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MUDr. Ondřej Petr

Mozková aneurysmata - modality léčby a přirozený průběh.

Bezpečnost a efektivnost léčebných strategií aneurysmat na a. cerebelli inferior posterior.

Intracranial Aneurysms – Treatment Options and Natural Course.

Safety and Efficacy of Treatment Strategies for Posterior Inferior Cerebellar Artery Aneurysms.

Disertační práce

Vedoucí závěrečné práce:
Prof. MUDr, Vladimír Beneš, DrSc.

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ABSTRACT

BACKGROUND: Posterior inferior cerebellar artery (PICA) aneurysms are an uncommon, heterogeneous group of aneurysms with poorer neurological outcomes compared to other intracranial aneurysms. At first, as part A, we conducted a systematic review of the literature to evaluate the safety and efficacy of treatment strategies for PICA-aneurysms.
Subsequently, as part B, we performed a multicenter retrospective study to analyze the outcome in a large series of patients treated with contemporary microsurgical and endovascular techniques.
METHODS: For the meta-analysis, a systematic search of Medline, EMBASE, Scopus and Web of Science was done for studies published through November 2015. We included studies that described treatment of PICA-aneurysms with ≥10 patients. Random-effects meta-analysis was used to pool the following outcomes: complete occlusion, technical success, periprocedural morbidity/mortality, stroke rates, aneurysm recurrence/rebleed, CN-palsies rates, and long-term neurological morbidity/mortality. As the second part, aiming to report the current trends and results in treatment strategies for PICA-aneurysms, records of 94 patients treated for PICA-aneurysms between 2000 and 2015 at 3 large referral neurovascular centers were retrospectively reviewed.
RESULTS: In the meta-analysis, we included 29 studies with 796 PICA-aneurysms. When considering all ruptured PICA-aneurysms, complete occlusion rates were 97.1% (95%CI=94.5%-99.0%) in the surgical group and 84.3% (95%CI=73.8%-92.6%) in the endovascular group. Aneurysm recurrence occurred in 1.4% (95%CI=0.3%-3.3%) after surgery and in 6.9% (95%CI=3.6%-10.9%) after endovascular treatment. Overall neurological morbidity and mortality were 14.4% (95%CI=8.7%-21.2%) and 9.8% (95%CI=5.8%-14.8%) after surgery and 15.1% (95%CI=10.5%-20.2%) and 17.1% (95%CI=11.5%-23.7%) after endovascular treatment, respectively. When considering all unruptured PICA-aneurysms, complete occlusion rates were 92.9% (95%CI=79.5%-100%) in the surgical group and 75.7% (95%CI=45.4%-97.1%) in the endovascular group. Overall long-term good neurological outcome rates were 91.5% (95%CI=74.4%-100%) in the surgical series and 93.3% (95%CI=82.7%-99.5%) in the endovascular group. Analyzing the current results from 3 referral neurovascular centers, 83 patients met inclusion criteria and of these, 2 died before treatment leaving 81 treated patients (43 underwent endovascular and 38 surgical treatment). Among patients treated endovascularly, procedure-related complications occurred in 4 cases (11.8%). Six patients (19.4%) suffered from complications directly associated with surgery. Recurrences occurred in 3.2% of surgical and in 17.6% of endovascularly treated patients, requiring treatment. Patients with unruptured asymptomatic aneurysms had good outcomes. In the group of 67 ruptured aneurysms, 12 endovascularly (35.3%) and 11 surgically (35.5%) treated patients had Glasgow Outcome Scale (GOS) score 1-3. Of patients in poor neurological condition (Hunt & Hess (H&H) IV-V at admission), 65.2% suffered poor clinical outcomes. Fifty percent of patients with distal and 31.9% patients with proximal ruptured PICA-aneurysms suffered a poor neurological outcome.
CONCLUSION: Our meta-analysis as well as the current results from 3 referral neurovascular centers demonstrated that both treatment modalities are technically feasible with high rates of technical success and effective with sufficient long-term aneurysm occlusion rates. However, complications are not negligible. Outcomes were mostly impacted by clinical state at admission. Our data confirm that surgical treatment is associated with superior angiographic outcomes. These findings should be considered when deciding the best therapeutic strategy for treatment of PICA-aneurysms. Yet, therapy of PICA-aneurysms should be performed on a selective, case-by-case basis in order to maximize patient benefits and limit the risk of periprocedural complications also depending upon the specific expertise of one's department.

Key words: PICA, aneurysm, microsurgery, endovascular treatment, meta-analysis

ABSTRAKT

ÚVOD: Aneurysmata na arteria cerebelli inferior posterior představují poměrně málo častou a heterogenní skupinu se špatnou neurologickou prognózou ve srovnání s jinými intrakraniálními aneurysmaty. První část této práce přináší systematický přehled literatury, která hodnotí bezpečnost a efektivnost léčebných strategií PICA-aneurysmat. V druhé části je představena multicentrická retrospektivní studie, jejímž cílem bylo analyzovat klinický outcome u velké série pacientů léčených současnými technikami mikrochirurgické a endovaskulární léčby.

METODY: Pro metaanalýzu byly systematicky vyhledávány studie publikované do listopadu 2015 pomocí databází Medline, EMBASE, Scopus a Web of Science. Byly zahrnuty studie týkající se léčby PICA-aneurysmat, ve kterých bylo zařazeno ≥ 10 pacientů. Pomocí statistických metod metaanalýzy (random-efekt) byly analyzovány následující parametry: dosažení kompletní okluse, technická úspěšnost, periprocedurální morbidita/mortalita, výskyt iktů, rekurence/hemoragie aneurysmatu, výskyt paralýz kraniálních nervů a dlouhodobá neurologická morbidita/mortalita. Druhou část práce představuje retrospektivní studie zahrnující data 94 pacientů léčených pro PICA-aneurysma od roku 2000 do roku 2015 ve třech neurovaskulárních centrech.

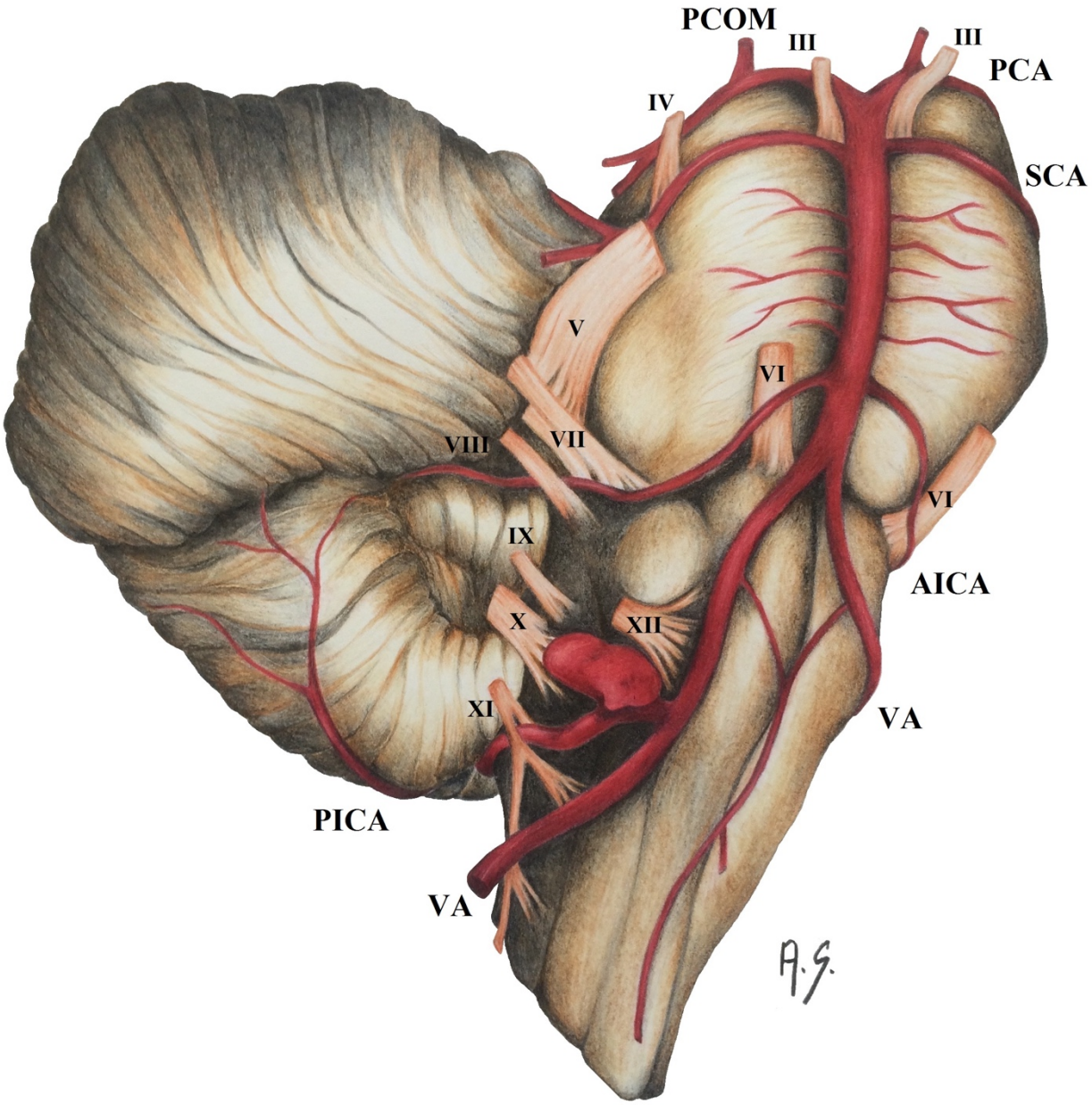
VÝSLEDKY: Do metaanalýzy bylo zahrnuto 29 studií s celkovým počtem 796 PICA-aneurysmat. U prasklých aneurysmat byla dosažena kompletní okluse v 97.1% (95%CI=94.5%-99.0%) u skupiny chirurgicky léčených pacientů a 84.3% (95%CI=73.8%-92.6%) ve skupině endovaskulárně léčených. Rekurence aneurysmatu se vyskytovala v 1.4% (95%CI=0.3%-3.3%) po chirurgickém výkonu a v 8.1% (95%CI=3.6%-10.9%) po endovaskulárním výkonu. Celková neurologická morbidita byla 14.4% (95%CI=8.7%-21.2%) and mortalita 9.8% (95%CI=5.8%-14.8%) po chirurgické léčbě a 15.1% (95%CI=10.5%-20.2%) a 17.1% (95%CI=11.5%-23.7%) po léčbě endovaskulární. U neprasklých PICA-aneurysmat byla kompletní okluse dosažena v 92.9 % (95%CI=79.5%-100%) u skupiny chirurgicky léčených pacientů a 75.7% (95%CI=45.4%-97.1%) ve skupině pacientů absolvujících léčbu endovaskulární. Celkový dobrý dlouhodobý neurologický outcome byl 91.5% (95%CI=74.4%-100%) u chirurgicky léčených pacientů a 93.3% (95%CI=82.7%-99.5%) u endovaskulárně léčených pacientů.

ZÁVĚR: Prezentovaná metaanalýza i výsledky studie ze tří neurovaskulárních center ukázaly, že obě léčebné modality dosahují vysoké míry úspěšnosti a efektivnosti technického provedení se současně dostatečnou mírou dlouhodobé okluse aneurysmatu. Přesto vyskytující se komplikace nejsou zanedbatelné. Na klinický outcome má určující vliv stav pacienta při příjmu do hospitalizačního zařízení. Naše data potvrdila, že chirurgická léčba PICA-aneurysmat je spojena s vynikajícím angiografickým nálezem. Tyto závěry by měly být zváženy při managementu pacientů s PICA-aneurysmaty. Každopádně volba léčby těchto pacientů by měla být diskutována případ od případu tak, aby získaný benefit byl pro pacienta co nejvyšší a risk výskytu periprocedurálních komplikací byl maximálně limitován. V neposlední řadě záleží také na zvyklostech a zkušenosti daného pracoviště.

Klíčová slova: arteria cerebelli inferior posterior, aneurysma, mikrochirurgie, neurochirurgie, endovaskulární léčba, metaanalýza

ABBREVIATIONS

ACA	Anterior cerebral artery
AICA	Anterior inferior cerebellar artery
AcomA	Anterior communicating artery
AVM	Arteriovenous malformation
AVF	Arteriovenous fistula
BA	Basilar artery
CCA	Common carotid artery
CI	Confidence interval
CN	Cranial nerve
CPA	Cerebellopontine angle
CSF	Cerebrospinal fluid
CT	Computed tomography
CTA	CT angiography
DSA	Digital subtraction angiography
GDCs	Guglielmi detachable coils
GOS	Glasgow outcome scale
H&H	Hunt and Hess classification
IA	Intracranial aneurysm
ICA	Internal carotid artery
ICH	Intracerebral hemorrhage
IVH	Intraventricular hemorrhage
MCA	Middle cerebral artery
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
N/A	Not available
OA	Occipital artery
OAG	Occipital artery graft
OR	Odds ratio
PCA	Posterior cerebral artery
PKD	Polycystic kidney disease
PEG	Percut. endoscopic gastrostomy
PComA	Posterior communicating artery
PICA	Posterior inferior cerebellar artery
RAG	Radial artery graft
SAH	Subarachnoid hemorrhage
SCA	Superior cerebellar artery
STA	Superficial temporal artery
VA	Vertebral artery
VBJ	Vertebro-basilar junction
VP	Ventriculoperitoneal



Artist rendering of the vetrolateral surface of the brainstem and cerebellum.
[A. Sejkorová]

1. INTRODUCTION

Intracranial aneurysms (IAs) are acquired dilatations of intracranial arteries. They are typically located at the arterial branching points near the skull base. When an IA ruptures, it causes subarachnoid hemorrhage (SAH) with typical clinical symptoms. SAH is a devastating event associated with cumulative mortality up to 50% at 6 months.[1-3] Notably, even though SAH is the primary cause for only about 5-10% of strokes, it occurs frequently in a fairly young age without any warning signs.[4, 5] Furthermore, SAH-related morbidity rates are not negligible, resulting in similar loss of productive life years when compared to that for cerebral infarction and intracerebral hemorrhage.[4] The most important goal in the treatment of aneurysm patients is to prevent hemorrhage from the IA achieving by complete aneurysm occlusion. To sufficiently exclude the aneurysm from cerebral circulation, both surgical and endovascular treatment strategies are being used in most high-volume neurovascular centers.

Distribution of IAs along the different intracranial arteries is uneven so that certain arteries and their segments are more affected than others, possibly due to flow-related reasons.[6] However, the results for this still remain unclear.

One of the rare aneurysm locations is the posterior inferior cerebellar artery (PICA) as these represent between 0.5% and 3% of all intracranial aneurysms.[7-16] They provide special features such as the high proportion of fusiform and dissecting aneurysms and are oftentimes closely adjacent to cranial nerves and the brainstem. In addition, they are often associated with other vascular anomalies such as arteriovenous malformations (AVMs), and other or multiple IAs. Moreover, they may have a small size in conformity with the comparatively small caliber of the PICA itself, and a broad base with originating branches. The course of all arteries in the posterior circulation can be tortuous, and additionally, the course of PICA belongs to one of the most variable among cerebral arteries.[17]

All above-mentioned facts have to be taken into careful consideration when deciding the final treatment strategy, making especially endovascular therapy not easy.

The best treatment strategy and technique for PICA-aneurysms continue to be debated.[18, 19] Over the last three decades, several series using both endovascular and open surgical techniques

have reported results and complications of treatment for these aneurysms.[7, 8, 10, 20-25] However, most of these series are small [26-30] and it is difficult to have an understanding of the complications and outcomes for treatment of PICA-aneurysms. Furthermore, many prior studies have reported high morbidity and mortality rates of patients having ruptured PICA-aneurysms irrespective of management techniques. [24, 31-33]

2. HISTORY OF INTRACRANIAL ANEURYSM TREATMENT

"I know of no successful outcome from operative attack upon an aneurysm of the posterior cranial fossa, but for those upon the vertebral and posterior inferior cerebellar arteries, which afford good exposure, cures will certainly come in time." (Walter Dandy, 1944) [34]

2.1 PRIMORDIAL ERA OF NEUROVASCULAR SURGERY
(prior to microscopic neurosurgery)

2.1.1 INTRACRANIAL ANEURYSMS IN DAYS OF YORE (historical context)

Found in the Ebers Papyrus and attributed to Imhotep (2725 B.C.), the first note of an arterial aneurysm reported the treatment of a bulging aneurysm with a fire-glazed instrument by an Egyptian physician.[35] In 117 B.C., Flaenius Rufus, a physician from Ephesus remarked that dilatation of artery wall could occur after trauma[36] but it was the Greek physician Galen of Pergamum who first appropriately gave a definition of an arterial aneurysm in general in 200 A.D.[37] During the next 1500 years, only Islamic physicians deepened their understanding of aneurysms, their origins, and sites.[38, 39]

The contemporary description of aneurysm as a dilatation of a weakened artery wall was given by Lancisis in 1728.[40] The history of clearly defined PICA-aneurysms begun with the first mention by Cruveiher et al in 1829.[41] This French pathologist reported a spherical aneurysm

originating from the VA-PICA junction.[41] The first case of an aneurysm arising from a distal segment of the PICA was reported by Fernet[42] who described the first case of a distal PICA-aneurysm in 1864. Intracranial aneurysms were definitely described for the first time in the autopsy reports by Morgagni (1761, Padua),[43] Biumi (1765, Milan),[44] and Blane (1800, London).[45]

At that time no reports regarding the intracranial aneurysm treatment were found until Heinrich Quincke came with the lumbar puncture as the first possible examination of living patients in 1891.[46]

2.1.2 HUNTERIAN LIGATION

In 1805, Cooper did carotid ligation for an extracranial carotid artery aneurysm with a catastrophic result.[47] Undiscouraged, he repeated the same operation three years later, this time with success.[48, 49] Notably, arterial ligation was widened in the 18th century by John Hunter who showed a safe and repeatable procedure of proximal femoral artery ligation for popliteal aneurysms as an alternative to leg amputation.[50] Named in his honor, Hunterian ligation of the internal carotid artery (ICA) was accepted by many surgeons as a treatment for intracranial vascular pathologies. In 1809, Benjamin Travers firstly described a successful treatment of an intracranial lesion (carotid cavernous fistula) by this method.[51]

2.1.3 CAROTID OCCLUSION

In 1885, in London, Sir Victor Horsley performed a surgery on a 48-year old woman deemed to have a tumor in the middle cranial fossa. Intraoperatively, a pulsating lesion, probably an intracranial giant aneurysm, was found. This finding compelled Horsley to reconsider his surgical approach. He performed a ligation of the right common carotid artery. The patient was reported to be doing well five years later.[52] Thereafter, many surgeons also repeated this procedure on the carotid arteries because of incidentally discovered intracranial aneurysms during the brain tumor surgery. However, performing the carotid ligations to treat these aneurysms, as a consequence, the occlusions often caused cerebral strokes with subsequent neurological deficits. These results led to the need of differentiation of patients in whom this procedure could be done without following severe neurological sequelae. Therefore, in 1911 a preoperative compression

test for differentiation of patients who would tolerate occlusion, was introduced by Matas.[53] It is worthy of note that this test was firstly applied till 1924 for a patient with traumatic aneurysm causing severe epistaxis.[54] Numerous additional sophisticated examinations were designed over the following years to enable gradual occlusion of the carotid artery, however, the mortality rates were around 20% and the stroke rate was as high as 30%.[54-56]

2.1.4 CEREBRAL ANGIOGRAPHY

The introduction of cerebral angiography by António Egas Moniz in 1927 not only revolutionized the diagnostics of cerebral aneurysms but also played a key role in starting the development of IA treatment.[57] Previously, plain x-rays pneumoencephalography and myelography represented basic imaging methods of the central nervous system. In this way, only some calcified aneurysms could be seen and even those were initially often mistaken for tumors such as calcified meningiomas. By 1931, Moniz completed a carotid angiographic examination including arterial and venous phases. In 1933, Moniz also reported the first VA angiography, done via injection to a surgically exposed subclavian artery.[58, 59]

In the same year, he wrote an article on IA diagnostics through angiography.[60] Not surprisingly, Dott reported the first operation of an aneurysm that was previously diagnosed by angiography.[61] In 1941, Hugo Krauenbühl was the first who diagnosed the first posterior circulation aneurysm in an angiography using an open retrograde subclavian injection.[62] For many years, vertebral angiographies were performed via direct puncture in the neck.[7, 63]

Angiography's usefulness as a diagnostic tool spread even more rapidly after developing the percutaneous carotid puncture technique reported by Lohman and Myerson in 1936 and Shimidzu in 1937,[64, 65] and later with Seldinger's technique of catheter angiography through the percutaneous transfemoral route described in 1953.[66] Nowadays, the angiography-related complications occur rarely, the incidence is less than 0.5%.[67]

2.1.5 WRAPPING AND TRAPPING

The first operations for posterior circulation aneurysms took place for presumed tumors. The first was likely done by Cushing in 1915. In 1928, Dandy performed the first ligation of the

cervical VA due to an intracranial aneurysm.[34] In 1931, Norman McComish Dott of Edinburgh (a pupil of Cushing's) was the first who dealt with ruptured aneurysm. Without angiographic assistance, he operated on a 53-year old patient who was the financial director of Dott's hospital with three previous hemorrhages and a CN III nerve palsy. Intraoperatively, a 3-mm aneurysm in the region of ICA bifurcation was wrapped with muscle harvested from the patient's thigh, and the patient made a good recovery.[61] Other reports by Tönnis,[68] Dandy,[34] and Jefferson[69] were published dealing with aneurysm wrapping.

