MMA verschlossen und zu 90,9% wurden Polyvinylalkohol (PVA) Partikel als Embolisat verwendet. Außerdem wurde eine geschätzte Tumordevaskularisation von mehr als 75% in 57,1% der Patienten gefunden.

*Tabelle 4: Operationscharakteristika und postoperative Komplikationen der kombinierten Behandlungsgruppe verglichen mit der Operationsgruppe.*

| ***Gruppen*** / **Parameter** | **Embolisation + Operation (N=22)** | **Operation (N=167)** | **p-Wert** |
|---|---|---|---|
| **Operationsdauer (min± SD)** | 358,0 ± 115,9 | 191,7 ± 93,0 | 0.023 |
| **Blutverlust (ml± SD)** | 581,8 ±195,5 | 376,0 ± 160,2 | <0.001 |
| **Postoperative Komplikation:** | 3 (13,6%) | 16 (9,6%) | 0.023 |
| Malignes Hirnödem | 1 (4,5%) | 0 | |
| Nachblutung | 0 | 4 (2,4%) | |
| Ischämischer Schlaganfall | 1 (4,5%) | 0 | |
| Epileptischer Anfall | 1 (4,5%) | 8 (4,8%) | |
| Wundinfektion | 0 | 2 (1,2%) | |
| Aphasie | 0 | 1 (0,6%) | |
| Pneumonie | 0 | 1 (0,6%) | |
| **Notoperation** | 1 (4,5%) | 4 (2,4%) | 0.465 |

Tabelle 4 demonstriert die Operationscharakteristiken und postoperative Komplikationen der beiden Behandlungsgruppen. In der kombinierten Behandlungsgruppe wurde eine signifikant längere Operationsdauer sowie signifikant höherer intraoperativer Blutverlust gefunden (p=0.023 und p<0.001). Ebenfalls wurde ein signifikanter Unterschied zwischen den Behandlungsgruppen in Bezug auf die postoperativen Komplikationen gefunden (p=0.023). In der kombinierten Behandlungsgruppe erfolgte eine notfallmäßige Revisionsoperation aufgrund eines postoperativen malignen Hirnödems, wohingegen in der Operationsgruppe vier Notoperationen wegen Nachblutungen durchgeführt wurden. Interessanterweise sind keine peri-interventionellen Komplikationen sowohl bei der Angiographie und Embolisation als auch bei der Operation aufgetreten.
Tabelle 5 fasst die Subgruppenanalyse der Patienten mit „Giant Meningiomas“, die einen Tumordurchmesser von mehr als 5 cm aufwiesen, zusammen. Es wurden keine

signifikanten Unterschiede zwischen den Behandlungsgruppen bezüglich der Patientencharakteristiken wie Alter und Geschlecht gefunden (p=0.647 und p=0.922). Im Gegensatz dazu wurde ein signifikanter Unterschied in der Tumorlokalisation zwischen den Gruppen gefunden (p=0.003). In 36,4% der Fälle in der kombinierten Behandlungsgruppe wurde ein Keilbeinflügelmeningeom gefunden. Dagegen zeigten 50% der Patienten in der Operationsgruppe ein Konvexitätsmeningeom. Der intraoperativere Blutverlust war signifikant niedriger in der kombinierten Behandlungsgruppe im Vergleich mit der Operationsgruppe (p=0.034), jedoch wurde kein signifikanter Unterschied in Operationsdauer gefunden (p=0.570).

*Tabelle 5: Subgruppenanalyse der kombinierten Behandlungsgruppe und der Operationsgruppe in Bezug auf „Giant Meningiomas" mit einem Tumordurchmesser von mindestens 5cm.*

| ***Gruppen*** **Parameter** | **Embolisation + Operation (N=22)** | **Operation (N=34)** | **p-Wert** |
|---|---|---|---|
| **Alter (Jahre± SD)** | 61,9 ± 12,0 | 64,0 ± 13,1 | 0.647 |
| **Geschlecht (weiblich)** | 12 (54,5%) | 18 (52,9%) | 0.922 |
| **Tumorlokalisation** | | | 0.003 |
| Sulcus olfactorius | 4 (18,1%) | 2 (5,9%) | |
| Keilbeinflügel | 8 (36,4%) | 4 (11,8%) | |
| Parasagittal | 4 (18,1%) | 1 (2,9%) | |
| Falx | 3 (13,6%) | 7 (20,6%) | |
| Tentorium | 1 (4,5%) | 3 (8,8%) | |
| Intraventrikulär | 1 (4,5%) | 0 | |
| Konvexität | 1 (4,5%) | 17 (50,0%) | |
| **Tumorvolumen (cm ± SD)** | 59,2 ± 23,7 | 54,5 ± 24,7 | 0.293 |
| **Blutverlust (ml ± SD)** | 581,8 ± 195,5 | 739,1 ± 200,7 | 0.034 |
| **Operationsdauer (min± SD)** | 358,0 ± 115,9 | 275,7 ± 110,1 | 0.570 |
| **Notoperation** | 1 (4,5%) | 0 | 0.210 |

## 6. Zusammenfassung

Die vorliegende Dissertation untersuchte die Effizienz und Sicherheit der endovaskulären Embolisation duraler Gefäße, insbesondere der MMA, bei CSDH und intrakraniellen Meningeomen. Beide Krankheitsbilder werden in neurochirurgischen Kliniken häufig gesehen und können oft für den behandelnden Neurochirurgen eine Herausforderung darstellen.

Die Resultate der ersten retrospektiven Studie zeigen, dass die MMA Embolisation eine komplikationsarme Behandlung darstellt und einen positiven therapeutischen Effekt bei Patienten mit CSDH aufweist. Dies ist besonders zutreffend für Patienten, die aufgrund ihrer Komorbiditäten auf Antikoagulantien oder Thrombozytenaggregationshemmer angewiesen sind. Die MMA Embolisation scheint effektiver zu sein als die Operation alleine, aufgrund der niedrigeren Komplikationsrate hinsichtlich der Rezidiv-CSDH und akuten subduralen Nachblutungen. Der Stellenwert der alleinigen MMA Embolisation bleibt jedoch noch unklar. In der akuten Phase der Patienten mit neurologischen Symptomen und Defiziten, die durch den raumfordernden Effekt des CSDH verursacht werden, hat die Embolisation der MMA vorerst keine Auswirkungen. Daher sollte die MMA Embolisation in diesen Fällen als eine adjuvante Behandlung zusätzlich zur Operation gesehen werden. Bei Patienten ohne neurologische Defizite sowie ohne raumfordernden Effekt des Hämatoms scheint die MMA Embolisation auch als alleinige Behandlung angewendet werden zu können.