Herbert Olivecrona, founder of Scandinavian neurosurgery, was the first who effectively treated a posterior circulation aneurysm in Stockholm in 1932. He operated on a patient thought to suffer from a tumor in the posterior fossa. The intraoperative finding was a large, thrombosed PICA-aneurysm. He performed trapping and excision of this aneurysm.[70] The patient was reported to be doing well 17 years later.[71] In 1936, Dandy developed a new technique to secure an ICA aneurysm in or near the cavernous sinus by ligating ICA both intracranially and extracranially, thus trapping the aneurysm.[72]

The first successful direct treatment was done by Schwartz on November 6, 1946. He performed a trapping of ruptured aneurysm of an unnamed branch of the basilar artery.[41] The next successful surgery was on January 23, 1947. Rizzoli et al trapped and excised a PICA-aneurysm.[73] The first reported operation after aneurysm diagnosis by angiography took place in 1956 performed by DeSaussure et al.[74] The surgeons used the trapping for PICA-aneurysm.

2.1.6 SURGICAL CLIPPING

A revolution in the surgical treatment of IAs accompanied the developing of metallic clips.[75] In 1911, Harvey Cushing invented what was to become known as "the silver clip" or "Cushing clip".[76] Cushing applied this clip in tumor surgeries for "placement on inaccessible vessels, which, though within reach of a clamp, are either too delicate or in a position too awkward for safe ligation".[76] The original silver clip, made out of round silver wire, was first modified in 1927 by McKenzie into a V-shaped clip using flat wire,[77] and later in 1949 by Duane into a U-shaped clip.[78] Cushing never used his invention for intracranial aneurysm surgery, instead, it was his competitor Walter Dandy who clipped the first aneurysm on March 23, 1937.[79] He dissected a saccular posterior communicating artery (PCoA) aneurysm causing oculomotor palsy, and clipped

the aneurysm at the neck with a Cushing-McKenzie type silver clip. The preoperative CN III palsy completely recovered six weeks after surgery.[79]

Drake,[80] for his part, operated on his first posterior circulation aneurysm in 1959. The patient underwent clipping of ruptured mid-basilar aneurysm through a subtemporal approach. The patient was reported to be doing well.[80] Before 1960, in Drake's series[80] of 25 patients with ruptured vertebrobasilar artery aneurysms, proximal vertebral artery occlusion was done in 10 patients. In total, 4 patients died, however, 16 showed no severe surgery-related complications.[80] Importantly, this novel clipping method provided neurosurgeons the possibility of selective exclusion of an aneurysm from the intracranial circulation, a concept that revolutionized the entire vascular neurosurgery and began the modern era of aneurysm surgery.

It is worthy of note that the first intracranial aneurysm treated in Czechoslovakia was already in 1949 performed by Petr.[81] Afterwards, Kunc,[82, 83] Fusek[84, 85] or Benes jr.[81] were Czech neurosurgeons who extensively contributed to further development of surgical treatment in intracranial aneurysms. Also owing to their results, surgical treatment is nowadays reputed to be one of gold standard modalities in aneurysm treatment.

2.2 MICRONEUROSURGERY

2.2.1 OPERATING MICROSCOPE

In the second half of the 19th century, microscopes were already utilized in industry and scientific research but in clinical surgery, their use was preceded by loupe magnification. The German physician Saemisch intraoperatively wearing loupes used true compound magnification for the first time in surgery in 1876.[86] In 1921, the Swedish otolaryngologist Carl Nylen, inspired by a paper of Maier and Lion on observations of endolymph movements in the ears of live pigeons using a dissecting microscope, conceived, built and used the world's first surgical monocular microscope.[87, 88] This invention was followed the next year by his chief Gunnar Holmgren, who attached an external light source to an existing Zeiss dissecting microscope, thus introducing the

first binocular surgical microscope.[88]

In the early 1950s, further technical advancements enabled widespread use of microscopes. Hans Littman from Zeiss Company invented the optical design for changing magnification without changing the focal length and he propounded the first series-produced operating microscope, Zeiss OpMi 1 (Zeiss Operating Microscope Number One) in 1953.[89, 90] Later in 1960, Littman also proposed the first two-person series-produced operating microscope, the diploscope, for the microsurgical laboratory in Burlington, Vermont.[91]

2.2.2 EVOLUTION OF MICRONEUROSURGERY

On August 1, 1957, Theodore Kurze, at the University of Southern California in Los Angeles, was the first neurosurgeon who used a microscope in the operating room.[91, 92] In 1960, Donaghy performed the first embolectomy and endarterectomy on the middle cerebral artery using the operating microscope.[93] In 1962, a cardiac surgeon in Zürich, Åke Senning, asked neurosurgeon Hugo Krayenbühl to remove an embolus from the MCA in a young patient with hemiplegia after cardiac surgery. At that time Krayenbühl did not believe this possible but the idea of surgery on small intracranial vessels lasted out and in 1965 he dispatched his pupil, M. Gazi Yaşargil, to the United States to learn the new art of microsurgery.[94] Yaşargil originally approached Jacobsen, who referred him to Donaghy's laboratory in Vermont, where he spent the next year mastering microsurgical techniques under the guidance of Miss Esther Roberts by means of performing anastomoses of the superficial temporal artery (STA) to the middle cerebral artery (STA-MCA bypass) in dogs.[92, 94]

Upon returning back to Zürich, Yaşargil performed the first STA-MCA bypass on a human patient on October 30, 1967.[94] Less than 24 hours later, Donaghy performed the same operation in Burlington, and both of these surgeries were successful.[92] Yaşargil's return to Zürich and the first microsurgical operation on February 1, 1967 marked the beginning of a new era in microneurosurgery. Yaşargil's devotion to development of operative approaches, techniques and instrumentation has been appraised by many of his colleagues.[95, 96] In 1979, Donaghy wrote: "Little was it realized at this time (in 1965), even by Hugo Krayenbühl, that this young Turk was destined to do more for the development of microneurosurgery in the human nervous system than any other man."[92]

2.2.3 MICRONEUROSURGERY IN ANEURYSM TREATMENT

Microneurosurgery has been immensely broadened in aneurysm surgery beginning in the 1960s. Starting in 1958, Kurze was the first person who systematically used the microscope for all his aneurysm cases, however, he never published or presented his series.[91] Adams and Witt presented their one-year experience of vascular microsurgery at the meeting of the Neurosurgical Society of America in 1964.[97] The first publication related to microsurgical aneurysm surgery was written by Pool and Colton[98] in 1966 describing their experience in 13 patients. In 1967, Rand and Janetta[99] reported a basilar bifurcation and a PICA-aneurysm, both ligated with silk thread under the microscope. They emphasized the power of microscope in distinguishing the small perforators in basilar bifurcation aneurysms and compared their experience with Drake's, who at that time had a 50% mortality in his series of eight basilar bifurcation aneurysms operated without the microscope but with loupes.[100]

Microneurosurgery was spreading rapidly during this time period as an increasing number of neurosurgeons realized the advantages of microsurgery on their results. The real groundbreaking series was that by Krayenbühl and Yaşargil in 1972,[101] describing Yaşargil's results over a four-year period from 1967 to 1971, in which total mortality was only 4% in 231 patients with microsurgically treated anterior circulation aneurysms. With further experience and development of instrumentation mortality in Yaşargil's series further decreased to 2% in the time period from 1970 to 1974, setting a new standard for aneurysm surgery.[102] Meanwhile Drake, already using a microscope (since 1970), pioneered surgery for posterior circulation aneurysms.[80]

2.3 ENDOVASCULAR SURGERY

2.3.1 BALLOON OCCLUSION

The first attempts to treat intracranial aneurysms from the endovascular side applying

injection of either hog or horse hair into the aneurysm sac during open surgery were described by Gallagher[103] in 1964. His idea was that the shingles on the end of the hair, placed inside the aneurysm, would create a mechanical nidus for clotting, however, complete occlusion due to thrombosis of the aneurysm was observed in only nine of the 15 patients. Also in 1964, Luessenhop and Velasquez performed an occlusion of a carotid aneurysm by endovascularly placing a silicone balloon into its neck.[104] Besides balloons, aneurysms were filled with an iron particle suspension (Alksne in 1969) and with isobytyl-2-cyanoacrylate (Sheptak in 1977), but the operations were done via a craniotomy or a burr hole.[105] Additionally, in 1965, Mullan et al[106] reported an electrically induced thrombosis of an aneurysm. Unfortunately, among the six aneurysms with angiographic follow-up, one aneurysm showed 10% filling at two weeks. The others were filling a minimum of 40%. In their report in 1974, they used the method also for basilar aneurysms.[107]

In 1971, Serbinenko, a Russian neurosurgeon from the Burdenko Institute in Moscow, described the application of inflatable balloons for temporary occlusion of intracranial vessels and carotid cavernous fistulae.[108] Three years later, he demonstrated the use of selective catheterization to deliver and deploy detachable balloons filled with a hardening agent (liquid silicone) for the treatment of various intracranial vascular lesions, including aneurysms, in more than 300 patients.[109] However, despite the first very promising results, substantial complications and recanalization of aneurysms occurred even when using other material to fill the balloon.[110-114] A revolution in endovascular therapy was realized with the introduction of microcatheters and microguidewires by Target Therapeutics (Fremont, CA, USA) in 1986, which enabled safer and more effective exploration of intracranial vessels.[115]

2.3.2 COIL EMBOLIZATION

In 1990, Dowd et al[116] described endovascular embolization of a PICA-aneurysm with platinum coils. The invention of Guglielmi detachable coils (GDC) in 1990 as one of the most important milestone, completely revolutionized the entire endovascular discipline.[117, 118] The initial free coils used for endovascular treatment were applied through the microcatheter with a special wire referred to as the coil pusher without a possibility to pulling them back.[119] Guglielmi, together with Sepetka invented the first generation of electrolytically detachable platinum coils. The main advantage was appropriate positioning inside the aneurysm before the release.[117] In

1991, Guglielmi[118] reported the first experience of series of 15 patients treated with this new method. The method both positively and rapidly addressed other endovascular experts. Consequently, numerous large series[120, 121] dealing with the use of GDCs in aneurysm treatment were published in the next years. These reported promising results of this novel technique.

2.3.3 OTHER ENDOVASCULAR TECHNIQUES AND ADVANCEMENTS

Further endovascular refinements rapidly occurred. Given the endovascular advancements and rapid developing of new techniques such as balloon remodeling technique for wide-necked aneurysms introduced by Moret in 1997[122] as well as introduction of new coils and other embolic material, an increasing number of aneurysms has been safely treated by endovascular methods.[123] Also in 1997, Higashida et al[124] reported their experience with combined endovascular treatment for a fusiform basilar artery aneurysm deploying coils through a stent.

Later, in 2008, as a novel paradigm in the endovascular treatment, Fiorella et al[125] published their first successful experience with flow diversion technique using a pipeline embolization device (PED). It is worth noticing that the introduction of the novel method endoluminal flow diversion has heralded the beginning of a new endovascular era also.[126]

3. VASCULAR ANATOMY OF POSTERIOR FOSSA

Treatment of PICA-aneurysms is often challenging from both microsurgical and endovascular perspective. Thus in-depth knowledge of complex anatomical relationships of cerebellar arteries to the brainstem and cerebellar surfaces is essential.

3.1 BASIC ANATOMY

PICA is the largest branch of the VA originating above the foramen magnum in more than 80% cases.[127] The PICA shows the most variable course of the cerebral arteries. The PICA arises from the vertebral artery at the anterolateral part of the brainstem near the inferior olive and goes posteriorly around medulla. At the anterolateral margin of the medulla, it passes cranial or caudal or rather between the rootlets of the hypoglossal nerve (CN XII), and at the posterolateral margin of the medulla it goes cranial or possibly between the fila of the glossopharyngeal (CN IX), vagus (CN X), and accessory (CN XII) nerves. After passing the aforementioned lower cranial nerves (CNs) it turns around the cerebellar tonsil and goes posteriorly to the caudal half of the roof of the fourth ventricle. Afterward, it penetrates the deep fissures between the tonsils, the vermis, and the hemisphere.

The branches of the PICA supply the caudal part of the vermis, the hemisphere, and the tonsil. The PICA evinces very often a tortuous course and the most variable supply area of all cerebellar arteries. Notably, high degree of parent vessel curvature and wide-necked aneurysms is associated with increased pressure, wall sheer stress, aneurysm growth.[128]

3.2 TOPOGRAPHICAL ANATOMY

3.2.1 ORIGIN OF THE PICA

In our study, the PICA was defined as the cerebellar artery that arises from the vertebral artery. Similarly, numerous anatomical studies[129-133] also defined the PICA as merely from the

vertebral artery. The PICA arose mostly from the medial or ventral surfaces of the vertebral artery. Directly after leaving the parent vessel, the initial course of the PICA is more often posterior, lateral or superior rather than the opposite directions. Lister et al[17] reported diameter of the PICA at its origin ranging from 0.5mm to 3.4mm (mean 2.0mm). The PICA was reported to be hypoplastic between 5% and 16% of cerebellar hemispheres.[130, 132]

3.2.2 CONJUNCTION TO THE LOWER CRANIAL NERVES

The PICA shows the most miscellaneous interconnection to the CNs of any artery. The vertebral artery as an origin of the PICA passes ventral to the CN IX, CN X, CN XI, and CN XII, and the proximal part of the PICA turns around or goes through often stretched or distorted rootlets of these nerves. The course of the PICA segment varies mostly passing from the lateral to the posterior aspect of the medulla between the rootlets of CNs IX, X, and XI. The facial (CN VII) and vestibulocochlear (CN VIII) nerves arise superior to the CN IX at the level of pontomedullary junction. In most cases, the PICA can be found turning around the brainstem inferior to the both latter nerves. However, in some cerebellopontine angles the proximal part of the PICA, after passing posteriorly to the level of the hypoglossal rootlets, looped superiorly toward the seventh and eighth CNs before reaching the CNs IX – XI.

3.2.3 SEGMENTS OF THE PICA

Based on the relations to the medulla and the cerebellum, five anatomical segments are distinguished on the trunk of the PICA.[17]

a) Anterior medullary, beginning at the origin of the PICA and extending up to the level of the rostrocaudal line through the most prominent part of the inferior olive;
b) Lateral medullary, beginning by passing the most prominent point of the inferior olive and extending up to the level of the origin of the CNs IX – XI; before reaching the cranial nerves, it forms various loops in the cistern lateral to the brainstem;

c) Tonsilomedullary, beginning by passing the aforementioned CNs posteriorly and reaching the caudal one-half of the tonsil;
d) Telovelotonsilar as the most complex of all segments, beginning at the midportion of the PICA-ascent and terminating by entering the fissures between the vermis, tonsil, and hemisphere;
e) Cortical, beginning by passing the vermis medially and the tonsil and the hemisphere laterally, and ending as the terminal cortical branches.

3.2.4 BRANCHES OF THE PICA

The main, medial and lateral trunks constitute the following perforating choroidal, and cortical branches:

I. Perforating arteries
    a. Direct
    b. Circumflex
        i. Short circumflex
        ii. Long circumflex
II. Choroidal arteries
III. Cortical arteries
    a. Hemispheric
    b. Tonsillar
    c. Vermian

It is worthy of notice that PICA may have various anatomical courses and anomalies. For instance, as PICA origins, not only VA, but the hypoglossal, proatlantal, or posterior meningeal arteries can give rise to the PICA. The PICA itself also varies from absent to bilateral, or duplicate. Perforating branches arising from the latero- and retromedullary segment supply the posterolateral part of the medulla oblongata[17, 134-137] while the anterior part is supplied by perforators originating from anterior spinal and vertebral arteries.

Yet, recent anatomical study[138] postulated that vascular territories of the medulla oblongata may overlap, and that several anastomoses exist between arteries on the surface of the medulla. In particular, the lateral and posterior medulla oblongata can be supplied from perforating arteries arising both from vertebral and posterior spinal arteries and from the PICA. It has been suggested that the contribution from the PICA is especially important if the lateromedullary segment makes a curve upwards.[138]

3.3 LOWER CRANIAL NERVES

3.3.1 ANATOMICAL FEATURES

The lower CNs lie freely suspended in cerebrospinal fluid. They are only fixed at the point of exit from the brainstem and at the point of entry to the dural layer at the cranial base. As the cranial nerves are not involved in any movements and are not surrounded in tissue, they are not adapted to stretching or to any significant mechanical forces.[139] Due to any surrounding tissue with tight contact with lower cranial nerves, they are dependent on direct blood supply from surrounding arteries and vessels in the pia mater. Both mechanisms may be impaired during vascular surgery.[140]

Particularly, deficits of CNs occur after rapid or intense manipulation caused by stretching and irritation during the microsurgical dissection. This can produce prompt structural disintegration and loss of function. In contrast, slow stretching and compression on lower cranial nerve by tumor growth is tolerated to some degree.[139, 141, 142]

3.3.2 HISTOLOGICAL FEATURES

From a histological perspective, the CNs do not have an epineurium. They also lack a firm perineurium and are only enclosed with a single or double layer of flattened sheath cells without a continuous basal lamina. The collagen volume in cranial nerves tissue is sparser when compared to that of peripheral nerves. Consequently, stretching forces on the nerves cannot be balanced with the connective tissue. The epineurium gives a wadding effect and absorbs the deforming forces on

the peripheral nerves.[139]

The intracranial segment of the cranial nerves undergoes a transformation in myelination structure as enters the subarachnoid space. This transition zone is called Obersteiner-Redlich zone, and it is deemed the most vulnerable part of the nerve. This area shows no recovery and is not protected by a myelin sheath. In the middle part, the nerve has a layer of oligodendrocytes, whereas the peripheral segment has a layer of Schwann cells.[143] Based on all facts mentioned above, the lower cranial nerves are mechanically much more fragile and injury-prone to any type of surgical manipulation when compared to the peripheral nerve.

3.4 SURGICAL ANATOMY

Microsurgical dissection of PICA-aneurysms is not difficult because both the VA and PICA are identifiable landmarks that lead directly to the aneurysm.[144] The VA is recognizable under the dentate ligament, and the PICA is detectable under the tonsil in the cerebellomedullary fissure.[145] One or both arteries are proximally traced to their convergence, and the aneurysm lies just beyond this convergence.[146] Arteries do not pass a complicated fissure or need large dissection. The caudal loop of the PICA is evident with minimal tonsillar retraction. The medulla and anterior tonsil are easily detached due to their smooth and never interdigitated surfaces like some other fissures.[147]

Troubles in dissection may occur because of the proximity to the CNs that can obstruct the pathway to the aneurysm.[17, 145, 148-154] CNs IX, X, XI, and XII can interfere with aneurysm access, and their manipulation can be a source of postoperative neurological deficits.[10, 134, 155, 156] Elaborated accesses to the PICA-aneurysm through these lower CNs are prerequisite for safe efficient microsurgical clipping. These approaches were systematically described by Rodríguez-Hernández et al.[157] In their study, they defined 3 anatomical triangles related to the position of lower CNs that create corridors to PICA-aneurysms. Authors also analyzed the relationships between these triangles and PICA-aneurysm anatomy, routes for surgical clipping, outcomes, and angiographically demonstrated anatomy.