Die Ergebnisse der zweiten Kohortenstudie demonstrieren, dass die präoperative endovaskuläre Tumorembolisation in ausgewählten Patienten mit tieflokalisierten „Giant Meningiomas" eine sichere und technisch gut durchführbare adjuvante Behandlung darstellt um eine substantielle Devaskularisierung des intrakraniellen Meningeoms zu erreichen. Diese Behandlung zeigt sich komplikationsarm und scheint einen positiven Effekt auf den intraoperativen Blutverlust, aber auch auf die Operationsdauer zu haben.

Schlussfolgernd zeigt diese Dissertation, dass die endovaskuläre Embolisation duraler Gefäße einen positiven therapeutischen Effekt bei sowohl CSDH als auch tieflokalisierten, intrakraniellen „Giant Meningiomas" aufweist.

## 6.1. Summary

The present dissertation examined the efficacy and safety of the endovascular embolization of dural vessels, in particular of the MMA, in CSDH and intracranial meningiomas. Both disease patterns are commonly seen in the neurosurgical clinic and may be challenging for the attending neurosurgeon.

The results of the first retrospective study show that MMA embolization is a treatment with low complication rates and a positive therapeutic effect on CSDH. This may especially apply in patients who depend on their anticoagulant or antiplatelet therapy due to their comorbidities. It seems to be more effective than surgery alone because of a lower complication rate regarding hematoma re-accumulation and acute re-bleeding. The significance of MMA embolization as a standalone treatment still remains unclear. In the acute phase of patients with neurological symptoms and deficits caused by mass effect of the CSDH, MMA embolization does not seem to have an immediate impact. Therefore, MMA embolization may be appreciated as an adjuvant therapy in these cases. In patients without neurological deficits as well as without mass effect, MMA embolization can also be used as a standalone treatment.

The results of the second cohort study demonstrate that preoperative endovascular embolization of the tumour in appropriately selected patients with giant meningiomas, especially those in deeper locations, is a safe and feasible treatment to reach a substantial degree in devascularisation of the intracranial meningioma. This treatment shows an acceptably low rate of complications and seems to have a positive effect on intraoperative blood loss as well as duration of surgery.

In conclusion, this dissertation shows that endovascular embolization of dural vessels may have a positive therapeutic effect on CSDH as well as intracranial giant meningioma in deeper locations.

## 7. Literaturverzeichnis


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# Appendix

## I. Manuskript Publikation 1

Onyinzo C, Berlis A, Abel M, Kudernatsch M, Maurer CJ. Efficacy and mid-term outcome of middle meningeal artery embolization with or without burr hole evacuation for chronic subdural hematoma compared with burr hole evacuation alone. J Neurointerv Surg. 2022 Mar;14(3):297-300. doi: 10.1136/neurintsurg-2021-017450. Epub 2021 Jun 29. PMID: 34187870.

# Efficacy and Midterm Outcome of Middle Meningeal Artery Embolization with or without Burr-Hole Evacuation for Chronic Subdural Hematoma compared with Burr-Hole Evacuation alone


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## Abstract

### Background

Chronic subdural hematoma (CSDH) is a common neurosurgical condition with high recurrence rates. Repeated microbleedings from fragile neo-vessels supplied by peripheral branches of the middle meningeal artery (MMA) are believed to be responsible for the growth and recurrence of CSDH. Thus, MMA embolization might be a promising method to prevent re-bleedings and recurrences. This study aims to assess efficacy, complication rates and midterm outcome of MMA embolization with or without burr-hole irrigation compared to burr-hole irrigation alone.

### Methods

Patients diagnosed with CSDH, who underwent MMA embolization and/ or surgical treatment were retrospectively recruited in this single center study. The outcome variables were defined as treatment-related complications, clinical outcome at discharge, rate of revision surgery, and computed tomography (CT)-findings during the follow-up period.

### Results

In total, 132 patients with CSDH were included in this study. The use of antiplatelet/ anticoagulant medication was significantly higher in the combined treatment and embolization group ($p<0.001$). A trend of less revision surgeries was found in the group of patients, who received MMA embolization combined with burr-hole irrigation ($p= 0.083$). Follow-up was available for 73 patients (55.3%) with a mean follow-up period of $3.4 \pm 2.2$ months. Eight patients (15.1%) of the surgery group showed hematoma reaccumulation and needed surgical rescue, whereas only one patient (5.0%) of the combined treatment group needed revision surgery. In all patients treated with only MMA embolization complete hematoma resolution was found.

### Conclusion

MMA embolization is a safe and efficacious minimal invasive adjuvant and/or alternative procedure for treatment of CSDH with a reduced recurrence rate.

## Keywords

Chronic Subdural Hematoma (CSDH), Middle Meningeal Artery (MMA) Embolization, Burr Hole Evacuation, Midterm Outcome, Revision Surgery

## Introduction

Chronic subdural hematoma (CSDH) is an increasingly prevalent and challenging neurosurgical disease.[1,3] This disease occurs in approximately 14 patients/ 100,000 and becomes more prevalent in patients older than 70 years with an occurrence of 18 patients/ 100,000[1]. However, the incidence of CSDH is expected to double in slightly more than 25 years, as the population ages.[2]

Nowadays, the pathophysiology behind the formation and growth of CSDH is known to be more complex than the traditional theory of head trauma causing a disruption of bridging veins[22]. Development of CSDH starts with the separation of the dural border cell layer, which leads to dural border cell proliferation.[3,23] An inflammatory response of the dural layer involving granulation tissue formation and macrophage deposition as well as angiogenesis and fibrinolysis of fragile capillaries, and formation of inflammatory membranes are responsible for the accumulation and persistence of a CSDH.[3-5]

On the basis of these pathophysiological mechanisms, various nonsurgical treatments for CSDH, such as corticosteroids, statins, angiotensin-converting enzyme inhibitors, and antifibrinolytics, have been proposed. However, the therapeutic effect is limited to selected patient groups.[6-9] A recent randomized controlled trial investigated the treatment with dexamethasone, which resulted in fewer favorable outcomes and more adverse events than placebo at six months.[34] Therefore, surgical hematoma evacuation to relieve the mass effect is commonly used and burr-hole irrigation is widely considered to be the therapeutic gold standard.[20,21] Nevertheless, it does not interrupt the underlying pathophysiological mechanisms, and therefore, recurrence occurs frequently. Recurrence rates after evacuation ranges between 5% and 30% in the literature[24-26]. Surgery also carries an inherent risk for patients receiving anticoagulant or antiplatelet therapy, because the effect of these agents must be reversed or patients must be weaned off before the surgical procedure[10].

Endovascular embolization of the middle meningeal artery (MMA) has recently been proposed as a promising adjunctive or alternative treatment, especially for patients on antiplatelet or anticoagulant therapy[11]. MMA Embolization showed positive results in several case reports and more recently in a multi-center study[12-19,28]. However, the role of MMA embolization in the management of CSDH is not yet clear. In this study, we aim to assess efficacy, complication rates and midterm outcome of MMA embolization results with or without burr-hole irrigation compared to burr-hole irrigation alone.

## Methods

This is a retrospective cohort study of patients diagnosed with CSDH in Schoen Clinic Vogtareuth between January 2018 and December 2020. The last embolization included in this study was performed on 10th November 2020. Medical records, radiographic studies, operative and angiographic reports, and follow-up evaluations were reviewed.

The subjects were divided into surgery group, combined treatment group (MMA embolization and surgery) and embolization group based on their treatment approach. The surgery group included patients, who received burr-hole trepanation for subdural irrigation under general or local anesthesia. Endovascular embolization of the MMA was performed with a 6-French guide catheter inserted into the right femoral artery via a 6-French sheath. The catheter was placed in the external carotid artery on the affected side. A microcatheter was then advanced to the main trunk of the MMA. The frontal and parietal branches of the MMA were selectively catheterized and – if safely possible - embolization was performed using 45 -150 µm Contour polyvinyl alcohol (PVA) particles (Boston Scientific, Natick, Massachusetts, USA) and or bare platinum coils, depending on the presence of dangerous anastomoses.

Patients on antiplatelet or anticoagulant therapy had their medication discontinued immediately on admission in an attempt to prevent hematoma expansion. Restarting these agents was weighted with a focus on the history of embolism, reasons for anticoagulant/ antiplatelet therapy and hemostatic function.

Control computed tomography (CT) was performed on the day after surgery or intervention to rule out any remarkable complication. After discharge, patients received a scheduled follow-up CT in our outpatient clinic, starting four weeks after discharge. When the follow-up CT showed disappearance of hematoma or hematoma reduction < 10mm without clinical symptoms, we considered CSDH to have been cured and ceased follow-up. When recurrence was identified, patients were admitted again for further assessment and rescue surgery.

We investigated medical history and the use of anticoagulant or antiplatelet therapy in all patients. Primary outcome variables were defined as treatment-related complications, clinical outcome at discharge, and the rate of surgical rescue and revision surgery, respectively. As a secondary endpoint we examined CT-findings in the follow-up period with regard to hematoma evacuation, residual effusion, or reaccumulation.

Statistical Package for Social Sciences-25 (SPSS-25) was used to code the variables of interest and perform statistical analyses. Descriptive statistics were used to show baseline characteristics and to calculate the mean and standard deviation (SD) of the different variables and/or number of patients per category and associated percentages. To evaluate the differences between the treatment groups in terms of clinical-radiologic features and treatment results, Person $\chi^2$ test and Fisher exact test were performed. Differences were considered significant for probability values of $p < 0.05$.

## Results

A total of 132 patients with CSDH met the inclusion criteria. Thirty-one MMA embolizations in combination with burr-hole irrigation (23.5%) were performed. Burr-hole irrigation and MMA embolization as a sole treatment were carried out in 82 (62.1%) and 19 patients (14.4%), respectively.

**Baseline characteristics**

Table 1 summarizes the baseline characteristics of all patients. Significant difference between the groups was found in terms of the use of antiplatelet or anticoagulant medication, which was higher in the embolization group (84.2%) and in the combined treatment group (61.1%) compared to the surgery group (36.6%) ($p<0.001$). Furthermore, most of the burr-hole irrigations were conducted under general anesthesia (92.7%), whereas MMA embolization was rather performed under local anesthesia (84.2%) ($p<0.001$). On comparing sex, initial hematoma width and laboratory tests including prothrombin time, aPPT and platelet count, no statistical differences were found.

**Table 1:** Comparison of baseline characteristics between the treatment groups.

| Characteristics | Surgery & Embolization (n= 31 , 23.5%) | Surgery (n= 82 , 62.1%) | Embolization (n= 19 , 14.4%) | p-value |
|---|---|---|---|---|
| **Age (years)** | 80.3 (± 7.5) | 77.4 (± 10.3) | 78.2 (± 7.5) | 0.325 |
| **Male sex** | 28 (90.3%) | 53 (64.6%) | 14 (73.7%) | 0.025 |
| **Use of antiplatelet drugs or anticoagulants** | 19 (61.3%) | 30 (36.6%) | 16 (84.2%) | <0.001 |
| **aPPT (sec)** | 31.4 (± 3.8) | 29.9 (± 3.6) | 30.7 (± 3.1) | 0.408 |
| **Prothrombin time (%)** | 89.4 (± 23.8) | 92.7 (± 14.9) | 87.7 (± 14.0) | 0.172 |
| **Platelet count ($x10^3/\mu L$)** | 221.8 (± 74.9) | 238.2 (± 66.1) | 229.2 (± 145.6) | 0.204 |
| **Initial hematoma width (mm)** | 22.8 (± 5.0) | 23.5 (± 4.7) | 19.2 (± 4.4) | 0.334 |

**Treatment related complications and treatment outcome**

Table 2 demonstrates the differences in treatment-related complications and clinical outcome at discharge between the group of patients, who received burr-hole irrigation alone and in combination with MMA embolization. A trend of less revision surgeries was found in the combined treatment group (p= 0.083). No statistical differences were seen when comparing these groups in terms of treatment-related complications or clinical outcome at discharge. There was no acute re-bleeding seen in the embolization group as well as no signs of ischemia, blindness or cranial nerve palsy related to the angiographic intervention. No vascular events in terms of stroke, cardiovascular or peripheral vascular events or neurological death were reported in the overall study population. However, two patients of the combined treatment group suffered from aphasia, which pre-existed at point of admission and was still noticeable at the point of discharge as well as during the follow-up period. In eleven patients (13.1%) of the surgery group revision surgery was necessary. Five of these patients (6.1%) showed an acute re-bleeding with three of them needing emergency craniotomy as surgical rescue. In the other eight patients of the surgery group, who needed surgical rescue, hematoma evacuation was performed using the existing burr-hole. One patient (1.2%) died during the hospitalization period due non-surgical complications. Another patient showed cerebrospinal fluid (CSF) fistula after burr-hole irrigation, which improved during the hospitalization period and did not need revision surgery. Hematoma reaccumulation during the follow-up period occurred in one patient (2.1%) who received MMA embolization in combination with burr-hole irrigation initially. This patient needed surgical rescue using the existing burr-hole for hematoma evacuation. In the group of patients, who received MMA embolization as a sole treatment, no surgical rescue was needed and no treatment-related complications occurred. A significant difference in terms of use of antiplatelet or anticoagulant medication was found between the groups (p=0.018), which was higher in the group of patients treated with surgery and MMA embolization (61.3%) compared to the surgery group (36.6%).