As mentioned above, three anatomical triangles clarifying the microsurgical accesses to PICA-aneurysms are the following: vagoaccessory triangle, suprahypoglossal triangle, and

infrahypoglossal triangle.[157] The vagoaccessory triangle is specified by the vagus nerve superiorly, the accessory nerve laterally, and the medulla medially. This triangle is the natural working corridor for the far lateral approach. It is separated into 2 smaller triangles by the CN XII. The suprahypoglossal triangle is the area in the vagoaccessory triangle above the CN XII, between CNs X, XI, and XII. The infrahypoglossal triangle is the area below the CN XII, between CNs XI and XII and the medulla.

The CNs IX, X and XI arise from the retroolivary sulcus and course to the jugular foramen, whereas the CN XII arises from the preolivary sulcus and courses to the hypoglossal foramen. [158] Owing to the different inceptions, the course and depth of the CN XII varies when compared to the CNs X and XI. As a consequence, the supra- and infrahypoglossal triangles are not simple 2D plains, but rather are 3D passages.

Rhoton[149, 159] and colleagues[17, 160] specified PICA segments related to the lower CNs anatomy. The detailed description of the PICA segments is provided in *Chapter 3 – VASCULAR ANATOMY OF POSTERIOR FOSSA, Section 3.2.3 – SEGMENTS OF THE PICA* (see page 13). The same boundaries that define the PICA's segments can localize a PICA-aneurysm relative to the medulla and the anatomical triangles.[157] Variability in the origin of the PICA from the VA, tortuosity of the parent VA, and aneurysm location along the PICA may position a PICA-aneurysm in any of these medullary zones.

3.4.1 MICROSURGICAL ANATOMY OF THE LATERAL PORTION OF THE FORAMEN MAGNUM AND ANATOMICAL PRINCIPLES FOR THE TRANSCONDYLAR FOSSA APPROACH

[161] The lateral skeletal wall of the foramen magnum consists of the jugular tubercle and the occipital condyle, which are both barriers.[162-164] The jugular tubercle is cranial to the hypoglossal canal, and the occipital condyle is caudal to it. On the external surface of the skull, the condylar fossa is located immediately above the occipital condyle. The posterior condylar canal, through which the posterior condylar emissary vein goes, enters at the bottom of the fossa. The posterior condylar canal passes between the posterior portion of the jugular tubercle and the occipital condyle and is in contact anteriorly with the distal end of the sigmoid sulcus or the jugular foramen at the level of the hypoglossal canal. It is mandatory for surgeons who operate on the lateral portion

of the foramen magnum to understand the venous anatomy. The lateral part of the foramen magnum is enclosed with the sigmoid sinus and jugular bulb laterally and the marginal sinus medially. The venous channels in the hypoglossal canal run between the jugular bulb and the marginal sinus. The posterior condylar emissary vein running in the canal is located between the distal end of the sigmoid sinus and the vertebral venous plexus. Because the condylar fossa shapes the outer surface of the jugular tubercle, removing only the fossa leads to removing the posterior portion of the jugular tubercle. The posterior condylar canal and the posterior condylar emissary vein are the anatomic landmarks for accurate removing the skeletal structure keeping the atlanto-occipital joint intact.[162] Even in the transcondylar fossa approach, a sufficient operative field is obtained in most cases of intradural lesion of the foramen magnum. The lateral portion of the cerebellomedullary fissure is located immediately ahead of the jugular tubercle. It comprises the foramen of Luschka and the lateral recessus. When the lateral portion of the fissure is dissected after the transcondylar fossa approach and the biventral lobule and the tonsil are carefully retracted, the surgical corridor extensively expands.

3.4.2 SURGICAL PROCEDURES OF THE TRANSCONDYLAR FOSSA APPROACH (ALSO CALLED SUPRACONDYLAR TRANSJUGULAR TUBERCLE APPROACH)

The park bench position or the prone position is usually used in this approach. Some surgeons[161] favor a horseshoe skin incision but the paramedian vertical straight incision is also practicable. The skin and the muscle are cut together moving aside to uncover the suboccipital surface. When the rectus capitis posterior major muscle covering the extracranial VA and the vertebral venous plexus is detached from the inferior nuchal line and reflected, the posterior condylar emissary vein is found in the condylar fossa without touching the vertebral venous plexus. Because the vein communicates with the vertebral venous plexus, it should be coagulated and cut before the venous plexus is injured.

Next, a unilateral suboccipital craniotomy is performed. The craniotomy extends from the midline superomedially to the sigmoid sinus laterally and along the foramen magnum across the midline to the opposite side inferiorly. The posterior portion of the foramen magnum is completely opened but the C1 laminectomy differs from case to case. The posteroinferior part of the occipital bone is removed consistently while sparing only the condylar fossa in the situs. Then the posterior

condylar emissary vein is interrupted. When the dura covering the cerebellar hemisphere is elevated with a spatula, the removed bone looks like a triangle between the sigmoid sinus laterally and the foramen magnum medially. This is so-called sigmoid-magnum triangle.[161] The apex of the triangle represents tight part of the jugular tubercle. The condylar fossa superior to the posterior condylar canal, as the posterior part of the jugular tubercle, is drilled extradurally and removed with the canal in sight as an anatomic landmark. Bone wax is applied to stop venous bleeding occurring from the posterior condylar canal. This step is crucial when removing only the jugular tubercle. The skeletal removal along the canal anteriorly leads to removing the posterior part of the jugular tubercle. First, the center of the sigmoid-magnum triangle is drilled and the lateral margin of the drilled hole is left for protection. Finally, the shell of this thin bony margin is removed.

The dura is incised along an oblique line, starting superolaterally and coming down toward the midline at the level of the foramen magnum and then straight down further to the C1. The dural flap is tilted off inferolaterally. With minimal retraction of the cerebellum after the lateral portion of the cerebellomedullary fissure is dissected, the origin of the PICA and the entire courses of the CNs IX and X are visible. The operating corridor is large and the lesion is close to a surgeon. Dissection of the lateral part of the cerebellomedullary fissure is performed on a selective case-by-case base. If necessary, the transcondylar fossa approach can also be easily converted to the classical transcondylar approach after the occipital condyle and lateral mass are partially removed.

4. ANEURYSM MORPHOLOGY

4.1 MORPHOLOGICAL CLASSIFICATION OF INTRACRANIAL ANEURYSMS IN DAILY CLINICAL PRACTICE

Intracranial aneurysms are predominantly categorized into three groups:

a) Saccular;
b) Fusiform;
c) Dissecting.

By far the vast majority of intracranial aneurysms are saccular, mostly located at the bifurcation of an artery. Fusiform aneurysms are defined as spindle-shaped wall dilatations without a distinctly recognizable aneurysm neck. Their variety is not known, estimated as less than 1% of all aneurysms.[165]

4.2 OTHER MORPHOLOGICAL CLASSIFICATIONS

Attempting to identify higher and lower-risk groups, Mizutani et al[166] categorized aneurysms of the posterior circulation, especially vertebral artery aneurysms into four types:

a) Type I, dissecting aneurysm;
b) Type II, segmental ectasia;
c) Type III, dolichoectatic dissecting aneurysm;
d) Type IV, saccular aneurysm.

Notably, besides the aforementioned groups, additional categories are distinguished:

i) Dolichoectatic;
ii) Serpentine;
iii) Atherosclerotic aneurysms.

The overwhelming majority of dissecting aneurysms have fusiform morphology, with a dissection of the vessel wall resulting in outward bulging. Dolichoectasia is defined as an expansion, lengthening, and tortuosity of the vessel, and in the case of occurring the thrombosis in dolichoectatic aneurysms, this is designated as a serpentine aneurysm. Atherosclerotic aneurysms have fusiform morphology with additional atherosclerotic changes in the walls. Some aneurysms are of traumatic[167, 168] or mycotic[169] origin.

Importantly, to differentiate a non-saccular aneurysm from a common artery, based on radiologic measurements, Flemming et al[170] suggested dilatations greater than 1.5 times the normal artery diameter to be meant for aneurysms. Similarly, Sacho et al[171] applied the same definition for fusiform aneurysms.

4.3 ADDITIONAL CLASSIFICATION OF DISSECTING ANEURYSMS

With regard to fusiform dissecting aneurysms, these aneurysms are sporadically categorized into two groups:[172]

a) acute dissecting aneurysms - presenting a classical angiographic "pearl-and-string" sign, linear defects, or double lumen;
b) chronic dissecting aneurysms – having only a dilatated structure of the artery.

4.4 INCIDENCE AND DETECTION OF ARTERY DISSECTION

Aneurysms of the posterior inferior cerebellar artery are rare occurring between 0.5% and 3% of all intracranial aneurysms.[7-16] When concerning all PICA-aneurysms, the incidence of fusiform PICA-aneurysms is variable, ranging from 6% to 62%.[173-179]

Detection of the dissecting form of aneurysms may be difficult because of often missing classic findings,[175, 176] especially in small vessels (for example those located on distal segments of the PICA). It is important to note that the finding of small peripheral aneurysms should prompt

consideration of infectious causes.[135, 180]

Even though the dissection usually appears between intima or internal elastic layer and the media of the artery,[181, 182] the additional subadventitial dissection is thought to be the cause of subarachnoid hemorrhage in these cases.[183] Besides, the degenerative, atherosclerotic weakening of the arterial wall, often in combination with hypertension, has been reputed to be a promoter of intramural dissection.[181, 183-187]

4.5 DEFINITION OF MORPHOLOGICAL CLASSES IN THE STUDY

Due to similarity of the treatment approaches for fusiform and dissecting aneurysms, both groups may be considered as one. Accordingly, we considered fusiform and dissecting PICA-aneurysms for a separate entity and limited our morphological classification to two following categories: saccular and non-saccular.

5. DEFINITION OF PICA AND ANEURYSM LOCATION

5.1 DEFINITION

PICA is defined as the cerebellar artery that arises from the vertebral artery. Distal PICA-aneurysm also so-called true PICA-aneurysm[188] are located apart from the VA-PICA junction.

5.2 LOCATION OF PICA ANEURYSMS

The majority of PICA-aneurysms arise from VA-PICA junction and the proximal segment of the PICA, whereas aneurysms in the distal PICA represent less than 1% of all aneurysms.[174, 177] For example, to our best knowledge, in the largest published series of 91 distal PICA-aneurysms,

Lehto et al[178] reported a distal PICA-aneurysm in 1.4% of all aneurysms. The authors explained the slightly greater number by 4-vessel angiography or an autopsy performed on each patient admitted due to SAH or a suspected aneurysm.

Other studies also described more rare locations of PICA-aneurysms, namely extradural[189-192] or within the fourth ventricle.[193-195] Even cases with "PICA-communicating artery aneurysms" were reported in prior studies.[196-198] Apart from this, PICA-VA seems to be a preferred location for de novo aneurysms,[199] besides they were not diagnosed in the primary imaging.[200]

5.2.1 ANATOMICAL LOCATION

According to the above-mentioned anatomical segments of the parent artery the PICA-aneurysms can be divided into 5 subgroups:[17, 135] 1) anterior medullary, 2) lateral medullary, 3) tonsillomedullary, 4) telovelotonsilar, and 5) cortical.

5.2.2 SURGICAL LOCATION

In the daily clinical practice, another simplified and more surgery-oriented classification was firstly described by Drake et al[80] laying the emphasis upon surgical/topographical anatomy. The authors divided the PICA-aneurysms into 2 groups:

a) **Proximal PICA** - aneurysms which are located on the first cm of PICA;
b) **Distal PICA** - aneurysms.

This division reflects the microsurgical anatomy related to surgical approaches and the relationship of the PICA with the cranial nerves and brainstem.

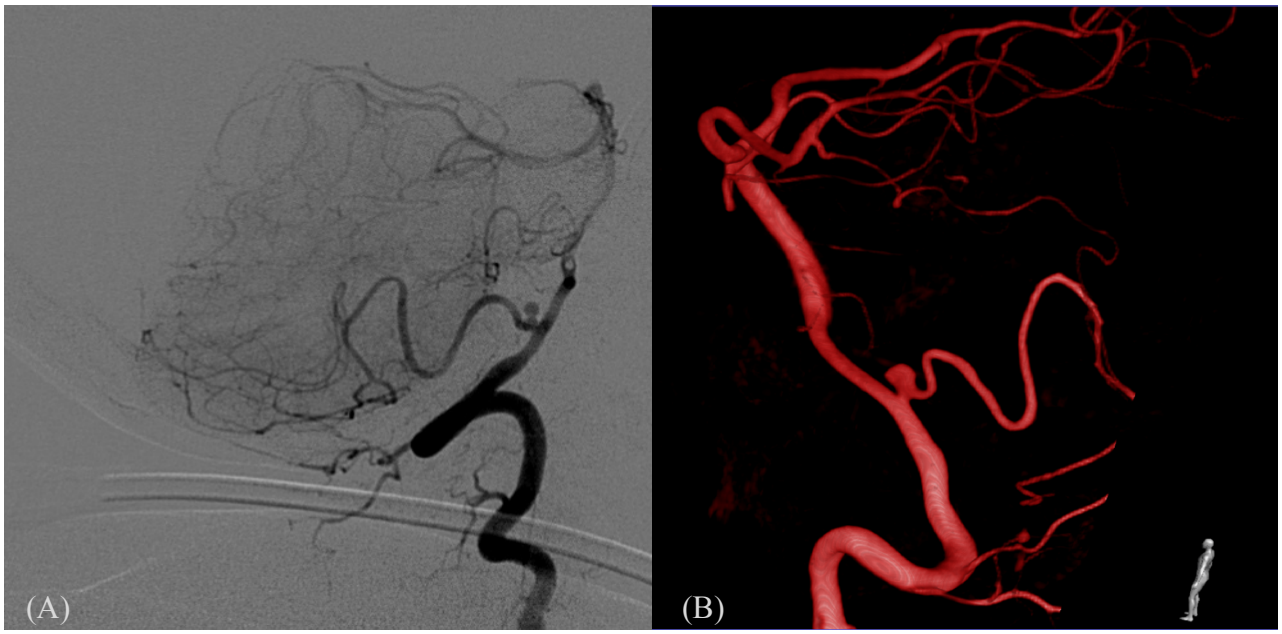


Figure 1 A-B.
A 46-year old woman suffered the SAH H&H IV with loss of consciousness. DSA (catheterization of the right VA, lateral view of the vascularization in the posterior fossa) showed a proximal ruptured PICA-aneurysm (3mm) (A).
A 27-year old woman presented with SAH H&H III and lower cranial nerve dysfunction. 3-D angiography showed a left ruptured proximal PICA-aneurysm (4mm) (B).

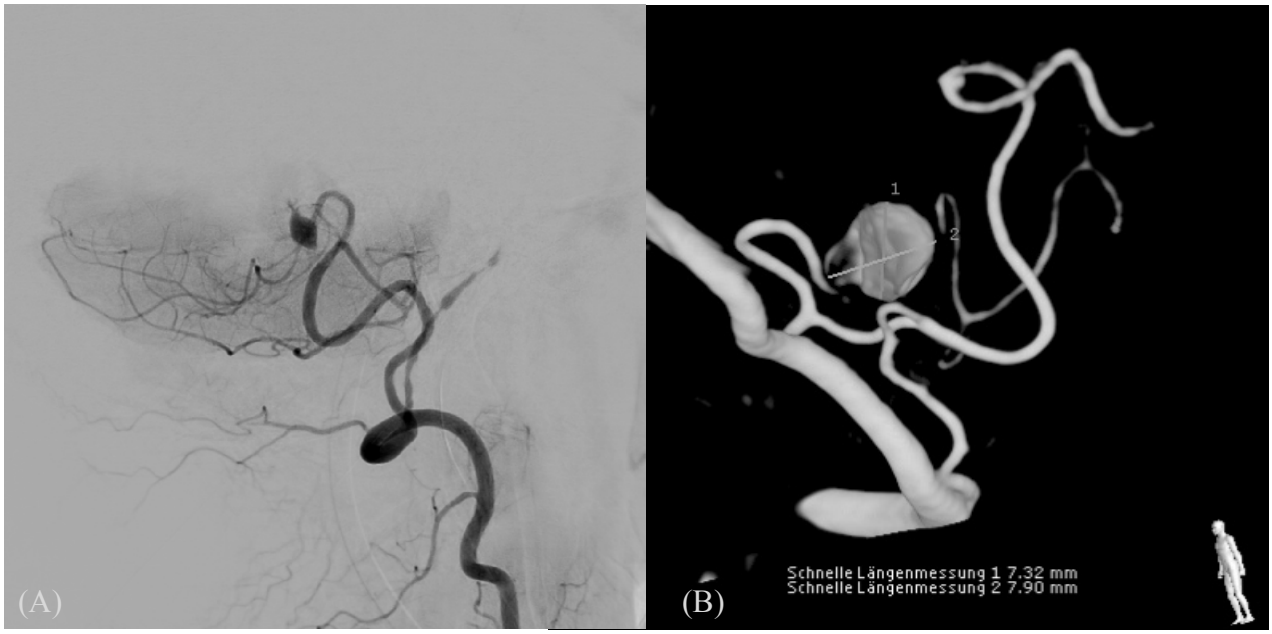


Figure 2 A-B.
A 52-year old man suffered the SAH H&H III. DSA (injection of right VA, lateral view) showed a distal ruptured PICA-aneurysm (4.5mm) (**A**).
A 36-year old women presented with SAH H&H IV and coma. 3-D CTA showed a right-sided fusiform distal ruptured PICA-aneurysm (**B**).

6. CONTROVERSIES IN TERMINOLOGY

The contemporary literature reflects a few controversies concerning the terminology of PICA-aneurysms.

6.1 CONTROVERSIES IN ORIGINS OF THE PICA

First, the definition of PICA varies across the studies: it is defined as either a cerebellar artery originating from the VA with blood supply for the cerebellum,[17, 201] or an artery rising from the VA or the basilar artery (BA) with a blood supply for the posterior inferior part of the cerebellum.[202] As mentioned above, anatomically, there are even more but rare variations and anomalies that are not usually taken into consideration for PICA-aneurysm classification.

6.2 CONTROVERSIES IN ANEURYSM LOCATIONS

In general, the definition of proximal and distal varies among publications and according to the aim of the authors. For example, in some studies on distal cerebellar aneurysms,[203-206] the term 'distal' comprises all those aneurysms that originate on parent vessels branching from the main arteries of the circle of Willis. Furthermore, many available series deal with posterior circulation aneurysms, and often the location along the cerebellar artery segments is not specified.[151, 207, 208] Also in most prior series,[209-211] VA-PICA junction aneurysms are included within the proximal PICA-aneurysms.

The other disputation comprises the classifications of PICA-aneurysm location. Habitually, PICA-aneurysm is defined as an aneurysm located either directly at the VA-PICA junction or on the PICA-artery itself. Broadly speaking, two proximal and distal PICA-aneurysms are distinguished. The term "proximal" PICA-aneurysm includes either aneurysms at the VA-PICA junction only, comprises also those originating from the anterior medullary segment,[212] or any medullary segment of the PICA.[211, 213]

6.3 CLARIFICATIONS IN THE STUDY

6.3.1 CLARIFICATION OF ORIGIN OF THE PICA

Serving our research purpose, we defined as PICA the artery originating from the VA and supplying the cerebellum.

6.3.2 CLARIFICATION OF ANEURYSM LOCATION

In our study, in the first part, describing and analyzing the outcomes related to *"Safety and Efficacy of Treatment Strategies for Posterior Inferior Cerebellar Artery Aneurysms: A Systematic Review and Meta-analysis,"* proximal PICA-aneurysms were defined either as those located on the anterior medullary and lateral medullary segment of the parent artery according to Lister's classification[17] or as those located on the first 1 cm of PICA according to Drake's classification.[80]

In the second part of the study, for the clinical purpose and daily clinical practice, also reporting the *"Current Trends and Results of Surgical and Endovascular Treatment Modalitites – What Factors Has a Key Role in Neurological Outcome? Experience From Three International Referral Centers,"* we defined the proximal PICA-aneurysm as those located on the first cm of PICA, according to the aforementioned broadly accepted Drake's classification.[80]

7. INCIDENCE OF PICA ANEURYSMS

Aneurysms of the posterior inferior cerebellar artery are rare as these represent between 0.5% and 3% of all intracranial aneurysms.[7-16] The first large series comprised 26 distal PICA-aneurysms among 1767 vertebrobasilar aneurysms reported by Drake et al[80] and following by Lewis et al[135] (22 aneurysms) and Tokamura et al[214] (30 aneurysms). Additionally, when concerning all PICA-aneurysms, incidence of fusiform PICA-aneurysms is variable, ranging from 6% to 62%.[135, 167, 178, 214-216]

PICA-aneurysms, by virtue of their rarity and strategic location, represent a unique technical challenge. In treating patients with suspected SAH whose CT imaging shows no obvious SAH, the possibility of VA-PICA aneurysms should be taken into due consideration giving a special attention to the fourth ventricle. It is essential that cerebral angiography must be performed with separate injections of each vertebral artery. Sometimes, PICA-aneurysms might be missed on the initial imaging and thus the imaging (angiography) has to be repeated again, commonly within a time interval of 2 weeks.

8. ASSOCIATION WITH OTHER VASCULAR ANOMALIES

8.1 ASSOCIATION WITH ARTERIOVENOUS MALFORMATIONS

PICA-aneurysms are often associated with other cerebrovascular anomalies. The most common of these lesions is cerebral AVM in up to one third of the cases.[135] The formation of distal basin aneurysms can occur due to unusual hemodynamic stress which is directly related to AVM.[135, 216-219] Tokimura et al[214] postulated that hemodynamic stress plays a more important role in the development and growth of distal PICA-aneurysms than in the case of any other cerebrovascular lesions. The also stated that the development of distal PICA-aneurysms may be attributable to not only to factors involving the VA but also to anomalies in the posterior circulation.

PICA-aneurysms associated with cerebellar AVMs may not remain stable and have been shown to be dynamic lesions that evolve over time.[220, 221] Aneurysms originating near the nidus are considered as potentially carrying an increased risk of hemorrhage.[222, 223] Others, however, report that the risk of hemorrhage is higher for the AVM.[224]

8.2 ASSOCIATION WITH OTHER VASCALUR ANOMALIES

Other vascular lesions comprise arteriovenous fistulas (AVFs),[216] multiple distal PICA-aneurysms[135, 167, 214, 216] or other associated aneurysms.[135, 167] Additionally, PICA-aneurysms are also attributed to higher rates of anatomical anomalies among VA, PICA, and anterior inferior cerebellar artery (AICA).[214, 216] With regard to high rates of cerebrovascular lesions, together with atypical anatomical variants, some authors expressed concerns about aneurysm formation because of hemodynamic stress,[167, 214, 218-220, 225] hyperdynamic flow,[220] time,[226, 227] or embryological failure causing the artery wall weakness.[167, 216, 218, 219] Due to their rarity and small size, the radiological assessment is often very difficult.[178, 179]

9. NEUROLOGICAL SYMPTOMS

The consequences of a PICA occlusion vary and may be overshadowed by the effects of occlusion of the parent vertebral artery. The sequelae range from asymptomatic occlusion to infarction of brainstem areas or cerebellum with edema, hemorrhage, or death. Occlusion of the PICA results in stroke in the lateral medulla, posteriorly to the inferior olivary nucleus. The following clinical syndrome refers to as the lateral medullary syndrome including ipsilateral facial hypesthesia due to impaired spinal tract of the CN V, contralateral syringomyelic loss of sensitivity (pain and temperature) related to impaired spinothalamic tract. Additionally, dysphagia, dysarthria, and hoarseness can occur because of damage of nucleus ambiguus, as well as ataxia, vertigo, and nystagmus and other ipsilateral cerebellar signs due to lesion of vestibular nuclei, cerebellar tracts in the brainstem. Notably, ipsilateral Horner's syndrome may appear in the case of lateral medullary reticular substance lesion. One of the most common accompanying symptoms are nausea and vomiting due to irritation of tractus and nucleus solitarius.

10. CLINICAL FEATURES

10.1 PATIENT AGE

Patients with ruptured PICA-aneurysms present with younger age when compared to those with aneurysms originating from the other sites.[228] For example, Dernbach and colleagues[229] reported a mean age of 44.7 years, with an equal sex distribution. In a series of 27 surgically treated ruptured PICA-aneurysms, Viswanathan et al[228] reported a mean age of 44.6 years. Lewis et al[135] noted a mean age of 51 years in their series. The majority of patients with distal PICA-aneurysms present with hemorrhage.

10.2 NEUROLOGICAL DEFICITS

The most common clinical symptoms are headache and meningism without any neurological deficits.[228] Other focal neurological deficits occur rarely although various symptoms such as cranial nerve palsy, hemiparesis or truncal ataxia were reported earlier.[230-232] Some symptoms that reflect low-lying or extracranial pathological conditions of the PICA include focal neck discomfort or quadriparesis associated with lesions projecting into the cisterna magna or upper cervical spinal canal.[134, 192, 233-235]

10.3 ANEURYSM LATERALIZATION AND SIZE

It seems to be a female predominance and laterality of PICA-aneurysms in several studies.[134, 236]

In general, aneurysm size represents one of the most important factors in determining hemorrhage risks and treatment options, particularly in those patients presenting with unruptured lesions.[135] The “safe” size under which hemorrhage is less probable is most often quoted as less than 10 mm.[237, 238] This rule clearly is not true for distal PICA-aneurysms. Peripheral PICA-

aneurysms originating from the distal part of parent vessel most likely have thinner walls, rendering them more prone to hemorrhage.[239]

It is here worth noticing that in a study reporting a natural history of intracranial aneurysms, Richardson et al[240] stated the highest mortality rates related to SAH in patients with aneurysms originating from the vertebrobasilar system.

11. LOCATION OF HEMORRHAGE

11.1 HEMORRHAGE FROM PROXIMAL PICA ANEURYSMS

Rupture of proximal PICA-aneurysms is often apparent by the presence of hyperdensity in the homolateral basal cisterns, with or without extension into the fourth ventricle.[241] In case of isolated intraventrical hemorrhage (IVH) without perimesencephalic or cisternal SAH, rupture of distal PICA-aneurysm should be taken into consideration as a possible hallmark for these aneurysms, even though similar SAH distribution may occur after rupturing the proximal ones also.[228] Identification of any small focal parenchymal clot adjacent to the ventricular system should alert the clinician to this possibility. In nonhypertensive younger patients, vermian or cerebellar hemisphere clots (often having extension into the ventricular system) are most likely caused by an underlying structural vascular lesion such as an AVM.[135] In contrast, hypertensive cerebellar hemorrhages usually appear in men during their sixth through eighth decades, arise in the dentate nucleus but can expand to involve the vermis medially, and generally do not reach the ventricular system unless quite large.[242]

11.2 HEMORRHAGE FROM DISTAL PICA ANEURYSMS

Rupture of a distal PICA-aneurysm causes IVH in 78% - 100% of patients.[135, 214-216] Aneurysms originating from the tonsillomedulary segment (Lister class 3, see above) often cause

isolated IVH.[134, 241] Cerebellar intraparenchymal hematoma likely indicates rupture of aneurysms along the cortical or telovelomedullary segments. The hemorrhage may also reach the ventricle system. It is worth mentioning that IVH is associated with higher rates of hydrocephalus[135, 214, 216, 243] resulting in lower rates of favorable neurological outcome.[167, 244-246] Kallmes et al[241] studied the hemorrhagic patterns of PICA-aneurysms shown on CT scans. The authors postulated that the incidence of IVH or acute hydrocephalus was 95%.

12. TREATMENT INDICATIONS

As generally accepted, aneurysm size belongs as one of the most important factors in determining the risk of rupture. However, concerning especially the distal PICA-aneurysms, they tend to rupture even at smaller sizes most likely because of thinner walls.[167, 214, 239] They also have a greater rate of rebleeding.[215] As already mentioned above (see *the Chapter 11*), rupture of PICA-aneurysms often cause intraventricular hemorrhage (IVH)[135, 214-216] and hydrocephalus.[135, 214, 216, 243] Securing the ruptured aneurysm allows all necessary measures including aggressive treatment of vasospasm. Thus an ultra-early treatment regardless of the approach is crucial (imperative) in these aneurysms. Furthermore, rebleeding rates of ruptured PICA-aneurysms may be as high as 78%.[215, 247, 248] Because of a highly variable and tortuous course of PICA with a various number of perforators arising from the proximal part, the proximity to the lower cranial nerves, deep location in the posterior cranial fossa and a high proportion of fusiform and dissecting aneurysm, the treatment of PICA-aneurysms is highly challenging regardless of therapy approach. However, in defiance of high Hunt&Hess grades after rupture, the majority of patients ultimately show favorable neurological outcome.[210, 212]

Aneurysm neurosurgeons accept the appeal of the minimally invasive character and the exciting advancements in endovascular technique. Today's goal is to integrate therapeutic modalities and select treatments that optimize patient outcomes. In the current era, the role of microsurgery for PICA-aneurysms can be viewed as a competitive alternative to endovascular therapy, or as an alternative when endovascular therapy is unfavorable or unsuccessful.[150] In our opinion also, microsurgery is a competitive option to endovascular therapy for PICA-aneurysms.

There is no algorithm or protocol in selecting patients for either surgical or endovascular treatment. This decision should be conferred in an interdisciplinary team of neurovascular experts making individualized recommendations that account for other relevant clinical and anatomic factors.

The team has to consider the many other factors that tip the balance toward one modality, including aneurysm size, morphology, neck size, aspect ratio, projection, branch anatomy, intraluminal thrombus, wall calcification, parenchymal hematoma, intracranial pressure, presence of vasospasm, patient age, neurological condition, medical comorbidities, patient preferences, and institutional expertise. Patients arrive with treatment biases determined by personal preferences, family preferences, and interactions with referring physicians, and the team must move beyond these biases.

With microsurgery as an alternative, discussions about coiling and minimal invasiveness must include incomplete treatments, aneurysm recurrence after coiling, surveillance angiography, and possible retreatment.[150] Discussions about open surgery and the durability of aneurysm occlusion should include relatively higher surgical risks, longer recovery periods, and cognitive side effects. Perhaps this heightened level of patient education overwhelms or confuses patients and families, yet it enables them to make informed treatment decisions. The choice depends on a patient's gut reaction to this tradeoff between treatment risks and long-term efficacy, and a surprising number of patients do not automatically select the least risky treatment.[150]

In defiance of rapidly developing endovascular techniques and their progressive adjuncts, PICA-aneurysms, especially those located on the distal part of the parent artery, are most likely the best instance of an aneurysm for which microsurgery continues to play a primary role. An unusually large portion of PICA-aneurysms have broad necks, multiple lobules, efferent arteries originating from the base, non-saccular morphology, intraluminal thrombus, or distal locations that make endovascular therapies suboptimal.

Microsurgery for PICA-aneurysms is suitable because exposure through a far lateral craniotomy is excellent, proximal control is immediately available, and minimal microdissection is required to access the tonsillomedullary fissure and follow the PICA and VA toward their convergence on the aneurysm neck.[209, 213, 249] The lower cranial nerves and medullary perforators are located throughout the field, but they are easily evaded. Microsurgical approaches for unusual PICA-aneurysm anatomy are miscellaneous.[10, 201, 236, 250-252] For example, wide necks can often be reconstructed with tandem clipping techniques by using the fenestrated clip blade to close the bulk

of the neck and the fenestration to rebuild the PICA origin.[150] When the PICA cannot be preserved, other alternatives such as revascularization are available. These comprise extracranial-to-intracranial bypass with the occipital artery, intracranial-to-intracranial bypass with the contralateral PICA (PICA-to-PICA bypass),[253] and reconstructive techniques with end-to-end repair or reimplantation of the PICA onto the VA. Performing these techniques in this deep surgical field is very demanding but postoperative findings are satisfactory.

In general, small, superiorly projecting aneurysms with narrow necks are ideal aneurysms for both surgical and endovascular treatment with outstanding outcomes and either modality.[135, 254-265] Thus microsurgery ought to be a competitive option for these aneurysms. In contrast, giant, posteriorly projecting aneurysms with broad necks and dysmorphic branches are very challenging aneurysms for both treatment strategies, and poor neurological outcomes have been reported after both modalities.[150, 266]

It is worthy of notice that many authors prefer microsurgical treatment for distal PICA-aneurysms.[150, 216, 253] As advantages, they state safe occlusion of wide-necked aneurysms with preservation of the parent artery and perforators, direct observation of the vessel wall, and possibility for revascularization, evacuation of hematoma, and decompression, if necessary.

In contrast, several recent studies have reported promising results of endovascular treatment of PICA-aneurysms including selective coil embolization, occlusion of parent vessel with ethylene vinyl alcohol copolymere (Onyx; Covidien/ev3 Neurovascural, Irvine, California, U.S.), n-butyl cyanoacrylate, or coils.[212, 243, 267-271]

Ultimately, irrespective of the final treatment strategy, comprehensive expertise and deliberate judgment is mandatory for treating the PICA-aneurysms.

13. SURGERY

Direct open surgery offers several advantages, for example, the removal of blood leads to immediate decompression, and surgery avoids additional procedures such as ventricular drainage and ventriculoperitoneal (VP) shunting and facilitates the identification of the bleeding source in patients with multiple lesions.[216]

13.1 SURGICAL APPROACHES

As mentioned above (see *the Chapter 3.4*), surgical treatment of PICA-aneurysms is challenging due to the unique anatomical features such as deep location, proximity to the brainstem and lower cranial nerves, and the presence of perforating arteries for the medulla arising from the proximal segments of the PICA.[211, 212, 267, 268] The aforementioned conditions and many others such as presence of any anatomical variations of the parent vessel or the need for an anastomosis or bypass procedure should be considered before surgery. An in-depth search for brainstem perforating arteries is crucial prior to trapping although it has been claimed to be safe for aneurysms arising distal to the choroidal point.[228] Maintaining a caudal to rostral view beneath the cranial nerves rather than through them has significantly decreased postoperative lower cranial nerve dysfunction that used to be the major cause of morbidity.[228]

A thorough knowledge of posterior skull base anatomy is imperative when approaching PICA-aneurysms. Depending on the aneurysm location, the surgical approach varies from midline to extreme far lateral. Awareness of other associated vascular anomalies is also essential being prepared for PICA reconstruction or AVM resection.

Microsurgical approaches to PICA-aneurysms should be planned and tailored based on size, shape, rupture status, and clinical condition of the patient.[178] While planning the surgical trajectory, the location of the aneurysm based upon the segmental anatomy of PICA; its relationship to the anatomical midline (10 mm or less being considered significant), brainstem and cerebellum, and the variability in the vessel's origin should be carefully assessed.[272-274]

13.1.1 APPROACHES TO PROXIMAL PICA ANEURYSMS

Lateral approaches to the foramen magnum,[162, 275-281] which have often been utilized to operate on lesions anterior to the medulla oblongata or lesions of the VA, are very useful. The far lateral approach,[277] transcondylar approach,[275], and extreme lateral approach[281] are well-known lateral approaches.

For VA-BA-PICA junctional, anterior medullary, lateral medullary and tonsillomedullary aneurysms situated close to midline anterior to the brainstem, the lateral suboccipital approach, the far lateral or extreme lateral transcondylar approach are routinely used.[277, 282-284] Removal of the posterior condyle,[285] C1 lateral mass,[277] and/or the jugular tubercle[275] is supportive in extending the surgical access.[283] The surgical technique was described in detail by Ojemann et al[286] and Samson and Batjer.[287] The suboccipital craniotomy may be performed using the lip of the foramen magnum as an entry point. The craniotomy is then broadened laterally, revealing the transverse and sigmoid sinuses. Some surgeons do not routinely remove the arch of C1 or the lateral occipital condyle.[288] After opening the dura, the VA can be recognized easily at the point where it penetrates the dura. This step is essential for obtaining the proximal control. The PICA origin is found near the origin of CN XII. After obtaining the proximal and distal control, the aneurysm neck is uncovered with sharp dissection. Finally, clipping of the dissected PICA-aneurysm is performed.

The lateral suboccipital approach was first described by Heros[277] in an attempt to minimize postoperative neurological morbidity. Bertalanffy et al[217] used the lateral suboccipital transcondylar approach including removal of the posterior arch of C1 approach for the treatment of proximal PICA-aneurysms. Similarly, D'Ambrosio et al[209] also recommended excision of the posterior arch of C1, with occipital condylar removal approaching the proximal PICA-aneurysms inferiorly to the cranial nerves. As an alternative, Salcman et al[289] suggested a three-quarter prone position for retromastoid exploration. The extreme tortuosity of the VAs and PICA may sometimes have an impact on the laterality of the approach. In proximal PICA-aneurysms, far lateral suboccipital approach without removing the condyle and lamina of C1 provides sufficient exposure for clip deployment without significant manipulation of the lower cranial nerves. Yet, some authors[275, 283] advocate extra bone drilling in regards to decreased cerebellar retraction and better exposure. However, this can lead to significant new postoperative neck pain[288] and increased risk of CSF-leakage.[209] Besides, all these do not remove the lower cranial nerve obstacles

emphasized by Kawase et al.[290] Wu et al[288] suggested slow releasing CSF from the cisterna magna, cerebellopontine angle (CPA) cistern in order to widen the intraoperative space.

As another possibility, retrolabyrinthine transsigmoid approach favored by Giannota and Maceri[291] contributes to direct anterolateral revelation of the cranial nerves, however, this is being used rarely.

13.1.2 APPROACHES TO DISTAL PICA ANEURYSMS

Lesions originating from the distal three segments of PICA (Lister class 3-5)[17] are approached by a standard midline/ paramedian suboccipital craniectomy.[80] Aneurysms located beneath the tonsil can be tackled after subpial tonsillar resection rather than mobilizing the tonsil to avoid premature rupture. The PICA can be sacrificed distal to the choroidal point,[228] but if the aneurysm is more proximal and cannot be clipped, an end-to-end anastomosis or a distal bypass should be performed to preserve blood supply to the deep cerebellar nuclei and brainstem.
Regarding the midline suboccipital or more precisely subtonsillary approach originally described to reach the fourth ventricle, and anatomical details have been previously reported.[292-298]

The patients are usually in a prone position with the head placed in a neutral position whereas the cervical spine is anteriorly flexed. A midline vertical skin incision is made from the inion to the C1. A suboccipital midline craniotomy extended to the posterior rim of the foramen magnum is performed. If needed, the posterior arch of C1 may be removed, however with preserving the atlantooccipital joints. We usually do not perform the removal of the arch for the distal PICA-aneurysms. The dura is opened in Y-like fashion. Cerebellomedullary arachnoid is sharply and meticulously dissected unilaterally to allow mobilization of cerebellum's tonsils. Opening of the tonsillovermian fissure further increases the exposure to the medulla. This step is necessary only in particular PICA-aneurysms depending on the specific aneurysm location. This maneuver allows the access to the inferior end of the fourth ventricle and the medulla oblongata. The courses of the PICA are highly variable, however, it is crucial to identify and preserve all vascular structures at that moment. Regarding veins, the cerebellomedullary fissure vein drains the superior and ventral surfaces of the tonsils and parts of the inferior vermis. It runs laterally within the fissure to empty into the tributaries of the superior petrosal sinus. At its medial origin, the cerebellomedullary fissure veins can communicate by means of the lateral uvular vein with the

inferior vermian vein. To completely dissect and secure an aneurysm, after acquiring the proximal control of the parent artery, temporary clipping is frequently used due to the predisposed character of the distal PICA-aneurysms to rupture. Finally, clip deployment with preserving the parent artery is performed with subsequent intraoperative routine ICG-angiography to confirm the complete aneurysm occlusion and parent vessel patency. These can also be checked through intraoperative Doppler-ultrasound examination. Afterward, the dura is closed in a watertight fashion. The bone flap is fixated either with Aesculap's CranioFix® titanium clamp systemback or titanium miniplates and screws. Muscles and superficial tissues are closed in the usual manner.

13.2 SURGICAL TECHNIQUES

Microsurgical strategies in treatment of PICA-aneurysms comprise direct clipping,[135, 167, 214-217] clipping with wrapping,[216] wrapping,[167, 215] resection,[214, 217] proximal occlusion or trapping with revascularization,[135, 167] and distal occlusion.[299] Of these, direct clipping is the most used surgical method to occlude the PICA-aneurysm. When considering the revascularization techniques for distal PICA-aneurysms, the indications remain unclear. With regard to the blood supply of cerebellum, there are plentiful collaterals across the cerebellar vessels. Additionally, no substantial brainstem ischemia or permanent severe neurological deficit appear after occlusion of the distal part of PICA.[216, 243, 300] However, for the proximal part of PICA revascularization is recommended.[135-137]

Notably, Liew et al[213] stated that in the case of preserving of brainstem perforating arteries sacrifice of proximal PICA might be safe. In comparison, Lehto et al[178] reported that if occlusion of the PICA proximal to the telovelotonsillar segment was mandatory, or adequacy of collateral circulation was in question, revascularization such as OA-PICA, PICA-PICA bypass, or an end-to-end anastomosis was performed.