**Table 2:** Comparison of the complications and treatment outcome between the surgery group and the group of patients treated with surgery and MMA embolization.

| Outcome | Surgery + Embolization (n=31 , 27,4%) | Surgery (n=82 , 72,5%) | p-value |
|---|---|---|---|
| **Complications:** | | | |
| - No complication | 30 (96.8%) | 72 (87.8%) | |
| - Hematoma reaccumulation | 1 (3.2%) | 4 (4.9%) | 0.456 |
| - Acute re-bleeding | 0 | 5 (6.1%) | |
| - CSF fistula | 0 | 1 (1.2%) | |
| **Clinical outcome at discharge:** | | | |
| - No deficit | 29 (93.5%) | 69 (84.1%) | |
| - Aphasia | 2 (6.5%) | 5 (6.1%) | |
| - Hemiparesis | 0 | 5 (6.1%) | 0.516 |
| - Dysphagia | 0 | 2 (2.4%) | |
| - Death | 0 | 1 (1.2%) | |
| **Required surgical rescue:** | 1 (3.2%) | 11 (13.4%) | 0.083 |

**Follow- up CCT-findings**

A total of 73 out of the included 132 patients (55.3%) were followed-up in the outpatient clinic with a mean follow-up period of 3.4 months and a standard deviation of 2.2 months. Six patients (8.2%) received MMA embolization as a sole treatment, 16 patients (21.9%) in combination with burr-hole evacuation, and in 51 patients (69.9%) only burr-hole irrigation was carried out (see table 3).

A reaccumulation with mass effect was only seen in one anticoagulated patient (5.0%), who received the combined treatment as mentioned earlier. The patient needed surgical rescue 10 days after discharge, which was done by using the existing burr-hole. Eight patients of the surgery group (15.7%) showed hematoma reaccumulation with mass effect and needed surgical rescue with two of them needing emergency craniotomy. The other patients underwent hematoma removal using the existing burr-hole. Six out of these eight patients were on

MMA embolization was first described in a Japanese case report by Mandai et al[14] in 2000 and is recently gaining more and more interest as a treatment method for CSDH. A current meta-analysis by Srivatsan et al[27] included 18 papers with a total of 191 patients. They concluded that embolization of the MMA reduces recurrence rates of primary as well as recurrent CSDH when compared with burr-hole craniostomy and craniotomy alone.[27] The first prospective multi-center study, including 154 MMA embolizations, was recently published in 2021 by Kan et al[28] showing that MMA embolization may provide a safe and efficacious minimal invasive alternative to conventional surgery techniques. They described the need for re-treatment in only nine patients (6.5%) and CSDH thickness improvement in 140 patients (90.9%) during the follow-up.[28] However, 46.1% of the embolizations were performed in general anesthesia, whereas in our study, 85% were carried out under local anesthesia. Currently, three single-center studies compared MMA embolization with surgical treatment with auspicious results.[18,19,29] In addition, several small single-center case series and one large single-center, single-arm series have reported promising outcome.[11,12,30,31] This present study corroborates the existing results with a trend for less need for revision surgeries and low complication rates in the group of patients, who received MMA embolization. Interestingly, in our study no acute re-bleeding as well as no signs of ischemia, blindness or cranial nerve palsy were seen in the embolization group related to the angiographic intervention as a recognized complication of MMA embolization. Up to date, it is known that there might be a potential flow of embolization materials into the vasa nervorum of the facial nerve, which occurred in one patient in the series of Kan et al[28], or into the ophthalmic artery through the meningeoophthalmic connection.[33]

We statistically analyzed the baseline differences between the embolization, combined treatment and surgery group to identify any confounding variables. There was a difference between the groups found in terms of the number of patients on antiplatelet or anticoagulant therapy, which was significantly higher in the combined treatment and especially in the antiplatelet or anticoagulant therapy before surgery. In all patients treated with only MMA embolization complete hematoma resolution was found during the follow-up with 83.3% of them using antiplatelet or anticoagulant medication. In contrast, only 41.2% of the surgical and 68.8% of the combined treatment group were on antiplatelet or anticoagulant medication.

**Table 3:** CCT-findings during the follow-up period.

| CCT-Findings | Surgery + Embolization (n=16, 21.9%) | Surgery (n=51, 69.9%) | Embolization (n=6, 8.2%) | p-value |
|---|---|---|---|---|
| **Complete resolution** | 7 (55.8%) | 21 (43.1%) | 6 (100%) | 0.074 |
| **Residual cSDH < 10 mm** | 8 (40.0%) | 22 (42.1%) | 0 | |
| **Required surgical rescue** | 1 (5.0%) | 8 (15.7%) | 0 | |

## Discussion

This retrospective single-center study presents the efficacy, complication rates and midterm outcome of MMA embolization results with or without burr-hole irrigation compared to burr-hole irrigation as a standalone procedure.

In theory, MMA embolization may be an effective treatment for CSDH due to the underlying pathophysiology. Repeated microbleedings from immature neo-vessels from the MMA are believed to be responsible for the growth and recurrence of CSDH.[32] Previous angiographic studies illustrated that MMA branches are directly connected to the CSDH.[11,14,17] This connection is due to sinusoids penetrating the outer hematoma membrane. In selective angiography of the vessels, these sinusoids have appeared as cotton-like network. Kim et al[18] demonstrated that in postinvertentional CT contrast extravasates into the subdural space, and therefore, showed communication between the vessels and the collection.

embolization group. The reason for that may be the inability to stop antiplatelet or anticoagulant therapy, and therefore, using embolization as a prevention for hematoma recurrence whether or not in combination with burr-hole irrigation. However, patients on antiplatelet or anticoagulant therapy should have a higher risk of recurrence, and this may further point to efficacy of MMA embolization.[27] Previous studies identified anticoagulant drugs as an independent risk factor for recurrence of CSDH.[38,39]

An important consideration is whether MMA embolization as a standalone treatment is sufficient enough for treating CSDH. Symptoms and neurological deficits from CSDH occur mostly due to the mass effect of the subdural collection. In the acute phase, MMA embolization does not seem to reduce the mass effect and thus, symptoms and deficits may most probably not be alleviated. Therefore, MMA embolization may be seen as a separate adjuvant therapy or as a standalone treatment in patients without mass effect and neurological deficits. Three recent single-center studies pointed out that the addition of MMA embolization to surgical treatment leads to an increase in hematoma resorption as well as reduced recurrence rates.[35-37]

The present study is limited by its retrospective review of medical records, which may contain incomplete, conflicting or missing data. The selection of patients to undergo MMA embolization was based on individual surgeon preference that may result in a considerable bias. In addition, this is a single-center study, and therefore, the study population is small. There was no randomization in comparison to burr-hole irrigation. Lastly, the follow-up period is relatively short with a mean follow-up period of 3.4 months, because when the follow-up CT has showed disappearance of hematoma or a minimal residual effusion without clinical symptoms, the follow-up was ceased. However, the lost to follow-up was high with 45% of the patient population. Possible explanations may be an older study population with multi-morbid and/ or immobile conditions. Other reasons may be time and distance constraints due to a diverse study population. Randomized controlled multi-center studies with long-term follow-up are necessary and warranted in order to demonstrate the continued efficacy and safety of this treatment.