13.2.1 CLIPPING

The brainstem and cranial nerves may be compromising the surgical view to these aneurysms. Moreover, one or more parent vessels at the VA-BA junctional region may be ending into or taking origin from the neck of this aneurysm. Application of clip may cause narrowing or twisting of these vessels leading to luminal compromise.

In those patients in whom a far lateral approach is used, control of the proximal ipsilateral VA should be obtained in its extradural portion in the suboccipital triangle after its emergence from C1 foramen transversarium.[301] In comparison to the PICA course, the VA shows a fairly constant and well-localized position while traversing over the C1 posterior arch prior to its entry into the dura.[277, 282] In the case of tortuous VA with a high shoulder, the artery can be uncovered from the contralateral "aneurysmal dome" side or by using the translabyrinthine approaches.[289, 291]

It is important to note that PICA usually originates dorsal or lateral to the aneurysm. Sometimes, however, it can be located posteriorly or medial to its neck. The applied clip blades are usually pointing forwards, distal to VA-PICA junction parallel to the long axis of VA.[301] Fenestrated clips may protect lower CNs or the origin of PICA. Most of these anterior aneurysms are located ventral to lower CNs.[289] While crossing the rootlets of these nerves, occasionally, dysphagia, rhinolalia, hoarseness, nasal regurgitation or aspiration pneumonia related to their functional impairment can occur even when the arachnoidal plane stays meticulously preserved.[10, 134, 236]

Although the proximal control of VA is very important and necessary, using the temporary clip occlusion should be performed as few as possible, unless the aneurysm ruptures during operation. The temporary clips may physically limit the already confined and deep space in the operation, leading to an increased risk of mechanical trauma to the caudal CNs and the lower brainstem.[236] As mentioned above, for distal PICA-aneurysms a midline suboccipital approach is indicated. The treatment should be performed as soon as feasible after patient admission. Some authors postulated that the optimal treatment of the saccular aneurysms is clipping of the neck without parent vessel occlusion.[10, 289] Because of the small caliber of distal PICA and the relative dominant diameter of the aneurysm, the place of the clip is vital.[288] In a surgical series of 29 ruptured PICA-aneurysms, Wu et al[288] stated that the clip should be placed near to the neck even on the body partly to leave a patent PICA. In the case of aneurysm location relative to the origin

of brainstem perforating branches or the lesion is fusiform with branches, the authors chose a treatment option of scorf's clipping to preserve the branches, which is similar with wrap-clipping as reported by Horiuchi et al.[167]

If an aneurysm, particularly a dissecting one, includes predominantly a side-wall blow out, it is enticing to place a right-angled fenestrated clip with the blades being parallel to the base of the impaired part.[135] Yet, Lewis et al[135] reported their experience with lesions at other sites, where the apparently healthy residual part of the artery is often debilitated and aneurysm recurrence may easily appear. For aneurysms in which PICA flow must be preserved, sufficient aneurysm exclusion with preserved lumen of parent artery is attainable through stacking a row of fenestrated clips. Use of Yasargil ring clips or clip placement obliquely across PICA is useful for evading the perforators.

13.3 INTRAOPERATIVE STANDARD EXAMINATIONS

In the last decade, the intraoperative microvascular Doppler was routinely used in many neurovascular centers as a method for intraoperative assessment of vascular flow as reported.[302] Nowadays, intraoperative ICG-angiography has widely been replacing the intraoperative Doppler examination. Nonetheless, given its non-invasive character and simple reliable use the during the surgery to show the occlusion of the aneurysm and the patency of parent vessels and branch arteries, it still remains a valuable examination in neurovascular surgery.

Finally, it is important to note that intraoperative electrophysiological monitoring including bilateral somatosensory evoked potentials and monitoring of CNs IX, XI, and XII may be useful especially in treating of unruptured PICA-aneurysms.

13.4 SURGERY-RELATED COMPLICATIONS

The incidence of lower cranial nerve palsies after surgical treatment of PICA-aneurysms has been reported to be high occurring in roughly up to 60% of cases depending on the series.[10, 134, 155, 209, 236, 303, 304] It is important to note that the surgery-related morbidity is commonly transient[236, 289] and improves in approximately three to six months.[10, 236, 289] However, lower cranial

nerve palsies could result in disastrous sequelae especially in infirm patients with a poor preoperative condition. The decisive risk factors for the development of nosocomial pneumonia (that carries a mortality rate of 20-50%)[305] comprise low nutritional status, lower Glasgow Scale Score (GCS), vertebrobasilar stroke, and the need for mechanical ventilation.[236]

Dysphagia, hoarseness, dysarthria, diplopia, lateral medullary syndrome, airway problems, and aspiration pneumonia have been reported as postoperative complications of VA-PICA-aneurysm surgery.[10, 134, 275, 289, 303] In fact, a major cause of morbidity associated with VA-PICA-aneurysms or more precisely proximal PICA-aneurysms is lower cranial nerve dysfunction.[134, 155, 275, 289] Postoperatively, patients can present with severe lower cranial nerve dysfunction manifested as mentioned above.[142, 306]

In a series of 34 patients undergoing surgical treatment for PICA-aneurysms reported by Horowitz et al,[10] up to 68% of patients showed a new postoperative neurological deficit. It may be caused by extensive manipulation during the dissection of the aneurysm due the proximity to the cranial nerves.[228] In defiance of the extended exposure e.g. after condylar drilling by far lateral approach, the cranial nerve palsy rates did not decrease significantly.[10, 155, 217, 289]

It is important to note that some clinical symptoms such as weak cough, hoarseness, excessive secretion, oxygen desaturation, or recurrent pneumonia may be misinterpreted as surgery-related dysphagia or aspiration. Many patients have decreased infraglottic sensation and cannot sense aspirated material, resulting in so-called silent aspiration.[306] Dysphagia in these patients can remind that of patients who suffered a mild PICA stroke.[307] Aspiration has to be avoided by protected measures. These comprise tube feeding, gastrostomy, and/or tracheostomy.[308] Despite such strategies, patients remain at risk of developing pneumonia because of contamination of the tracheobronchial tree by aspirated oropharyngeal secretions. Adequate nutrition is also crucial for these patients who are at risk for malnutrition secondary to surgery, dysphagia, and other complications.[309] The cumulative risk of aspiration together with accompanying not negligible risk of malnutrition may lead to increasing disability and eventual death.[141] It is an imperative to provide adequate and sufficient intensive care for these patients. Pronlonged ICU stay is not unusual. This finding could be extrapolated from various other studies.[309-311]

The ability of a patient to cope with cranial nerve palsy depends on the CN involved, the

number and combination of cranial neuropathies, and the time course of development.[142] Many cases of lower CN neuropraxia that occurred secondary to mild to moderate mechanical trauma resolved completely in 3 to 6 moths.[236] For example, Al-khayat et al[236] reported that 75% of lower cranial nerve palsies resolved completely within 6 months. Similar findings were described in other studies.[10, 289] The ability of patients to compensate for unilateral lower cranial nerve dysfunction also has been observed.[307, 308] The adaptive capabilities of patients vary widely, and factors such as age, intelligence, motivation, and comorbidity have a significant impact on neurological outcome.[141, 308] Other postoperative complications include CSF-leakage[209] and new neck pain.[288] It is worth mentioning that intraoperative aneurysmal rupture, perforating vessel injury, inadvertent arterial occlusion, and inadequate arterial hypotension may also elicit new postoperative deficits.[217]

Some authors[301] concede that an endovascular intervention may have provided similar good results. They also reported that patients, when given an option between surgical clipping and endovascular approach chose the former due to the lesser expense of the surgical procedure. A complication rate of as high as 13% has been reported with embolization of PICA-aneurysms.[20] As is well illustrated in prior studies,[17, 273] PICA often has extremely variable and tortuous course with multiple anomalies and variability in position of the aneurysm relative to the brainstem. Superselective catheterization of the PICA is often demanding, sometimes even impossible or might be associated with complications during the endovascular procedure as exemplifying by artery wall dissection that can occur during catheterization.

The mortality is mostly related more to vasospasm as a result of subarachnoid hemorrhage rather than due to technical aspects of surgery or endovascular treatment.[301] Thus, surgeons have a responsibility to be well-versed with the surgical approaches and nuances for clipping these aneurysms in case the endovascular treatment fails or is not possible or, if salvage surgery is required for SAH occurring during the interim period between the endovascular coiling and the development of luminal thrombosis within the aneurysm.[312]

14. ENDOVASCULAR TREATMENT

Endovascular treatment is a minimally invasive modality that offers efficient therapy of PICA-aneurysms without inherent risk associated with surgical approaches, particularly lower cranial nerve palsies.[174] As the use of endovascular methods for the treatment of intracranial aneurysms has become more extended, endovascular treatment of PICA-aneurysms has similarly become more accepted.[20, 208, 210, 211, 243, 300, 313, 314] Numerous prior studies reported successful endovascular treatment of PICA-aneurysms.[20, 156, 204, 210, 211, 225, 243, 267, 314, 315] In a light of results from the ISAT-study,[11, 316] endovascular coil treatment is significantly more likely to result in survival without disability 1 year after SAH than neurosurgical treatment.

Yet, most of these former series comprised a small number of patients with limited radiological follow-up. To our best knowledge, in the largest published series of 76 endovascularly treated PICA-aneurysms, Chalouhi et al[212] postulated that endovascular therapy is a feasible, safe and effective treatment in patients with proximal and distal PICA-aneurysms, providing excellent patient outcome and adequate protection against re-hemorrhage. However, the long-term incidence of aneurysm recanalization appears to be high, especially in distal PICA-aneurysms and requires careful angiographical follow-up.[212]

The PICA supplies the posterolateral portion of the medulla oblongata through perforating arteries originating from its proximal segments, along with the cerebellar tonsils, vermis, and cerebellar hemispheres through terminal branches. Due to an anastomotic plexiform network at the surface of the medulla, the risk of brainstem ischemia with proximal PICA occlusion is meant to be low in appropriately selected patients, as corroborated by several prior studies.[17, 134, 135, 157, 212] Moreover, in some cases, the medulla is exclusively supplied by the anterior spinal artery and direct branches of the vertebral arteries (other than the PICA). On the other hand, collateral supply from the ipsilateral AICA, SCA, or contralateral PICA seems also to be sufficient to prevent or limit the extent of cerebellar infarctions in many cases. Nevertheless, it is important to assess the presence and extent of collateral supply before considering parent vessel occlusion, as surgical intervention with bypass grafting remains a valuable option when collateral flow is insufficient.[157, 249, 317, 318]

14.1 PERCUTANEOUS PUNCTURE APPROACHES

Endovascular treatment may encounter difficulties due to the small caliber and subsequent risk of thrombosis.[175, 211, 212] In general, as already mentioned above, identification of the neck and selective catheterization may be exacting or even not feasible especially in peripheral aneurysms. When aneurysms are small, the risk of abrupt "jumping" of the catheter or guide wire into the sac increases the chances of its rupture.[300] Moreover, if the microcatheter tip does not conform favorably to the anatomy, the system may be very unstable and further coils may migrate or displace the catheter into the parent vessel.[300]

In addition, an acute angle of the PICA origin from the VA may preclude wire catheterization of the PICA itself.[174, 175, 267] A retrograde approach to the PICA via the contralateral VA or via the posterior communicating artery (PCA) is the alternative access to an inferiorly angulated PICA.[175] In some instances, even the PICA itself may be demanding to catheterize, especially when it runs inferiorly at an acute angle, and may require technically exacting procedures such as transcirculation approaches. In fact, without adjunctive techniques such as stenting or balloon remodeling many patients would have undergone deconstructive procedures or would have probably been referred for open surgical treatment.[174] Unfortunately, these techniques are currently inapplicable in distal aneurysms given the small caliber of the PICA and the mechanical limitations of available stents and balloons.[212] Thus, in many patients with distal aneurysms, the only available endovascular option is to occlude the aneurysm along with the PICA.[174]

Nevertheless, retrograde access to the PICA via the contralateral VA or via the PCA represents a valuable alternative.[175, 212, 268, 319, 320] This technique has proved to be feasible in the aforementioned prior studies. In the case of acute angulation of both VAs, a combined use of a balloon inflated in the proximal segment of the BA and the shaping technique may be helpful in direct catheterization of the aneurysm.[321]

14.2 ENDOVASCULAR TECHNIQUES

A recent preference for endovascular treatment of intracranial aneurysms has resulted from studies comparing microsurgical and endovascular outcomes for mainly anterior circulation

aneurysms.[11, 322] Recent techniques include embolization with Onyx (ev3, Irvine, California, USA) or TRUFILL n-BCA (DePuy Synthes, Raynham, Massachusetts, USA),[323] coil embolization,[243] stenting,[225] and vessel sacrifice.[324, 325]

Another potential future treatment option may be a flow-diverting stent, such as the ev3 Pipeline Embolization Device (PED).[326] However, remaining challenges include preservation of small parent vessel diameter and the need for antiplatelet agents in patients with subarachnoid hemorrhage.

Among the contemporary endovascular methods, Onyx liquid as the embolic agent has proven to be a rapid and effective means of achieving obliteration of dissecting and/or pseudoaneurysms.[318] The appropriate application of the liquid embolic agent immediately prior to the aneurysm plays here a key role, enabling the filling of the aneurysm, without any, or rather limited distal migration.

14.2.1 BALLOON REMODELING

Balloon remodeling (balloon-assisted coil embolization) is a safe and efficient endovascular technique for the treatment of intracranial aneurysms with unfavorable characteristics such as wide-necked aneurysms.[212, 327, 328] It also offers higher rates of immediate adequate aneurysm occlusion.[327, 328] However, balloon navigation into the parent vessel is sometimes technically difficult because of the tortuosity or acute angularity of the vessels.[329] In proximal PICA-aneurysms located on an acutely angulated PICA, navigating the balloon catheter from the ipsilateral VA is often exacting or even unfeasible and possibly increases the risk of perforation of the aneurysm that is located at or directly distal to the VA-PICA junction.

14.2.2 PARENT VESSEL OCCLUSION

One of suggested solution in such cases is the parent vessel occlusion.[211, 212, 267, 268] Several series reported that the parent vessel occlusion of the PICA can be related to a cerebellar infarction

occurring up to 36% of cases, but these strokes are commonly tolerated with a low rate of neurological morbidity.[211, 212, 267, 268]

The fact that many aneurysms originating from the distal PICA have dissecting morphology may give an explanation of the necessity for deconstructive techniques. Even though direct coiling of dissecting PICA-aneurysms can be practicable in some cases,[315] some authors favor parent artery trapping to avoid leaving the point of initial intimal tear untreated and minimize the subsequent risk of recurrence and rebleeding.[204, 330]

14.3 ENDOVASCULAR INTERVENTION-RELATED COMPLICATIONS

Procedural complications (procedure-related morbidity rates) are not negligible as these range between 7% and 22%.[211, 212, 268, 331-333] Procedure-related mortality is not low either occurring between 0% and 7%.[208, 211, 212, 300, 334] Unlike the previously published results regarding the incidence of intraprocedural aneurysm rupture, recent refinements to microcatheters and detachable coils and increasing expertise with aneurysm treatment have contributed to reduction of intraprocedural rupture rates. Furthermore, proximal and distal trapping of the PICA seems to be safe with only minimal subsequent morbidity.[204, 211, 225, 243] As such, in a large series of 76 PICA-aneurysms published by Chalouhi et al,[174] the parent vessel occlusion led to infarctions in 36.4% of cases, however, none of which resulted in permanent morbidity. In fact, all infarctions were remarkably well tolerated (or even clinically silent) and involved only the cerebellum sparing the brainstem. The anatomy of the PICA has been well known and allows for these observations.[17, 134, 135, 157]

In 2003, Mukonoweshuro et al[20] reported their experience with the endovascular treatment of PICA-aneurysms. 23 patients underwent endovascular procedure with Guglielmi detachable coils and 95% or greater occlusion was noted in 82.6% of patients. Complications included 13% neurological morbidity, but no deaths or re-hemorrhages occurred. One year later, Bradac and Bergui[300] described 18 patients harboring PICA-aneurysms that were treated endovascularly. They reported a complete occlusion in 78% of patients and observed an intraprocedural rupture rate of 11%. In 2006, Mericle et al[210] described their institutional endovascular experience of 31 patients with PICA-aneurysms. Of these, 30 showed excellent angiographic occlusion. Angiographic follow-up was performed in 15 of these patients with no change in the angiographic outcome.

Peluso et al[211] also described results of endovascular treatment in 46 patients with PICA-aneurysms. Complete or near-complete angiographic occlusion rates were achieved in 83% of cases. They noted technical difficulties in a not inconsiderable number of patients including intraprocedural rupture rates in 19% of cases and mortality in 4.3% of patients. However, they were able to demonstrate that endovascular methods are useful for many aneurysms originating from the PICA. Pandey et al[208] described the endovascular treatment of all posterior circulation aneurysms where VA- and PICA-aneurysms were analyzed together. Aneurysms of the VA-PICA that were treated endovascularly constituted 2.2% of all aneurysms and 15% of all posterior circulation aneurysms treated endovascularly. They reported 95% to 100% embolization in 83% of cases and noted re-hemorrhage rates in 2.4%. Of those cases with 90% occlusion rates after initial embolization, 50% were eventually re-treated.

In a recent series of 20 endovascularly treated patients for PICA-aneurysms, Crowley et al[268] reported intraprocedural rupture rate higher than that generally seen with the endovascular treatment of aneurysms. Rates of intraprocedural rupture have been reported to be between 1% and 5%, and factors thought to be associated with increased risk of rupture include an initial presentation of SAH and aneurysm location in the posterior circulation.[335-340] Conversely, intraoperative rupture rates for patients undergoing surgical clipping has been reported as being between 8% and 19%, and, similarly to rupture during endovascular treatment, it has been associated with worse outcomes.[341-343]

14.4 ANGIOGRAPHIC OUTCOMES

When considering the long-term complete aneurysm occlusion, all endovascularly treated aneurysms may recanalize at some point during follow-up, indicating that follow-up imaging is very important in these cases. This applies to PICA-aneurysms showing the recurrence rates as high as 27%.[8, 208] Thus some authors recommend stent after balloon remodeling technique. This special endovascular means theoretically combines benefits of two separate techniques including high occlusion rates and increased packing density in balloon remodeling as well as a mechanical scaffold for endothelial growth and potential flow diversion.[327, 344, 345] Thanks to developing technical advances, the deployment of currently available stents are facilitated through the coaxial

lumen of the double-lumen balloon catheter when compared to previously used single-lumen catheters. The best endovascular technique for PICA-aneurysm continues to be debated but contemporary experience with the stent after balloon technique seems to be promising. Yet, additional costs together with possibly increased risk due to protracted intraprocedural manipulation may partly question the necessity of these extensive techniques.[321]

Achieving a high occlusion is essential as a substantial relationship has been found between the degree of initial aneurysm occlusion and subsequent aneurysm recurrence or reopening especially in posterior circulation aneurysms, with a significant increase of recurrence in patients with incompletely occluded aneurysms (<90%).[208] Chalouhi et al[212] reported recurrence rates of endovascularly treated PICA-aneurysms of 18%. Similarly, Peluso et al[211] described PICA-aneurysm recurrence rates of 20%. In comparison, Heye et al[321] showed cumulative complete and near-complete occlusion rates of PICA-aneurysms after balloon-assisted coiling of 100% with a mean postoperative radiological follow-up of 24.2 months.

14.5 STRENGTHS AND LIMITATIONS

PICA-aneurysms are predisposed to have high recurrence rates, especially when treated with selective coiling. The above mentioned studies highlight a major limitation of endovascular treatment of PICA-aneurysms, namely a high rate of aneurysm recanalization. As such, aneurysm recurrence and retreatment rates are worrying. Even more concerning are the alarmingly high rates of recurrence in selectively coiled aneurysms, reaching about one fifth in proximal aneurysms and as much as one half in distal aneurysms.

Importantly, the only plausible explanation for the high rate of recanalization is the suboptimal packing density of aneurysms (especially distal ones) to preserve the patency of the parent artery and also possibly to an underlying dissecting morphology in a not inconsiderable number of cases. For these reasons, it is of utmost importance to obtain angiographic follow-up.[212]

With a recanalization rate of 20%-31%, the durability of endovascular treatment also has been called into question[212, 346] and required retreatment rates of 17% - 23%.[212] Bohnstedt et al[347] found a 5.4% (2 of 37) recurrence rate among endovascularly treated aneurysms requiring retreatment. Incomplete embolization or recanalization of aneurysms has proved to have an

increased risk for rebleeding.[348, 349]

Despite this potential drawback, the rate of re-hemorrhage seems to be fairly low (for example 1.4% in the largest published series[212] of 76 endovascularly treated PICA-aneurysms), which proves that PICA-aneurysms may be reliably secured with endovascular therapy.[212] In addition, some authors believe that endovascular therapy could be a reasonable first-line option for proximal PICA-aneurysms.[212] This is further corroborated by the challenges posed by surgical clipping of these aneurysms and the high incidence of postoperative lower cranial neuropathy with resultant dysphagia, diplopia, hoarseness, and aspiration pneumonia.[10, 236] Oppositely, endovascular therapy has a less favorable efficacy profile in distal PICA-aneurysms, especially when using the selective coiling, together with substantial technical difficulties and high recurrence rates. When sufficiently distal, embolization with a liquid embolic agent of distal PICA-aneurysms holds significant promise for treating these aneurysms.

In conclusion, the major benefit of the endovascular approach is the avoidance of periprocedural injury of cranial nerves. Its main obstacles are small caliber and tortuous PICA arteries, together with numerous wide-necked morphology. Besides, in general awareness, the durability of total aneurysm occlusion is known as a major weakness of endovascular treatment. In treating PICA-aneurysms, parent vessel occlusion has proven to have a high rate of durability of complete aneurysm occlusion, however with increased risk for ischemic complications, ranging between 17% and 40%.[212, 267, 268, 271, 350] Occlusion of PICA distal to medullary segments is largely well tolerated.[212, 243, 269]

In our opinion, because surgical treatment is usually straightforward and can be undertaken with little morbidity in distal PICA-aneurysms, we believe that microsurgery remains an effective and valuable option in this subset of patients.

15. CLINICAL / NEUROLOGICAL OUTCOME

In the recent literature, overall good neurological outcome of patients with treated PICA-aneurysms seems more likely to be acceptable, with 80%-85% of patients with Glasgow Outcome Scale (GOS) 4 or 5.[135, 167, 214, 216]

It is important to note that at our institution, and many other centers, surgical clipping is commonly not performed on very ill patients with a Hunt and Hess (H&H) grade of IV or higher.[351-353] Patients with poor H&H grades are considered to show most likely a poor neurological outcome.[209, 354] Because of the likelihood of a poor outcome in patients with H&H grades IV and V, some clinicians even do not provide treatment in patients with these poor clinical grades.[351-353] However, aggressive treatment strategy is essential in these patients.[210, 212] For example, as previously demonstrated by Mericle et al,[210] patients with ruptured PICA-aneurysms showing poor initial H&H grade hold a high potential for favorable clinical outcomes. In their study of 31 endovascularly treated PICA-aneurysms, the authors noted that up to 50% of patients with poor clinical condition on admission made an excellent clinical recovery. They postulated that results might be associated with their aggressive management of hydrocephalus as well as the minimally invasive nature of the endovascular strategy. The authors also suggested a treatment protocol that included placement of ventriculostomy for EVD at the time of presentation in patients with ruptured PICA-aneurysm, if the H&H grade was 3 and higher. This approach can sometimes rapidly improve a patient's clinical condition.

Likely, in the series of 76 patients harboring PICA-aneurysms, Chalouhi et al[212] reported good outcome at the time of discharge in 63.2% of patients who presented with a poor clinical grade (Hunt&Hess Grade IV or V). Given the results of the latter studies, it is very important that clinicians should not refrain from offering treatment to those patients with PICA-aneurysms presenting with poor clinical condition.[212] Early endovascular aneurysm treatment and aggressive management of hydrocephalus and vasospasm appear to be key factors in promoting good patient outcomes.[210, 212]

Ultimately, the overall results are closely dependent upon the patient's clinical state at admission.[355] Obstructive hydrocephalus is another known risk factor associated with poor neurological outcome.[167] This is caused by obstructing the foramina of Luschka and the foramen of Mangendie or the aqueduct of Sylvius because of the PICA proximity to the brainstem.[10, 209]

Other associated cerebrovascular anomalies also may inversely contribute to the neurological outcome.[288] Conversely, parameters such as gender, size, aneurysm location and aneurysm morphology had no significant impact on the outcome.[288]

16. AIMS OF THE STUDY

A. **PART A**: To clarify the safety and efficacy of surgical and endovascular treatment strategies for PICA-aneurysms, we conducted a systematic review of the literature analyzing clinical and technical outcomes by type of treatment, aneurysm rupture status, and aneurysm location.

B. **PART B**: As the second part, describing the current trends and results in the surgical and endovascular treatment approaches for PICA-aneurysms, we aimed to report a series of 83 patients with PICA-aneurysms from 3 international referral centers.

17. PART A: SAFETY AND EFFICACY OF TREATMENT STRATEGIES FOR POSTERIOR INFERIOR CEREBELLAR ARTERY ANEURYSMS – – A SYSTEMATIC REVIEW AND META-ANALYSIS

17.1 METHODS

A comprehensive review of the literature was performed using the keywords "posterior inferior cerebellar artery", "PICA", "aneurysm", "posterior inferior cerebral artery", "vertebral", "hemorrhag", "haemorrhag", "malform", "clip", "coil", "microsurg", "embolization", "flow diversion", "endovasc", "catheter", "stent", "occlud", "occlusive", "revascular" and "percutaneous" in both "AND" and "OR" combinations, to search Pubmed, Ovid Medline, Ovid EMBASE, Scopus and Web of Science. Inclusion criteria were the following: English language, >10 patients, studies published from January 2000 to November 2015, with adequate data on postoperative/postprocedural complications, outcome, and aneurysmal occlusion rate. The exclusion criteria were the following: studies including only dissecting PICA-aneurysms (due to variable natural histories and different treatment techniques of these aneurysms), case reports, conference abstracts, in vitro, cadaveric or animal studies, review articles, guidelines and technical notes.

The electronic search was supplemented by contacting experts in the field and reviewing the bibliographies of included studies for relevant publications. Abstracts, methods, results, figures and tables of full text for detailed review were searched by three independent reviewers (neurosurgeons O.P. and A.S., and radiologist W.B.) for data on aneurysmal occlusion technique, occlusion rates, procedure-related morbidity and mortality, and treatment-related complications. The reference lists of retrieved articles were also screened for additional studies. Furthermore, in the case of multiple publications from the same institution and or the same authors, only the most recent and updated study was considered to avoid inclusion of overlapping patients.

For each study, the following descriptive clinical and anatomic information was extracted: patient demographics, location, and size of aneurysms, surgical / endovascular indications, the number of parent vessel occlusions and treatment modality. We studied the following outcomes: pre-treatment morbidity, aneurysm rebleeding, aneurysm recurrence, complete occlusion at last

follow-up, long-term good neurological outcome, long-term neurological morbidity, long-term neurological mortality, perioperative / periprocedural morbidity, perioperative / periprocedural mortality, intraprocedural aneurysm rupture, parent vessel occlusion, perioperative / periprocedural stroke, acute hydrocephalus, permanent shunting, cranial nerves palsies and technical success.

Proximal PICA-aneurysms were defined either as those located on the anterior medullary and lateral medullary segment of the parent artery according to Lister's classification[17] or as those located on the first 1 cm of PICA according to Drake's classification.[80] Pre-treatment morbidity was defined as a Hunt&Hess classification and/or WFNS classification of SAH of 3 or more. Favorable neurological outcome was defined as a modified Rankin Scale score of 2 or less or as a Glasgow Outcome Scale (GOS) score 4 and 5. In cases where these two scales were not available, favorable neurological outcome was determined if the study used terms such as "no morbidity", "no worsening" or "good recovery". Long-term neurological morbidity was defined as either an mRS score greater than two, a GOS score less than four, or worsening of pre-treatment status of the patient post-operatively relative to the preoperative baseline score. Aneurysm occlusion was defined as complete occlusion confirmed by imaging examination (DSA, CTA, or MRA) after surgery/endovascular procedure. Perioperative / periprocedural complications were defined as those occurring within 30 days of the surgical procedure.

We performed three subgroup analyses in this study: 1) a subgroup analysis by aneurysm rupture status on presentation to the surgical or endovascular treatment, 2) a subgroup analysis by type of treatment (surgical versus endovascular treatment), and 3) a subgroup analysis by aneurysm location (proximal versus distal location).

17.2 STATISTICAL ANALYSIS

All included studies were non-comparative. We estimated from each study the cumulative incidence (event rate) and 95% confidence interval (CI) for each outcome. Event rates for each intervention were pooled in meta-analysis across studies using the random-effects model.[356] For all outcomes, we quantified between-study heterogeneity using a homogeneity test based on Cochran's Q statistics and by calculating the I-squared I^2 statistics.[357, 358] Anticipating

heterogeneity between studies, we chose this model a priori because it incorporates within-study variance and between-study variance. We were unable to test for publication bias due to the non-comparative nature of these studies.

17.3 RESULTS

17.3.1 LITERATURE REVIEW

The initial comprehensive literature search yielded 2215 articles. 199 case reports were excluded. On initial abstract and title review, 1980 were excluded as they were deemed not relevant to the current study. 235 studies were reviewed in additional detail. 11 studies were removed as they were conference abstracts. 97 studies were excluded although they dealt with surgical and/or endovascular treatment of PICA-aneurysms, however, did not report any information about study population, treatment technique and/or postoperative/postprocedural outcome of the patients. 98 studies were excluded as they were either dealing with dissecting PICA-aneurysms or had too few patients. A flow diagram describing our literature search process is provided in **Figure 1A**.

In total, 29 studies with 796 target posterior inferior cerebellar artery aneurysms were included. There were 660 ruptured and 136 unruptured PICA-aneurysms. There were 501 PICA-aneurysms of proximal location and 236 PICA-aneurysms belonged to the distal location (origin). 59 target PICA-aneurysms were not classified due to missing published data. 452 target aneurysms (56.8%) were treated surgically and endovascular treatment of PICA-aneurysm was performed in 344 target aneurysms (43.2%). Data are summarized in **Table 1A**.

17.3.2 OVERALL OUTCOMES

When considering all patients, complete occlusion rates were 92.2% (95%CI=86.5%-96.6%). Pre-treatment morbidity was 40.8% (95%CI=29.9%-52.2%). Perioperative mortality was 7.2% (95%CI=4.4%-10.6%). Procedure-related morbidity was 8.7% (95%CI=5.7%-12.3%). Procedure-related mortality was 1.4% (95%CI=0.7%-2.4%). Overall long-term neurological morbidity and mortality rates were 13.3% (95%CI=10.1%-16.9%) and 8.0% (95%CI=5.0%-

11.6%), respectively. Overall long-term favorable neurological outcome was 80.7% (95%CI=76.5%-84.5%). Data are summarized in **Table 2A**.

17.3.3 OUTCOMES BY TYPE OF TREATMENT AND RUPTURE STATUS

17.3.3.1 OUTCOMES OF SURGICAL TREATMENT FOR RUPTURED PICA ANEURYSMS

When considering surgical treatment of ruptured PICA-aneurysms, complete occlusion rates were 97.1% (95%CI=94.5%-99.0%). Aneurysm recurrence rates were 1.4% (95%CI=0.3%-3.3%) and rebleed rates were 1.9% (95%CI=0.6%-3.9%). Pre-treatment morbidity was 42.3% (95%CI=23.1%-64.5%). Perioperative mortality was 9.3% (95%CI=5.2%-14.5%). Procedure-related morbidity was 10.8% (95%CI=4.7%-19.0%). Procedure-related mortality was 1.7% (95%CI=0.4%-3.7%). Long-term neurological morbidity and mortality rates were 14.4% (95%CI=8.7%-21.2%) and 9.8% (95%CI=5.8%-14.8%), respectively. Long-term favorable neurological outcome rates were 80.9% (95%CI=75.0%-86.2%). Data are summarized in **Table 3A**.

17.3.3.2 OUTCOMES OF ENDOVASCULAR TREATMENT FOR RUPTURED PICA ANEURYSMS

When considering endovascular treatment of ruptured PICA-aneurysms, complete occlusion rates were 84.3% (95%CI=73.8%-92.6%). Aneurysm recurrence rates were 6.9% (95%CI=3.6%-10.9%) and rebleed rates were 2.7% (95%CI=1.0%-5.1%). Pre-treatment morbidity was 60.1% (95%CI=44.4%-74.9%). Perioperative mortality was 15.1% (95%CI=9.3%-22.0%). Procedure-related morbidity was 14.1% (95%CI=7.4%-22.4%). Procedure-related mortality was 3.5% (95%CI=1.0%-7.3%). Long-term neurological morbidity and mortality rates were 15.1% (95%CI=10.5%-20.2%) and 17.1% (95%CI=11.5%-23.7%), respectively. Long-term favorable neurological outcome rates were 72.4% (95%CI=66.2%-78.2%). Data are summarized in **Table 3A**.

17.3.3.3 OVERALL OUTCOMES FOR RUPTURED PICA ANEURYSMS

When considering all ruptured PICA-aneurysms, complete occlusion rates were 93.4% (95%CI=88.7%-96.9%). Aneurysm recurrence rates were 3.2% (95%CI=1.7%-5.0%) and rebleed rates were 2.3% (95%CI=1.2%-3.8%). Pre-treatment morbidity was 49.6% (95%CI=36.3%-63.0%). Perioperative mortality was 11.7% (95%CI=8.1%-15.8%). Procedure-related morbidity was 11.5% (95%CI=7.0%-16.8%). Procedure-related mortality was 2.0% (95%CI=0.9%-3.4%). Long-term neurological morbidity and mortality rates were 14.7% (95%CI=11.0%-18.7%) and 12.5% (95%CI=9.0%-16.5%), respectively. Long-term favorable neurological outcome rates were 77.0% (95%CI=72.3%-81.3%). Data are summarized in **Table 4A**.

17.3.3.4 OUTCOMES OF SURGICAL TREATMENT FOR UNRUPTURED PICA ANEURYSMS

When considering surgical treatment of unruptured PICA-aneurysms, complete occlusion rates were 92.9% (95%CI=79.5%-100%). Aneurysm recurrence rates were 15.3% (95%CI=2.3%-34.9%) and rebleed rates were 8.5% (95%CI=0.0%-25.6%). Perioperative mortality was 7.1% (95%CI=0.0%-20.5%). Procedure-related morbidity was 31.0% (95%CI=12.3%-53.3%). Procedure-related mortality was 7.1% (95%CI=0.0%-20.5%). Long-term neurological morbidity and mortality rates were 8.5% (95%CI=0.0%-25.6%) and 7.1% (95%CI=0.0%-20.5%), respectively. Long-term favorable neurological outcome was 91.5% (95%CI=74.4%-100%). Data are summarized in **Table 5A**.

17.3.3.5 OUTCOMES OF ENDOVASCULAR TREATMENT FOR UNRUPTURED PICA ANEURYSMS

When considering endovascular treatment of unruptured PICA-aneurysms, complete occlusion rates were 75.7% (95%CI=45.4%-97.1%). Aneurysm recurrence rates were 12.4% (95%CI=1.4%-29.8%) and rebleed rates were 3.7% (95%CI=0.0%-10.6%). Perioperative mortality was 3.7% (95%CI=0.0%-10.6%). Procedure-related morbidity was 5.6% (95%CI=0.3%-

15.3%). Procedure-related mortality was 3.7% (95%CI=0.0%-10.6%). Long-term neurological morbidity and mortality rates were 5.1% (95%CI=0.2%-14.4%) and 3.7% (95%CI=0.0%-10.6%), respectively. Long-term favorable neurological outcome was 93.3% (95%CI=82.7%-99.5%). Data are summarized in **Table 5A**.

17.3.3.6 OVERALL OUTCOMES FOR UNRUPTURED PICA ANEURYSMS

When considering all unruptured PICA-aneurysms, complete occlusion rates were 86.7% (95%CI=74.6%-95.5%). Aneurysm recurrence rates were 9.0% (95%CI=2.9%-17.6%) and rebleed rates were 3.5% (95%CI=0.3%-9.0%). Perioperative mortality was 7.2% (95%CI=4.4%-10.6%). Procedure-related morbidity was 15.3% (95%CI=7.3%-25.4%). Procedure-related mortality was 3.5% (95%CI=0.3%-9.0%). Long-term neurological morbidity and mortality rates were 5.5% (95%CI=1.3%-11.9%) and 6.4% (95%CI=1.8%-13.1%), respectively. Long-term favorable neurological outcome was 90.2% (95%CI=82.4%-96.0%). Data are summarized in **Table 6A**.

17.3.3.7 OVERALL OUTCOMES BY TYPE OF TREATMENT

Complete occlusion rates were higher in patients undergoing surgical treatment (98.0%, 95%CI=96.3%-99.1%) when compared to those undergoing endovascular treatment (79.7%, 95%CI=70.2%-87.9%) (P<0.0001). Patients undergoing surgical treatment had significantly lower rates of aneurysm recurrence (1.1%, 95%CI=0.3%-2.3%) when compared to those undergoing endovascular treatment (8.1%, 95%CI=5.2%-11.7%) (P<0.0001). There was no statistically significant difference in pre-treatment morbidity between groups (34.8% in the surgical group versus 42.5% in the endovascular group, P=0.468). However, patients undergoing surgical treatment had lower rates of perioperative mortality (3.6%; 95%CI=1.7%-6.2%) when compared to those undergoing the endovascular treatment (10.2%; 95%CI=5.8%-15.5%) (P=0.017). Procedure-related morbidity rates were 8.9% (95%CI=4.9%-14.0%) in the surgical group and 11.7% in the endovascular group (95%CI=6.3%-18.6%) (P=0.467). Patients undergoing surgical treatment had similar rates of procedure-related mortality (1.2%; 95%CI=0.3%-2.5%) when compared to those undergoing the endovascular treatment (2.6%; 95%CI=1.0%-4.9%) (P=0.208).

Neurological morbidity rates were similar between groups (14.7% in the surgical group versus 12.8% in the endovascular group; P=0.591). Patients undergoing surgical treatment had significantly lower rates of neurological mortality rates (4.6%; 95%CI=2.0%-8.1%) when compared to those undergoing endovascular treatment (11.9%; 95%CI=7.2%-17.5%) (P=0.017). The rate of overall favorable neurological outcome in patients undergoing surgical treatment was83.2% (95%CI=79.4%-86.7%) compared to 77% (95%CI=68.5%-84.6%) for patients receiving endovascular treatment. Data are summarized in **Table 2A**.

17.3.4 OUTCOMES BY ANEURYSM LOCATION

17.3.4.1 SURGICAL TREATMENT

When considering surgical treatment of both proximal and distal PICA-aneurysms, there were no statistically significant differences in any of the safety and efficacy outcomes by aneurysm location. Complete aneurysm occlusion rates were similar in both groups (98.0% in the proximal location group versus 95.5% in the distal location group) (P=0.270). There were no statistical differences in terms of aneurysm recurrence rates (2.8% in the proximal location group versus 1.1% in the distal location group, P=0.313). Pre-treatment morbidity was 42.6% in the proximal location group and 51.8% in the distal location group (P=0.463). Perioperative mortality rates were similar in both groups (8.3% in the proximal location group versus 8.9% in the distal location group, P=0.900). There was a trend towards higher rates of procedure-related morbidity in patients harboring proximal PICA-aneurysms (11.2%, 95%CI=5.9%-17.7%) when compared to patients with distal PICA-aneurysms (5.5%, 95%CI=2.0%-10.5%) (P=0.127). Procedure-related mortality rates were similar in both groups (1.2% versus 1.3%; P=0.938). There were no statistically significant differences in terms of neurological morbidity (16.9% versus 11.4%; P=0.353), neurological mortality (7.1% versus 11.6%; 0.255) and favorable neurological outcome (80.9% versus 86.5%; P=0.261) between groups. Data are summarized in **Table 7A**.