## Conclusion

In our study cohort MMA embolization was safe, feasible and had a positive therapeutic effect on CSDH, especially in patients on anticoagulant therapy. It seems to be more effective than surgical treatment alone, because of a lower complication rate in terms of acute re-bleeding and hematoma reaccumulation. However, some questions still remain open, such as whether MMA embolization should be performed as a standalone treatment or in combination with hematoma evacuation for best results.

## Disclosure

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**Patient Consent for Publication** Not required.

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## II. Publikation 2

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# Safety and Efficacy of Preoperative Embolization in Giant Intracranial Meningiomas Compared with Resection Surgery Alone

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## Abstract

**Background:** Endovascular embolization of intracranial meningiomas is commonly performed as an adjunct to surgical resection and may reduce intraoperative blood loss and surgical time. However, it remains unclear whether preoperative embolization improves the surgical outcomes of meningioma patients.
**Objectives:** This study aimed to assess the safety and efficacy of preoperative embolization in patients with giant intracranial meningiomas.
**Methods:** This retrospective cohort study included patients diagnosed with cranial meningiomas who underwent surgical treatment. The population group was subdivided into 2 categories: Surgery alone and preoperative meningioma embolization. Outcome variables included the degree of devascularization, intraprocedural complications, intraoperative complications, intraoperative blood loss, surgical time, postoperative complications, and the necessity of blood transfusions.
**Results:** In this study, a total of 189 patients with meningiomas were enrolled. Among them, 22 patients underwent preoperative tumor embolization. The tumor volume was significantly larger in the combined treatment group compared to the surgery-alone group ($P = 0.002$). Additionally, there was a significant difference in tumor location between the groups ($P < 0.001$), with more meningiomas being situated deeper in the combined group. In the subgroup analysis of giant meningiomas, intraoperative blood loss was significantly lower in embolized patients compared to non-embolized patients ($P = 0.034$), while no difference in surgical time was observed ($P = 0.570$).
**Conclusions:** Preoperative embolization in appropriately selected patients with giant intracranial meningiomas, especially those in deeper locations, was safe and feasible, showing a substantial degree of tumor devascularization with an acceptably low rate of complications. This may have had a positive effect on intraoperative blood loss and the duration of surgery.

*Keywords:* Preoperative Embolization, Intracranial Meningioma, Giant Meningioma, Resection, Blood Loss, Operation Time

## 1. Background

Intracranial meningiomas, the most common primary brain tumors, frequently present challenges in neurosurgery due to their vascular nature (1-3). These tumors receive blood from the dura and the adjacent pial vasculature (4-10). Surgical resection and the removal of associated dura and bone, if needed, remains the primary treatment for meningiomas. However, their hypervascularization can make resection difficult and may necessitate blood transfusion (8, 11).

In recent decades, preoperative embolization of meningiomas has been proposed to reduce intraoperative blood loss, facilitate safer resection, and decrease complications (12, 13). Yet, the benefits of preoperative embolization for intracranial meningiomas still need to be fully understood, and the procedure carries potential risks, particularly for large or giant meningiomas. These risks include intratumoral hemorrhage, ischemic stroke, post-embolization edema, and cranial nerve palsy (14-22).

While there is no precise definition of giant meningiomas, they are typically classified as those larger than 5 cm in diameter (23-25). These rare tumors present unique challenges for neurosurgeons due to their size, deeper location, and vascular supply. Giant meningiomas are also associated with longer surgery times, increased blood loss, and difficulties in achieving tumor exposure due to surrounding arteries and bridging veins (21, 22).

The authors propose that preoperative angiography and embolization of giant meningiomas could provide crucial information about the tumor's vascular supply, potentially leading to reduced intraoperative blood loss and shorter surgery times.

## 2. Objectives

This retrospective study aims to evaluate the safety and efficacy of preoperative embolization in patients with giant intracranial meningioma treated at a single center from January 2012 to December 2022.

## 3. Methods

This is a retrospective cohort study of patients diagnosed with cerebral meningioma, a subset of whom underwent preoperative meningioma embolization at our institution between January 2012 and December 2022. The decision to treat patients with preoperative angiography and possible tumor embolization was made by the treating neurosurgeons and neuroradiologists based on preoperative contrast-enhanced MRI. Reasons for considering preoperative tumor embolization included tumor size with a maximum diameter of more than 5 centimeters and tumor location. Medical records were reviewed, and demographic, clinical, and operative variables were collected, including age at treatment, sex, initial clinical symptoms, location of the tumor on preprocedural contrast-enhanced MRI, tumor size, location of the vascular supply, number of feeding pedicles, number of embolized feeders, embolization agents, and WHO tumor grade. Outcome variables included the degree of devascularization, intraprocedural complications, intraoperative complications, intraoperative blood loss, surgical time, postoperative complications, and whether blood transfusions were necessary.

Embolization procedures were performed with patients under either general endotracheal anesthesia or local anesthesia, depending on the patient's compliance and the date of surgery. The neurosurgeon and neuroradiologist's personal preference largely determined the embolization choice. Still, it was also correlated with high tumor vascularity, large tumor size, and challenging intraoperative access to arterial tumor supply. Angiographic imaging was conducted using high-resolution biplane subtraction angiography (biplane Allura Xper FD20/20, Philips Healthcare, Best, The Netherlands). Femoral artery access was usually obtained via a 6-French sheath. Standard diagnostic angiography was performed to analyze vascular anatomy and characterize the vascular supply of the meningioma. If embolization appeared feasible, selective catheterization of tumor-supplying vessels was conducted via a 6-French guiding catheter. Superselective catheterization of the feeding arteries was performed with a microcatheter, and vascular supply to healthy brain tissue or dangerous collaterals were excluded via selective angiography. Embolization was performed using 45 - 150 $\mu$m Contour polyvinyl alcohol (PVA) particles (Boston Scientific, Natick, Massachusetts, USA) and bare platinum coils and Onyx, depending on vessel anatomy, the presence of dangerous anastomoses and whether the patient was awake or under general anesthesia. After meningioma embolization, patients were brought either into the operating room for tumor resection or to the intensive care unit (ICU) for monitoring when tumor resection was scheduled for the next day.

The Statistical Package for Social Sciences-25 (SPSSv.25) was used to code variables of interest and perform statistical analyses. Descriptive statistics were used to calculate the mean and standard deviation (SD) of the different variables and the number of patients per category and associated percentages. The Pearson $\chi^2$ test and Fisher exact test were performed to evaluate the differences between the treatment groups. Differences were considered significant for probability values of $P < 0.05$.