17.3.4.2 ENDOVASCULAR TREATMENT

When considering endovascular treatment of both proximal and distal PICA-aneurysms, there were no statistically significant differences in any of the safety and efficacy outcomes by aneurysm location. Proximal PICA-aneurysms had slightly lower rates of complete occlusion (82.6%, 95%CI=70.6%-92.0%) when compared to those in the distal location (92.5%, 95%CI=75.6%-100%) (P=0.230). Aneurysm recurrence rates were 5.7% in the proximal location group and 8.9% in the distal location group (P=0.490). Patients with proximal PICA-aneurysm had slightly lower rates of pre-treatment morbidity (48.7%, 95%CI=26.3%-71.4%) when compared to those with distal PICA-aneurysm (56.8%, 95%CI=29.9%-81.9%) (P=0.645). There was a trend towards higher rates of perioperative mortality in patients harboring proximal PICA-aneurysm (12.7%, 95%CI=6.4%-20.7%) when compared to patients with distal PICA-aneurysm (4.1%, 95%CI=0.0%-11.8%) (P=0.071). Procedure-related morbidity rates were 12.7% in the proximal location group and 7.3% in the distal location group (P=0.391). Procedure-related mortality rates were similar between groups (3.4% in the proximal location group and 2.9% in the distal location group; P=0.875). Neurological morbidity rates were 10.3% in the proximal location group and 17.1% in the distal location group (P=0.367). Patients harboring proximal PICA-aneurysm had higher rates of neurological mortality (13.7%, 95%CI=7.0%-22.0%) when compared to those with distal PICA-aneurysm (4.1%, 95%CI=0.0%-11.8%) (P=0.050). Lastly, there was a trend towards higher rates of long-term favorable neurological outcome favoring the proximal location group (78.8% versus 62.4%; P=0.117). Data are summarized in **Table 8A**.

17.4 STUDY HETEROGENEITY

Significant heterogeneity (I-squared value over 50%) was noted in the analyses of complete aneurysm occlusion, preoperative morbidity, perioperative mortality, procedure-related morbidity, perioperative stroke, acute hydrocephalus and shunting, cranial nerves palsies, parent vessel occlusion and neurological mortality at last follow-up. Therefore, confidence in a pooled summary estimate for these outcomes is limited. I-squared values are summarized in **Table 2A-8A**.

17.5 DISCUSSION

This systematic review and meta-analysis of 796 posterior inferior cerebellar aneurysms receiving either surgical or endovascular treatment demonstrated that in general, both treatment modalities are technically feasible with high rates of technical success of over 95%, and safe with good long-term neurological outcomes of approximately 80%. When considering treatment strategies for ruptured PICA-aneurysms, both treatment approaches have similar long-term neurological morbidity rates of approximately 15%. Not surprisingly, surgical treatment has higher long-term complete aneurysm occlusion rates. Similarly, when considering treatment of unruptured PICA-aneurysms, surgery shows higher long-term complete aneurysm occlusion rates. Notably, surgical treatment is associated with higher rates of procedure-related morbidity in these aneurysms. However, overall favorable neurological outcome rates are similar between both treatment modalities.

In our subgroup analysis by type of treatment, we found that surgical treatment also had higher overall complete occlusion rates and significantly lower rates of aneurysm recurrence. Meanwhile, endovascular treatment was associated with higher rates of overall neurological mortality and intraprocedural aneurysm rupture. Nevertheless, there were no differences in terms of procedure-related morbidity, mortality, or long-term favorable neurological outcomes suggesting that both treatment strategies of PICA-aneurysms are safe and effective. However, complications are not negligible with the procedure-related morbidity of approximately one tenth of treated patients in both groups. Lastly, both treatment strategies were associated with relatively high rates of acute hydrocephalus and cranial nerves palsies.

These findings are important as they confirm that both surgical and endovascular techniques are safe with appropriate favorable neurological outcomes. Our data suggest that surgical treatment is associated with superior angiographic outcomes. Furthermore, endovascular treatment of PICA-aneurysms is associated with higher rates of neurological mortality and intraprocedural aneurysm rupture. It is important to note that these differences could be a reflection of the patient populations as patients who have more morbidity or poorer neurological function on presentation may be more likely to undergo coiling. These findings should be considered when deciding the best therapeutic strategy for treatment of PICA-aneurysms. Yet, therapy of posterior

inferior cerebellar artery aneurysms should be performed on a selective, case-by-case basis in order to maximize patient benefits and limit the risk of periprocedural complications.

Aneurysms involving the posterior inferior cerebellar artery (PICA) usually are dysmorphic with a lesser incidence of saccular anatomy, a greater incidence of fusiform or dolichoectatic pathology, and more frequent distal locations on the parent artery.[13] The anatomical distinctions between the proximal and distal location of PICA-aneurysm are crucial because of the presence of perforating vessels that are more common in the proximal location.[17, 159, 359] Accordingly, in our study, we found substantial differences in procedure-related morbidity favoring the distal location (5.2% versus 10.6%). In particular, in the surgical group patients with distal PICA-aneurysm had lower rates of procedure-related morbidity (5.5%) when compared to those with proximal PICA-aneurysm (11.2%). Similarly, in the endovascular group patients harboring distal PICA-aneurysms showed lower procedure-related morbidity (7.3%) than those having proximal PICA-aneurysms (12.7%). Our findings seem to be lower compared with other prior studies.[8, 24] In the recently published series of 102 PICA-aneurysms, Bohnstedt et al [24] reported the procedure-related complications rates of proximal PICA-aneurysms of 24.1% in the surgical group and 20.3% in the endovascular group. The complication rates for distal PICA-aneurysms were 15.2% in the surgical group and 8.9% in the endovascular group.

Aneurysm recurrence following endovascular coiling is a common problem occurring in roughly up to one fifth of cases depending on the series. The incidence of endovascularly treated PICA-aneurysms has been reported to be between 0% and 18.8%.[8, 24, 360] Our combined analysis of almost 800 PICA-aneurysms found that patients undergoing endovascular treatment had a recurrence rate of 8.1%. In the surgical group, the rate of the aneurysm recurrence was 1.1%.

Comparisons of overall neurological outcomes between surgical and endovascular treatments of PICA-aneurysms in the literature are limited largely due to the small sizes and non-comparative character of most case series. [24, 361, 362] The overall neurological outcome of endovascularly treated PICA-aneurysms is reported to be between 66% and 82%.[8, 21, 268] Some recently published surgical series demonstrated higher rates of good neurological outcomes ranging from 80% to 89%.[2, 14, 24, 363-365] The largest surgical series of 91 distal posterior inferior cerebellar artery aneurysms to date by Lehto et al[7] reported that 91% of patients surviving beyond one year, recovered to their former or an independent state of life. Our findings are similar to those

in these prior reports, with the rates of good neurological outcomes of 77% of patients in the endovascular group and 83.2% of patients in the surgical group.

Regardless of methods, many studies reported high rates of technical success in treating PICA-aneurysms.[7, 8, 33] Chalouhi et al [8] reported 76 PICA-aneurysms treated preferentially using endovascular approaches. The technical success rate was 96.3%. Complete aneurysm occlusion was achieved in 63.4% of patients. In comparison, Lehto et al[7] demonstrated high rates of technical success and especially of complete occlusion in 94% of the saccular and in 88% of the fusiform aneurysms. Likewise, Sejkorova et al[33] reported high rates of technical success and complete aneurysm occlusion rate in 96.8% of patients treated surgically. In our analysis, the high rates of technical success of over 96% in both groups are in line with those in their prior reports.

Ultimately, the decision regarding whether to treat the PICA-aneurysm either with endovascular or surgical therapy should be taken on a case-by-case basis considering anatomical factors such as aneurysm location and its shape, feasibility of coiling and local neurosurgical and endovascular expertise.

17.6 STRENGTHS AND LIMITATIONS OF THE META-ANALYSIS

Our study is the first meta-analysis to date studying outcomes of treatment modalities of ruptured posterior inferior cerebellar aneurysms. Because of the large sample size, we were able to determine outcomes by aneurysm location and make a number of important conclusions. Other strengths of our study include the following: following an a priori established protocol, the comprehensive literature search that involves multiple databases, and the process of study selection that was performed by independent reviewers thus fulfilling the PRISMA guidelines.

We acknowledge that our meta-analysis has several limitations. The methodologic quality of the studies included was variable. Surgical / endovascular indications, primary clinical status and outcome assessment differed across studies. Yet, the finding that all studies produced consistent results and described similar treatment experience and postoperative / postprocedural outcomes reassure us that these methodologic differences do not negate the validity of the meta-analysis. Our study also suffers from publication bias as retrospective case series are prone to high rates of publication bias. In addition, because the majority of studies included in our meta-analysis

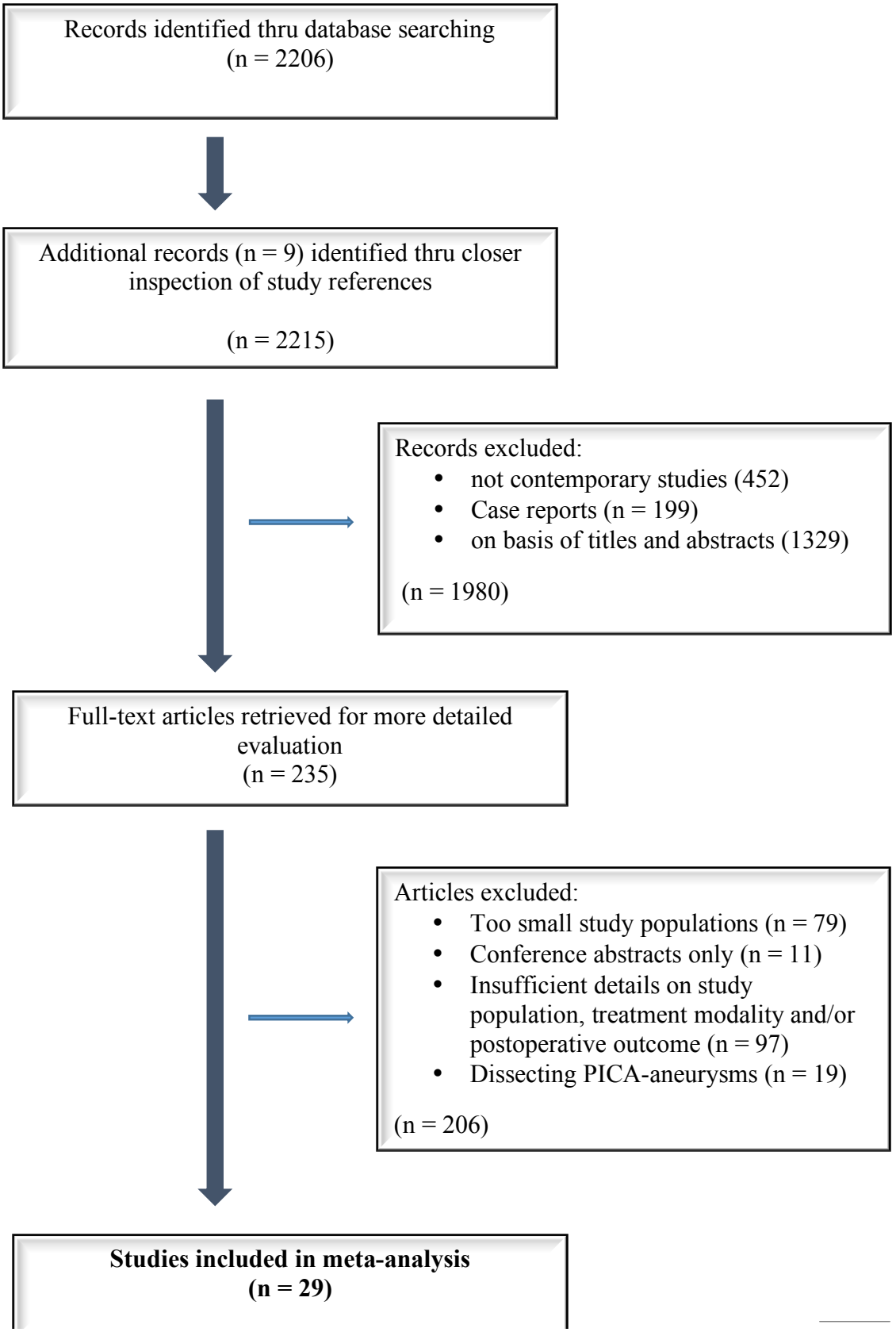
are retrospective, non-comparative case series, the meaningful direct comparison between treatment modalities and patient groups is limited. In addition, despite the exclusion of most dissecting PICA-aneurysms, our meta-analysis included not only saccular but also some dissecting and fusiform aneurysms. These aneurysms all have variable natural histories and sometimes require different treatment strategies. We excluded all papers that exclusively reported outcomes of dissecting aneurysms, however, there is likely a certain degree of heterogeneity in the types of aneurysms included in our analysis. Given the methodological limitations of the included studies, the quality of evidence of this meta-analysis is limited.

17.7 CONCLUSIONS OF THE META-ANALYSIS

The combined meta-analysis of almost 800 PICA-aneurysms treated with both surgical and endovascular techniques demonstrated that in general, that both the endovascular and the surgical treatment modalities are technically feasible with high rates of technical success of over 95% and safe with similar neurological morbidity and mortality rates. Our data suggest that surgical treatment of both ruptured and unruptured PICA-aneurysms is associated with superior angiographic outcomes. Yet, surgery of unruptured PICA-aneurysms can be associated with higher temporary procedure-related morbidity. These findings should be considered when deciding the best therapeutic strategy for treatment of PICA-aneurysms. However, the final decision-making should be performed on a selective, case-by-case basis in order to maximize patient benefits and limit the risk of periprocedural complications.

17.8 SUPPLEMENTAL MATERIAL

17.8.1 ***FIGURE 1A****. A flow diagram describing our comprehensive literature search*



17.8.2 ***TABLE 1A****. Study Characteristics*

Author, Journal, Year	**No. of Pts.**	**No. of PICA**	**Dissecting/Fusiform PICA-Aneurysms Excluded** (n)	**No. of analy-zed PICA**	**No. of Rup-tured PICA**	**No. of Unrup-tured PICA**	**No of Proxi-mal PICA**	**No. of Distal PICA**	**CN Palsies**	**Female / Male**	**Mean Age** (years)	**Mean / Median Aneurysm Size** (mm)	**Surgery** (n)	**Endovascular Treatment** (n)	**Follow-up** (months)	**Study Ty** (R=Retrosp P=Prospec
Lewis SB, Journal of Neurosurgery, 2002[2]	20	22	yes (9)	11	10	1	3	8	N/A	8 / 3	51 (31-73)	10.6 (3-25)	10	1	4.1 (1.5-11.1)	R
Horiuchi T, Neurosurgery, 2003[363]	24	27	yes (5)	19	18	1	7	12	N/A	15 / 4	62 (+/-12) 20-81	4.1 (+/-1.8) 1-10	19	0	N/A	R
Mukonoweshuro W, Neuroradiology, 2003[20]	23	24	yes (0)	23	23	0	19	4	2	19 / 4	53 (34-73)	6 (2-14)	0	23	11 (3-27)	R
Bradac GB, Neuroradiology, 2004[300]	18	18	yes (5)	13	12	1	11	2	N/A	9 / 4	57.4 (40-82)	N/A	0	13	18 (12-108)	R
D'Ambrosio AL, Neurosurgery, 2004[209]	20	20	no (3)	17	14	3	17	0	2	18 / 2	49 (+/-14)	10 (3-16)	17	0	12 (6-19)	R
Kleinpeter G, Minimally Invasive Neurosurgery, 2004[366]	14	15	yes (4)	10	8	2	7	3	N/A	7 / 3	50.6 (32-65)	9.1 (5-20)	10	0	N/A	R
Al-khayat H, Neurosurgery, 2005[236]	52	52	no (N/A)	52	32	20	52	0	3	41 / 11	56 (15-85)	N/A	52	0	N/A	R
Orakcioglu B, Acta Neurochirurgica, 2005[364]	16	16	yes (4)	12	11	1	7	5	N/A	8 /4	57.1 (37-68)	7.7 (2-20)	11	1	N/A	R
Sandalcioglu IE, Zentralblatt für Neurochirurgie, 2005[361]	20	20	yes (13)	15	13	2	10	5	1	11 / 4	52.3 (9-72)	8.1 (2-40)	3	12	9 (1-52)	R
Mericle RA, Neurosurgery, 2006[210]	31	31	no (N/A)	31	26	5	31	0	N/A	21 / 10	55 (25-77)	N/A	0	31	10 (0.5-48)	R
Peluso JP, American Journal of Neuroradiology, 2008[367]	46	47	no (N/A)	47	37	10	47	0	4	38 / 8	54.7 (24-83)	6.8 (2-32)	0	47	21.5 (6-84)	R
Sanai N, Neurosurgery, 2008[150]	44	47	no (N/A)	44	44	{3}	N/A	N/A	N/A	N/A	N/A	N/A	44	0	N/A	R

Jeon SG, Journal of Korean Neurosurgical Society, 2009[368]	14	14	yes (0)	14	12	2	13	1	N/A	12 / 2	53.5 (27-80)	4.4 (2.6-7.9)	0	14	34.7 (1-97)	R
Matsushima T, Skull Base, 2010[28]	13	13	no (N/A)	11	6	5	N/A	N/A	(3)	N/A	N/A	N/A	11	0	N/A	R
Nourbakhsh A, Journal of Clinical Neuroscience, 2010[369]	15	15	no (N/A)	14	13	1	10	N/A	7	13 / 1	53 (30-76)	8.5 (2-25)	11	3	38	R
Hong YH, Journal of Korean Neurosurgical Society, 2011[362]	20	20	yes (0)	20	20	0	18	2	2	18 / 2	55.9 (42-86)	N/A	11	9	14.8 (0.25-36)	R
Rodríguez-Hernández A, Journal of Neurosurgery, 2011[370]	50	51	no (N/A)	51	32	19	35	16	1	30 / 20	54.1 (24-85)	N/A	51	0	11 (+/- 9.9) 1.5-48	R
Tokimura H, Neurosurgical Review, 2011[365]	28	28 (30)	yes (6)	22	20	2	7	15	N/A	17 / 5	53.0 (27-77)	5.1 (2.5 - 12)	17	5	N/A	R
Crowley RW, Neurosurgery, 2012[268]	20	20	no (N/A)	20	13	7	15	5	N/A	17 / 3	60.5 (15-82)	N/A	0	20	22.4 (3-62)	R
Singh RK, Asian Journal of Neurosurgery, 2012[371]	20	20	yes (0)	20	20	0	12	8	3	17 / 3	41.6 (17-75)	N/A	20	0	N/A	R
Wu J, Clinical Neurology and Neurosurgery, 2012[372]	29	29	yes (3)	26	26	0	10	16	4	15/ 11	44.8 (15-70)	6.9 (2-22)	26	0	N/A	R
Bacigaluppi S, Neurological Sciences, 2013[373]	18	18	yes (2)	17	15	2	14	3	N/A	14 / 3	58.0 (36-82)	N/A	1	16	N/A	R
Chalouhi N, Journal of Neurosurgery, 2013[8]	76	76	no (9)	76	61	15	54	22	N/A	58 / 18	55.6 (28-83)	6.1 (2-25)	0	76	21 (1-96)	R
Gupta V, Neurology India, 2014[22]	13	13	yes (0)	13	13	0	13	0	N/A	8 / 5	46.9 (14-60)	N/A	0	13	6 to 36	R
Lehto H, World Neurosurgery, 2014[7]	80	91	no (28)	68	68	{23}	0	68	5	48 / 32	52	N/A	67 (+ 1)	0	105.6 (0-504)	R
Viswanathan GC, Turkish Neurosurgery, 2014[14]	27	27	no (2)	27	27	0	18	9	2	20 / 7	44.6 (25-68)	N/A	27	0	N/A	R

Bohnstedt BN, World Neurosurgery, 2015[24]	100	102	no (15)	64	54	10	41	23	11	47 / 17	N/A	N/A	38	26	12	R
Heye S, Journal of Neurointerventional Surgery, 2015[374]	29	29	no (N/A)	29	2	27	29	0	0	29 / 0	54 (31-85)	6.3 (3.4 - 12.3)	0	29	24.2 (5 - 53)	R
Sejkorova A, Neurosurgical Review, 2015[33]	15	15	yes (5)	10	10	0	1	9	1	4/ 6	56.4 (29-82)	N/A	5	5	N/A	R
	895	920	56 dissecting aneurysms excluded	796	660	136	501	236				aneurysms treated:	452	344		
endovascular series			47 dissecting aneurysms not excluded													
surgical series																
combined series																

Legend for Table 1A.

Case series including only surgically treated PICA-aneurysms are highlighted in green.
Case series including only endovascularly treated PICA-aneurysms are highlighted in blue.
Case series including both surgically and endovascularly treated PICA-aneurysms are highlighted in white.