## 4. Results

A total of 189 patients with meningiomas were admitted to our institution between January 2012 and December 2022 for resection surgery. In 22 patients (11.6%), preoperative tumor embolization was performed. In nine embolized patients (40.1%), surgery was carried out on the same day, and these patients underwent both procedures under one general anesthesia.

In 59.9% of the patients (n = 9), tumor resection was scheduled for the next day. Tumor embolization was possible under local anesthesia in seven of these nine patients. Figure 1 shows an example of a giant meningioma on the right greater sphenoid wing with pre- and post-embolization tumor angiography.

### 4.1. Baseline Characteristics

Table 1 summarizes the patient and tumor characteristics of all patients. When comparing age, sex, and WHO grade, no statistical differences were found

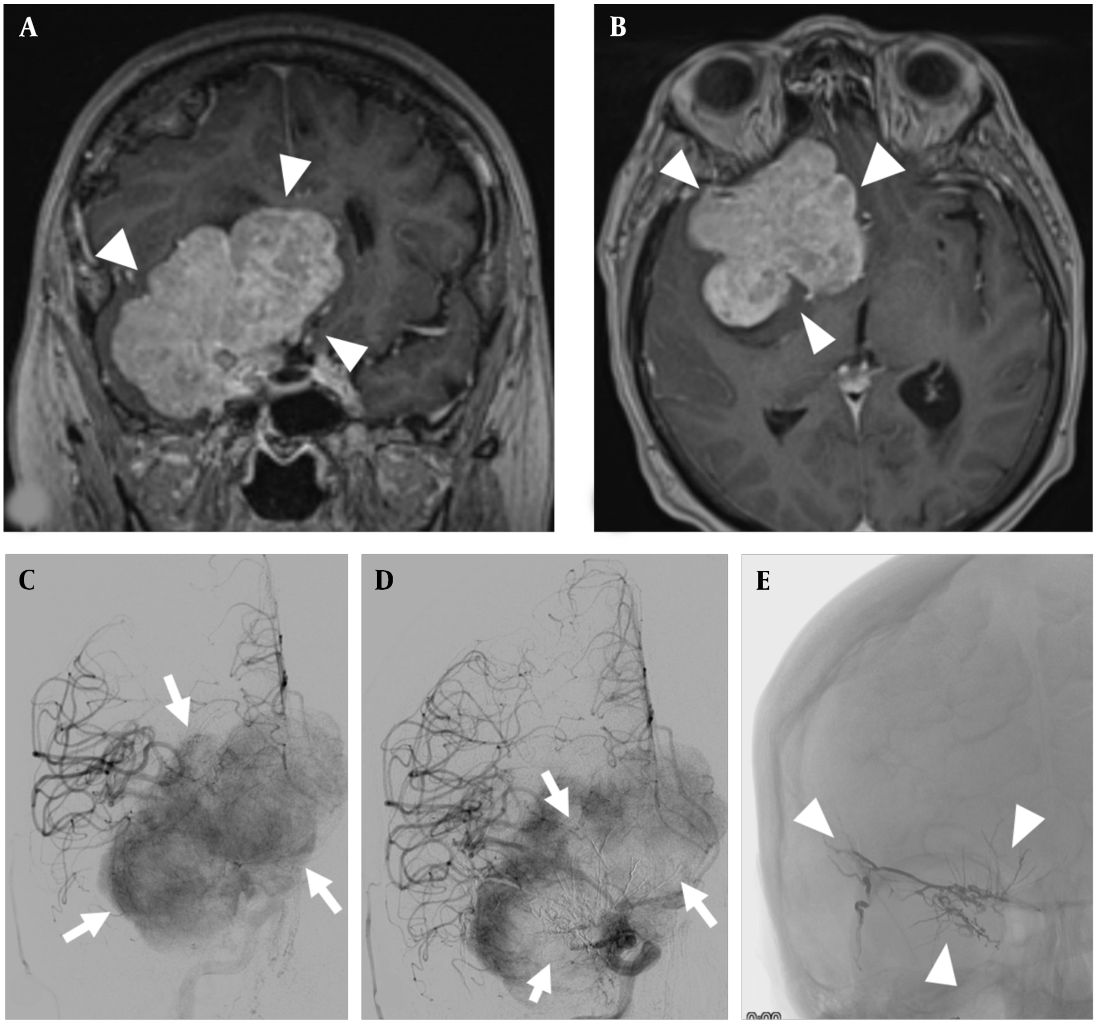


**Figure 1.** A and B, giant meningioma of the right greater sphenoid wing (arrowheads), coronal and transverse contrast-enhanced T1-weighted images; C, DSA with injection into the right common carotid artery showing a significant tumor blush in the late arterial phase (arrows); D, DSA with injection again into the right common carotid artery after embolization with a significant reduction in tumor blush in the center of the meningioma (arrows); E, radiograph without contrast injection showing the liquid embolic agent in the center of the tumor (arrowheads).

between the treatment groups. The tumor volume was significantly more significant in the combined treatment group, with 59.2 $cm^3$, compared to the surgery group with 15.7 $cm^3$ ($P = 0.002$). Furthermore, tumor location and initial symptoms differed significantly between the groups ($P < 0.001$ and $P = 0.004$, respectively). In the combined treatment group, the main symptoms in 22.7% of the patients were cognitive deficits, and 18.1% had hemiparesis. In this group, only 13.6% showed no symptoms at presentation.

In contrast, in the surgery group, 37.7% were symptomless, and 13.8% underwent radiological diagnostics in the workup for a persistent headache, while 10.8% had epileptic seizures. Regarding tumor location, the most significant quantity in the combined treatment group presented with a sphenoid wing meningioma at 36.4%. In the surgery group, almost half of the patients were admitted with a convexity meningioma.

### *4.2. Angiographic and Procedural Characteristics*

Table 2 presents the angiographic and procedural characteristics of the combined treatment group. The mean number of feeding pedicles was 2.1, and the mean number of embolized pedicles was 1.5. In most patients, MMA embolization was performed at 81.8%, and particle agents were used for embolization at 90.9%. In 57.1% of

**Table 1.** Patient and Tumor Characteristics of the Combined Treatment Group Compared to the Surgery Group in No. (%) or Mean ± SD.

| Variables | Embolization + Surgery (N = 22) | Surgery (N = 167) | P-Value |
|---|---|---|---|
| **Age (y)** | 61.9 ± 12.0 | 61.1 ± 13.0 | 0.843 |
| **Sex (female)** | 12 (54.5) | 122 (73.1) | 0.084 |
| **Initial symptoms** | | | 0.004 |
| No symptoms | 3 (13.6) | 63 (37.7) | |
| Cognitive deficits | 5 (22.7) | 7 (4.2) | |
| Headache | 2 (9.1) | 23 (13.8) | |
| Visual deficits | 3 (13.6) | 9 (5.4) | |
| Hemiparesis | 4 (18.1) | 11 (6.6) | |
| Aphasia | 2 (9.1) | 10 (6.0) | |
| Dizziness | 1 (4.5) | 10 (6.0) | |
| Epileptic seizure | 1 (4.5) | 18 (10.8) | |
| Dysosmia | 1 (4.5) | 3 (1.8) | |
| **Tumor location** | | | < 0.001 |
| Olfactory groove | 4 (18.1) | 7 (4.2) | |
| Sphenoid wing | 8 (36.4) | 11 (6.6) | |
| Parasagittal | 4 (18.1) | 17 (10.2) | |
| Falcine | 3 (13.6) | 34 (20.4) | |
| Tentorial | 1 (4.5) | 14 (8.4) | |
| Intraventricular | 1 (4.5) | 2 (1.2) | |
| Convexity | 1 (4.5) | 82 (49.1) | |
| **Tumor size ($cm^3$)** | 59.2 ± 23.7 | 15.7 ± 20.8 | 0.002 |
| **WHO grade** | | | 0.789 |
| I | 19 (86.4) | 138 (82.6) | |
| II | 3 (13.6) | 26 (15.6) | |
| III | 0 (0) | 3 (1.8) | |

the cases, an estimated devascularization of more than 75% was achieved.

### 4.3. Surgery Characteristics and Postoperative Complications

Table 3 presents the surgery characteristics and postoperative complications of the combined treatment group and the surgery group. In the combined treatment group, operation time and intraoperative blood loss were significantly higher than the surgery group (P = 0.023 and P < 0.001, respectively). The mean surgical time in the combined treatment group was 358.0 minutes, while it was 191.7 minutes in the surgery group. Additionally, the mean intraoperative blood loss was 581.8 milliliters in the combined treatment group, as opposed to 376.0 milliliters in the surgery group. Moreover, the 2 treatment groups had significant differences in postoperative complications (P = 0.014). In the combined treatment group, 1 patient experienced malignant edema, progressive stroke, and epileptic seizures, respectively, whereas secondary hemorrhage (2.4%) and epileptic seizures (4.8%) were most common in the surgery group. Notably, one rescue surgery was necessary in the combined treatment group due to malignant edema, whereas 4 rescue surgeries were required in the surgery group because of secondary hemorrhages (P = 0.465). It is worth mentioning that no intraprocedural complications occurred during angiography and embolization, and no intraoperative complications emerged during tumor resection in either group. Furthermore, no blood transfusion was required in the combined treatment group postoperatively, while 1 blood transfusion was administered postoperatively in the surgery group.

**Table 2.** Angiographic and Procedural Characteristics of the Embolization and Surgery Groups [a]

| Variables | Embolization + Surgery (N = 22) |
|---|---|
| **Number of feeding pedicles** | 2.1 ± 0.8 |
| 1 | 4 (18.1) |
| 2 | 12 (55.5) |
| 3 | 3 (13.6) |
| 4 | 2 (9.1) |
| **Number of embolized pedicles** | 1.5 ± 0.6 |
| 1 | 13 (59.1) |
| 2 | 8 (36.4) |
| 3 | 1 (4.5) |
| **Location of embolized pedicles** | |
| Middle meningeal | 18 (81.8) |
| Ophthalmic | 5 (22.7) |
| Internal maxillary | 2 (9.1) |
| Anterior cerebral | 1 (4.5) |
| Temporal superficial | 2 (9.1) |
| Posterior cerebral | 2 (9.1) |
| **Embolisates** | |
| PVA particles | 20 (90.9) |
| Coils | 6 (27.2) |
| Onyx | 1 (4.5) |
| N-butyl cyanoacrylate | 3 (13.6) |
| **Degree of devascularization** | |
| ≥ 75 | 12 (57.1) |
| 50 - 74% | 9 (42.9) |

[a] Values are expressed as No (%) or mean ± SD.

### 4.4. Subgroup Analysis of Giant Meningiomas

While there is no precise definition of giant meningiomas, most publications consider meningiomas larger than 5 cm in diameter as giant meningiomas (38 - 40). Table 4 presents the subgroup analysis of giant meningiomas, comparing the combined treatment and surgery groups. It is important to note that all patients who underwent preoperative meningioma embolization had meningiomas with a diameter exceeding 5 cm. Baseline characteristics, such as age and sex, exhibited no significant differences between the groups (P = 0.647 and P = 0.922, respectively). In terms of tumor location, a significant difference was observed (P = 0.003). In the surgery group, 50% of the tumors were in the convexity and 20.6% in the falcine region.

In contrast, in the combined treatment group, 36.4% of the tumors were situated in the sphenoid wing, while 18.1% were in the olfactory groove and parasagittal. Intraoperative blood loss was significantly lower in the combined treatment group, with a mean blood loss of 581.8 mL in preoperatively embolized patients compared to 739.1 mL in non-embolized patients (P = 0.034). However, surgical time did not exhibit a significant difference between the two groups (P = 0.570).

## 5. Discussion

The current literature shows that the potential benefits of preoperative meningioma embolization, including reduced intraoperative blood loss, operation time, and tumor softening, have been widely reported (10, 20, 26-29). On the contrary, the risks involve ischemic complications, hemorrhages, cranial nerve deficits, and peritumoral edema (30-32). However, it remains unclear whether preoperative embolization improves the surgical outcome of meningioma patients. One potential reason may be the appropriate patient selection. The patients we selected for preoperative embolization differed significantly in tumor size and tumor location from those who underwent surgery alone. The largest group of embolized tumors in our study were skull base meningiomas. Raper et al. illustrated that meningiomas targeted for preoperative embolization tend to be larger and in deeper locations compared to those not referred to embolization (20), which is consistent with our patient cohort. They also showed that the vascular supply of skull base meningiomas is frequently difficult to access in the early stages of resection. Therefore, resection of these tumors was associated with higher blood loss and a lower chance of gross resection compared to convexity lesions (20). Consequently, skull base meningiomas are an attractive target for preoperative embolization. However, it is well known that the vascular supply of these tumors is variable and complex, with important anastomotic connections between the external and internal carotid arteries and vital neurological structures (33). These anastomotic connections can also be found in the vascular network of the meningioma itself (33, 34). Thus, aggressive embolization may lead to permanent post-procedural neurological deficits. Rosen et al. reported that 21.6% of the patients showed post-procedural complications, including nine percent with significant neurological deficits after 24 hours (35). The current literature reports that most complications occur during or within a few hours of procedural completion (19). The overall complication rates after meningioma embolization vary between 6 and 21% in the literature (11, 19, 35).

In our study, major neurological complications were found in 2 embolized patients postoperatively, 9.1%.

**Table 3** Surgery Characteristics and Postoperative Complications of the Combined Treatment Group and Surgery Group [a]

| Variables | Embolization + Surgery (N = 22) | Surgery (N = 167) | P-Value |
|---|---|---|---|
| **Surgical time (min)** | 358.0 ± 115.9 | 191.7 ± 93.0 | 0.023 |
| **Intraoperative blood loss (mL)** | 581.8 ± 195.5 | 376.0 ± 160.2 | < 0.001 |
| **Postoperative complications** | 3 (13.6) | 16 (9.6) | 0.023 |
| Malignant edema | 1 (4.5) | 0 | |
| Secondary hemorrhage | 0 | 4 (2.4) | |
| Progressive stroke | 1 (4.5) | 0 | |
| Epileptic seizures | 1 (4.5) | 8 (4.8) | |
| Abscess/ wound infection | 0 | 2 (1.2) | |
| Aphasia | 0 | 1 (0.6) | |
| Pneumonia | 0 | 1 (0.6) | |
| **Rescue surgery** | 1 (4.5) | 4 (2.4) | 0.465 |

[a] Values are expressed as No (%) or mean ± SD.

**Table 4** Subgroup Analysis of Giant Meningiomas with a Maximum Diameter Exceeding 5 cm, Comparing the Combined Treatment Group and the Surgery Group [a]

| Variables | Embolization + Surgery (N = 22) | Surgery (N = 34) | P-Value |
|---|---|---|---|
| **Age (y)** | 61.9 ± 12.0 | 64.0 ± 13.1 | 0.647 |
| **Sex (female)** | 12 (54.5) | 18 (52.9) | 0.922 |
| **Tumor location** | | | 0.003 |
| Olfactory groove | 4 (18.1) | 2 (5.9) | |
| Sphenoid wing | 8 (36.4) | 4 (11.8) | |
| Parasagittal | 4 (18.1) | 1 (2.9) | |
| Falcine | 3 (13.6) | 7 (20.6) | |
| Tentorial | 1 (4.5) | 3 (8.8) | |
| Intraventricular | 1 (4.5) | 0 | |
| Convexity | 1 (4.5) | 17 (50.0) | |
| **Tumor size ($cm^3$)** | 59.2 ± 23.7 | 54.5 ± 24.7 | 0.293 |
| **Intraoperative blood loss (mL)** | 581.8 ± 195.5 | 739.1 ± 200.7 | 0.034 |
| **Surgical time (min)** | 358.0 ± 115.9 | 275.7 ± 110.1 | 0.570 |
| **Rescue surgery** | 1 (4.5) | 0 | 0.210 |

[a] Values are expressed as No (%) or mean ± SD.

One patient with an embolized convexity meningioma showed no neurological symptoms immediately after embolization and tumor resection the following day and could subsequently be discharged 14 days later. However, 22 days after resection, the patient was re-admitted with a middle cerebral artery stroke. In this patient, only embolization of the middle meningeal artery (MMA) was carried out; therefore, we think this complication is unrelated to the embolization procedure. The second patient underwent embolization of a sphenoid wing meningioma and tumor resection the subsequent day. Two days after resection surgery, the patient showed reduced vigilance, and the CT scan indicated progressive edema with midline shift. Rescue surgery in the form of decompressive hemicraniectomy was necessary. After rescue surgery and neurological rehabilitation, the patient had no permanent neurological deficits at follow-up. In this case, it remains unclear whether the embolization procedure, resection surgery, or a combination of both caused the malignant edema.

Several studies have suggested a beneficial effect of preoperative meningioma embolization. Some retrospective cohort studies have referred to reduced blood loss, a reduced need for transfusion, and fewer complications in embolized patients with no significant neurological deficits or adverse long-term effects (29, 36). However, Bendszus et al. found that significantly reduced blood loss may only be achieved by complete tumor devascularization in a prospective comparative cohort study (27). Furthermore, Waldron et al. reported a prospective case series with good outcomes after preoperative embolization of skull base meningiomas fed by the internal carotid artery, with a low complication rate (11).

Moreover, the adequate time interval between meningioma embolization and tumor resection remains controversial, with no preference for either early or delayed tumor resection after tumor embolization. Kai et al. suggested that one week after embolization, tumor resection leads to greater tumor softening and eases the resection, reducing blood loss and edema (23, 37). Another study predicted that after preoperative embolization with Onyx, surgery should be delayed for more than 10 days due to less edema (37). In contrast, shorter intervals between one and 7 days were recommended based on possible tumor revascularization and subsequent collateralization. In all of these studies, nonabsorbable embolization agents have been advised (21, 24, 25, 32).

At our institution, resection surgery was scheduled either directly after meningioma embolization or within 24 hours due to a possible increase in peritumoral edema post-procedurally, leading to elevated intracranial pressure. Based on the early tumor resection after embolization, tumors may not reach the ideal softening, thus limiting the improvement of surgical outcomes such as blood loss and operation time. However, our subgroup analysis of giant meningiomas with a more than 5 centimeters diameter showed significantly reduced intraoperative blood loss in preoperatively embolized patients. Additionally, operation time did not differ significantly between the groups, although the proportion of patients with superficial meningiomas was significantly lower in the combined group.

This study has several limitations, such as the retrospective review of medical records, which may contain incomplete or missing data, and the self-assessment of complications. The selection of patients to undergo preoperative meningioma embolization was based on individual surgeon preference, which may have resulted in considerable bias. In addition, as a single-center study, the study population is small. After correcting for tumor size, our study showed significantly reduced intraoperative blood loss in embolized compared to non-embolized patients with giant meningiomas. Although the 2 subgroups differed significantly in tumor location, with more tumors in deeper areas in the group of patients with embolization, there was no significant difference in surgical time. In our patients, the intra- and post-procedural complication rate was low compared with the existing literature. This likely depends on the availability of endovascular therapy options and may vary from site to site. However, further standardized prospective randomized controlled trials are needed to draw compelling conclusions about the role of preoperative embolization, with one focus on patients with giant meningiomas.

### *5.1. Conclusions*

In our study cohort, preoperative embolization in appropriately selected patients with giant intracranial meningiomas was safe and feasible and showed a substantial degree of tumor devascularization with an acceptable low rate of complications. This might have led to a positive effect on intraoperative blood loss and duration of surgery.

## Footnotes

**Authors' Contribution:** All authors made substantial contributions in terms of the study design, data collection, statistical analysis, interpretation of data, and manuscript preparation and revision.

**Conflict of Interests:** There is no conflict of interest; the authors have no personal, financial, or institutional interest in any materials or devices described in this paper.

**Data Availability:** The dataset presented in the study is available on request from the corresponding author during submission or after publication.

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