17.8.3 ***TABLE 2A***. *Overall Outcomes and Outcomes by Type of Treatment*

All PICA-Aneurysms	***All Patients***			***Surgery***			***Endovascular Treatment***			
	Overall % (95%CI)	*Raw Proportion*	I^2	*Overall % (95%CI)*	*Raw Proportion*	I^2	*Overall % (95%CI)*	*Raw Proportion*	I^2	*P*
Pre-treatment Morbidity (SAH H&H III-V)	40.8% (29.9%; 52.2%)	282 / 650	88.0%	34.8% (21.8%; 49.0%)	130 / 342	83.8%	42.5% (27.2%; 58.5%)	139 / 297	84.2%	0.468
Procedure-related Morbidity	8.7% (5.7%; 12.3%)	59 / 709	56.1%	8.9% (4.9%; 14.0%)	33 / 381	51.7%	11.7% (6.3%; 18.6%)	31 / 317	57.6%	0.467
Perioperative Mortality	7.2% (4.4%; 10.6%)	49 / 670	56.6%	3.6% (1.7%; 6.2%)	11/ 339	13.6%	10.2% (5.8%; 15.5%)	32 / 317	41.6%	0.017
Procedure-related Mortality	1.4% (0.7%; 2.4%)	8 / 773	0.0%	1.2% (0.3%; 2.5%)	3 / 419	0.0%	2.6% (1.0%; 4.9%)	8 / 343	14.2%	0.208
Rupture During Treatment	3.1% (1.5%; 5.2%)	21 / 604	37.1%	1.3% (0.3%; 3.1%)	2 / 276	0.0%	5.5% (2.6%; 9.3%)	19 / 317	31.9%	0.027
Neurological Morbidity at Last Follow-up	13.3% (10.1%; 16.9%)	105 / 769	47.1%	14.7% (10.0%; 20.0%)	66 / 444	48.8%	12.8% (8.5%; 17.8%)	39 / 314	28.2%	0.591
Neurological Mortality at Last Follow-up	8.0% (5.0%; 11.6%)	66 / 742	61.6%	4.6% (2.0%; 8.1%)	24 / 430	46.9%	11.9% (7.2%; 17.5%)	36 / 298	39.0%	0.017
Complete Aneurysm Occlusion at Last Follow-up	92.2% (86.5%; 96.6%)	633 / 724	83.7%	98.0% (96.3%; 99.1%)	390 / 396	0.0%	79.7% (70.2%; 87.9%)	232 / 317	68.7%	<0.0001
Aneurysm Recurrence	3.5% (1.9%; 5.5%)	28 / 759	44.0%	1.1% (0.3%; 2.3%)	2 / 434	0.0%	8.1% (5.2%; 11.7%)	25 / 314	9.5%	<0.0001
Aneurysm Rebleed	1.7% (0.9%; 2.7%)	9 / 799	0.0%	1.3% (0.4%; 2.6%)	3 / 445	0.0%	2.2% (0.9%; 4.0%)	5 / 343	0.0%	0.369
Perioperative Stroke	7.5% (4.9%; 10.8%)	52 / 742	54.0%	5.5% (2.6%; 9.3%)	19 / 388	44.3%	10.4% (6.2%; 15.4%)	31 / 343	40.8%	0.097
Acute Hydrocephalus	38.3% (23.8%; 53.9%)	128 / 314	86.0%	44.0% (28.8%; 59.8%)	63 / 199	71.7%	27.7% (8.5%; 52.0%)	58 / 154	83.0%	0.234
Shunt needed	20.4% (10.1%; 33.0%)	101 / 379	85.9%	26.4% (10.9%; 45.2%)	63 / 199	84.0%	14.6% (3.9%; 29.9%)	34 / 161	70.6%	0.286
CN Palsies at Last Follow-up	7.4% (3.7%; 12.2%)	37 / 471	65.4%	9.6% (4.6%; 16.1%)	30 / 328	64.0%	3.7% (0.3%; 9.8%	5 / 134	35.9%	0.117
Parent Vessel Occlusion	8.3% (5.1%; 12.2%)	76 / 727	64.3%	5.8% (2.7%; 9.8%)	28 / 373	46.4%	12.9% (6.6%; 20.7%)	49 / 343	68.2%	0.077
Technical Success	97.9% (96.8%; 98.8%)	773 / 788	0.0%	98.6% (97.3%; 99.5%)	431 / 434	0.0%	96.6% (94.0%; 98.5%)	331 / 343	0.0%	0.104
Favorable Neurological Outcome at Last Follow-up	80.7% (76.5%; 84.5%)	562 / 690	42.9%	83.2% (79.4%; 86.7%)	332 / 396	0.0%	77.0% (68.5%; 84.6%)	222 / 283	54.1%	0.170

17.8.4 ***TABLE 3A****. Ruptured PICA-Aneurysms - Outcomes of Surgical and Endovascular Treatment*

Ruptured PICA-Aneurysms	***Surgical Treatment***			***Endovascular Treatment***		
	Overall % (95%CI)	*Raw Proportion*	I^2	*Overall % (95%CI)*	*Raw Proportion*	I^2
Preoperative Morbidity (SAH H&H III-V)	43.2% (23.1%; 64.5%)	106 / 241	90.0%	60.1% (44.4%; 74.9%)	137 / 224	80.3%
Procedure-related Morbidity	10.8% (4.7%; 19.0%)	34 / 254	66.9%	14.1% (7.4%; 22.4%)	29 / 247	61.9%
Perioperative Mortality	9.3% (5.2%; 14.5%)	16 / 181	14.2%	15.1% (9.3%; 22.0%)	32 / 224	37.5%
Procedure-related Mortality	1.7% (0.4%; 3.7%)	3 / 254	0.0%	3.5% (1.0%; 7.3%)	8 / 247	37.8%
Rupture During Treatment	2.1% (0.3%; 4.9%)	2 / 163	0.0%	5.5% (1.7%; 11.1%)	15 / 224	51.3%
Neurological Morbidity at Last Follow-up	14.4% (8.7%; 21.2%)	39 / 279	51.4%	15.1% (10.5%; 20.2%)	34 / 233	9.4%
Neurological Mortality at Last Follow-up	9.8% (5.8%; 14.8%)	29 / 272	27.1%	17.1% (11.5%; 23.7%)	36 / 224	27.6%
Complete Aneurysm Occlusion at Last Follow-up	97.1% (94.5%; 99.0%	217 / 222	0.0%	84.3% (73.8%; 92.6%)	134 / 163	61.7%
Aneurysm Recurrence	1.4% (0.3%; 3.3%)	2 / 269	0.0%	6.9% (3.6%; 10.9%)	10 / 186	0.0%
Aneurysm Rebleed	1.9% (0.6%; 3.9%)	3 / 280	0.0%	2.7% (1.0%; 5.1%)	5 / 247	0.0%
Perioperative Stroke	7.4% (3.5%; 12.5%)	16 / 227	35.1%	10.9% (5.5%; 17.8%)	24 / 247	53.5%
Acute Hydrocephalus	50.5% (33.4%; 67.6%)	71 / 150	77.1%	52.8% (32.8%; 72.3%)	56 / 94	62.6%
Shunt needed	25.0% (10.2%; 43.4%)	62 / 187	83.4%	20.7% (5.6%; 41.1%)	32 / 104	72.5%
CN Palsies at Last Follow-up	13.6% (7.0%; 21.8%)	27 / 216	55.5%	6.0% (0.0%; 16.0%)	5 / 87	60.8%
Parent Vessel Occlusion	5.1% (2.5%; 8.6%)	12 / 229	6.5%	11.7% (3.8%; 22.8%)	27 / 186	73.5%
Technical Success	97.3% (95.0%; 99.0%)	263 / 269	0.0%	96.9% (94.4%; 98.8%)	240 / 247	0.0%
Favorable Neurological Outcome at Last Follow-up	80.9% (75.0%; 86.2%)	196 / 238	17.0%	72.4% (66.2%; 78.2%)	153 / 210	0.7%

17.8.5 ***TABLE 4A****. Outcomes by Aneurysm Rupture Status*

Ruptured PICA-Aneurysms	***Surgical Treatment***			***Endovascular Treatment***		
	Overall % (95%CI)	*Raw Proportion*	I^2	*Overall % (95%CI)*	*Raw Proportion*	I^2
Preoperative Morbidity (SAH H&H III-V)	43.2% (23.1%; 64.5%)	106 / 241	90.0%	60.1% (44.4%; 74.9%)	137 / 224	80.3%
Procedure-related Morbidity	10.8% (4.7%; 19.0%)	34 / 254	66.9%	14.1% (7.4%; 22.4%)	29 / 247	61.9%
Perioperative Mortality	9.3% (5.2%; 14.5%)	16 / 181	14.2%	15.1% (9.3%; 22.0%)	32 / 224	37.5%
Procedure-related Mortality	1.7% (0.4%; 3.7%)	3 / 254	0.0%	3.5% (1.0%; 7.3%)	8 / 247	37.8%
Rupture During Treatment	2.1% (0.3%; 4.9%)	2 / 163	0.0%	5.5% (1.7%; 11.1%)	15 / 224	51.3%
Neurological Morbidity at Last Follow-up	14.4% (8.7%; 21.2%)	39 / 279	51.4%	15.1% (10.5%; 20.2%)	34 / 233	9.4%
Neurological Mortality at Last Follow-up	9.8% (5.8%; 14.8%)	29 / 272	27.1%	17.1% (11.5%; 23.7%)	36 / 224	27.6%
Complete Aneurysm Occlusion at Last Follow-up	97.1% (94.5%; 99.0%	217 / 222	0.0%	84.3% (73.8%; 92.6%)	134 / 163	61.7%
Aneurysm Recurrence	1.4% (0.3%; 3.3%)	2 / 269	0.0%	6.9% (3.6%; 10.9%)	10 / 186	0.0%
Aneurysm Rebleed	1.9% (0.6%; 3.9%)	3 / 280	0.0%	2.7% (1.0%; 5.1%)	5 / 247	0.0%
Perioperative Stroke	7.4% (3.5%; 12.5%)	16 / 227	35.1%	10.9% (5.5%; 17.8%)	24 / 247	53.5%
Acute Hydrocephalus	50.5% (33.4%; 67.6%)	71 / 150	77.1%	52.8% (32.8%; 72.3%)	56 / 94	62.6%
Shunt needed	25.0% (10.2%; 43.4%)	62 / 187	83.4%	20.7% (5.6%; 41.1%)	32 / 104	72.5%
CN Palsies at Last Follow-up	13.6% (7.0%; 21.8%)	27 / 216	55.5%	6.0% (0.0%; 16.0%)	5 / 87	60.8%
Parent Vessel Occlusion	5.1% (2.5%; 8.6%)	12 / 229	6.5%	11.7% (3.8%; 22.8%)	27 / 186	73.5%
Technical Success	97.3% (95.0%; 99.0%)	263 / 269	0.0%	96.9% (94.4%; 98.8%)	240 / 247	0.0%
Favorable Neurological Outcome at Last Follow-up	80.9% (75.0%; 86.2%)	196 / 238	17.0%	72.4% (66.2%; 78.2%)	153 / 210	0.7%

17.8.6 ***TABLE 5A****. Unruptured PICA-Aneurysms - Outcomes of Surgical and Endovascular Treatment*

Unruptured PICA-Aneurysms	***Surgical Treatment***			***Endovascular Treatment***		
	Overall % (95%CI)	*Raw Proportion*	I^2	*Overall % (95%CI)*	*Raw Proportion*	I^2
Preoperative Morbidity (SAH H&H III-V)	7.1% (0.0%; 20.5%)	0 / 17	0.0%	5.7% (0.3%; 15.3%)	1 / 38	0.0%
Procedure-related Morbidity	31.0% (12.3%; 53.3%)	5 / 17	0.0%	5.6% (0.3%; 15.3%)	2 / 38	0.0%
Perioperative Mortality	7.1% (0.0%; 20.5%)	0 / 17	0.0%	3.7% (0.0%; 10.6%)	0 / 38	0.0%
Procedure-related Mortality	7.1% (0.0%; 20.5%)	0 / 17	0.0%	3.7% (0.0%; 10.6%)	0 / 38	0.0%
Rupture During Treatment	9.9% (0.0%; 29.8%)	0 / 10	0.0%	5.6% (0.2%; 15.7%)	1 / 35	0.0%
Neurological Morbidity at Last Follow-up	8.5% (0.0%; 25.6%)	1 / 17	0.0%	5.1% (0.2%; 14.4%)	1 / 38	0.0%
Neurological Mortality at Last Follow-up	7.1% (0.0%; 20.5%)	0 / 17	0.0%	3.7% (0.0%; 10.6%)	0 / 38	0.0%
Complete Aneurysm Occlusion at Last Follow-up	92.9% (79.5%; 100%)	17 / 17	0.0%	75.7% (45.4%; 97.1%)	14 / 20	38.1%
Aneurysm Recurrence	15.3% (2.3%; 34.9%)	2 / 17	0.0%	12.4% (1.4%; 29.8%)	2 / 20	0.0%
Aneurysm Rebleed	7.1% (0.0%; 20.5%)	0 / 17	0.0%	3.7% (0.0%; 10.6%)	0 / 38	0.0%
Perioperative Stroke	8.5% (0.0%; 25.6%)	1 / 17	0.0%	4.4% (0.0%; 13.4%)	1 / 38	0.0%
Acute Hydrocephalus	7.1% (0.0%; 20.5%)	0 / 17	0.0%	2.3% (0.0%; 11.7%)	0 / 18	0.0%
Shunt needed	8.5% (0.0%; 25.6%)	1 / 17	0.0%	2.8% (0.0%; 12.5%)	0 / 19	0.0%
CN Palsies at Last Follow-up	10.4% (0.0%; 30.4%)	1 / 15	0.0%	9.5% (0.0%; 31.4%)	1 / 15	24.4%
Parent Vessel Occlusion	9.9% (0.0%; 29.8%)	0 / 10	0.0%	16.6% (3.6%; 35.3%)	3 / 20	0.0%
Technical Success	92.9% (79.5%; 100%)	17 / 17	0.0%	94.3% (84.7%; 99.7%)	37 / 38	0.0%
Favorable Neurological Outcome at Last Follow-up	91.5% (74.4%; 100%)	16 / 17	0.0%	93.3% (82.7%; 99.5%)	33 / 35	0.0%

17.8.7 ***TABLE 6A****. Outcomes by Aneurysm Location*

	Proximal PICA-aneurysms			***Distal PICA-aneurysms***			
	Overall % (95%CI)	*Raw Proportion*	I^2	*Overall % (95%CI)*	*Raw Proportion*	I^2	*P*
Pre-treatment Morbidity (SAH H&H III-V)	43.5% (30.0%; 57.6%)	132 / 311	82.7%	54.7% (38.7%; 70.3%)	79 / 140	58.7%	0.296
Procedure-related Morbidity	10.6% (6.2%; 16.0%)	36 / 362	51.0%	5.2% (2.2%; 9.4%)	7 / 149	0.0%	0.084
Perioperative Mortality	10.0% (5.7%; 15.3%)	39 / 374	53.0%	6.6% (2.5%; 12.3%)	5 / 98	0.0%	0.329
Procedure-related Mortality	1.9% (0.8%; 3.4%)	5 / 403	0.0%	1.2% (0.0%; 3.5%)	0 / 172	0.0%	0.544
Rupture During Treatment	3.9% (1.7%; 6.8%)	16 / 365	29.7%	2.3% (0.1%; 6.7%)	0 / 85	0.0%	0.468
Neurological Morbidity at Last Follow-up	13.4% (8.9%; 18.6%)	51 / 392	46.3%	13.4% (7.9%; 20.1%)	23 / 187	19.9%	0.991
Neurological Mortality at Last Follow-up	9.9% (5.6%; 15.3%)	40 / 374	54.9%	10.5% (6.6%; 15.2%)	19 / 189	0.0%	0.870
Complete Aneurysm Occlusion at Last Follow-up	91.3% (84.2%; 96.6%)	279 / 318	71.2%	95.0% (90.7%; 98.1%)	127 / 132	0.0%	0.313
Aneurysm Recurrence	4.1% (2.4%; 6.2%)	14 / 413	0.0%	2.4% (0.6%; 5.2%)	3 / 177	0.0%	0.253
Aneurysm Rebleed	2.3% (1.1%; 4.0%)	7 / 413	0.0%	2.0% (0.4%; 4.6%)	1 / 188	0.0%	0.806
Perioperative Stroke	9.9% (5.5%; 15.4%)	33 / 383	56.5%	7.2% (3.7%; 13.9%)	10 / 161	0.0%	0.397
Acute Hydrocephalus	34.3% (12.9%; 59.3%)	51 / 141	87.2%	57.1% (40.4%; 73.1%)	26 / 48	16.3%	0.115
Shunt needed	11.7% (5.0%; 20.4%)	16 / 137	43.7%	35.1% (10.2%; 64.6%)	51 / 117	82.9%	0.105
CN Palsies at Last Follow-up	9.3% (2.8%; 18.6%)	24 / 249	75.8%	8.1% (3.7%; 13.9%)	8 / 122	0.0%	0.808
Parent Vessel Occlusion	5.6% (2.4%; 9.9%)	24 / 361	52.7%	18.8% (10.1%; 29.4%)	32 / 188	52.7%	0.012
Technical Success	98.0% (96.5%; 99.2%)	408 / 413	0.0%	96.0% (92.7%; 98.5%)	172 / 177	0.0%	0.220
Favorable Neurological Outcome at Last Follow-up	79.5% (73.2%; 85.1%)	283 / 351	43.4%	79.9% (69.8%; 88.4%)	121 / 146	35.4%	0.941

17.8.8 ***TABLE 7A***. *Outcomes of Surgical Treatment by Aneurysm Location*

	Proximal PICA-aneurysms			***Distal PICA-aneurysms***			
	Overall % (95%CI)	*Raw Proportion*	I^2	*Overall % (95%CI)*	*Raw Proportion*	I^2	*P*
Pre-treatment Morbidity (SAH H&H III-V)	43.5% (30.0%; 57.6%)	132 / 311	82.7%	54.7% (38.7%; 70.3%)	79 / 140	58.7%	0.296
Procedure-related Morbidity	10.6% (6.2%; 16.0%)	36 / 362	51.0%	5.2% (2.2%; 9.4%)	7 / 149	0.0%	0.084
Perioperative Mortality	10.0% (5.7%; 15.3%)	39 / 374	53.0%	6.6% (2.5%; 12.3%)	5 / 98	0.0%	0.329
Procedure-related Mortality	1.9% (0.8%; 3.4%)	5 / 403	0.0%	1.2% (0.0%; 3.5%)	0 / 172	0.0%	0.544
Rupture During Treatment	3.9% (1.7%; 6.8%)	16 / 365	29.7%	2.3% (0.1%; 6.7%)	0 / 85	0.0%	0.468
Neurological Morbidity at Last Follow-up	13.4% (8.9%; 18.6%)	51 / 392	46.3%	13.4% (7.9%; 20.1%)	23 / 187	19.9%	0.991
Neurological Mortality at Last Follow-up	9.9% (5.6%; 15.3%)	40 / 374	54.9%	10.5% (6.6%; 15.2%)	19 / 189	0.0%	0.870
Complete Aneurysm Occlusion at Last Follow-up	91.3% (84.2%; 96.6%)	279 / 318	71.2%	95.0% (90.7%; 98.1%)	127 / 132	0.0%	0.313
Aneurysm Recurrence	4.1% (2.4%; 6.2%)	14 / 413	0.0%	2.4% (0.6%; 5.2%)	3 / 177	0.0%	0.253
Aneurysm Rebleed	2.3% (1.1%; 4.0%)	7 / 413	0.0%	2.0% (0.4%; 4.6%)	1 / 188	0.0%	0.806
Perioperative Stroke	9.9% (5.5%; 15.4%)	33 / 383	56.5%	7.2% (3.7%; 13.9%)	10 / 161	0.0%	0.397
Acute Hydrocephalus	34.3% (12.9%; 59.3%)	51 / 141	87.2%	57.1% (40.4%; 73.1%)	26 / 48	16.3%	0.115
Shunt needed	11.7% (5.0%; 20.4%)	16 / 137	43.7%	35.1% (10.2%; 64.6%)	51 / 117	82.9%	0.105
CN Palsies at Last Follow-up	9.3% (2.8%; 18.6%)	24 / 249	75.8%	8.1% (3.7%; 13.9%)	8 / 122	0.0%	0.808
Parent Vessel Occlusion	5.6% (2.4%; 9.9%)	24 / 361	52.7%	18.8% (10.1%; 29.4%)	32 / 188	52.7%	0.012
Technical Success	98.0% (96.5%; 99.2%)	408 / 413	0.0%	96.0% (92.7%; 98.5%)	172 / 177	0.0%	0.220
Favorable Neurological Outcome at Last Follow-up	79.5% (73.2%; 85.1%)	283 / 351	43.4%	79.9% (69.8%; 88.4%)	121 / 146	35.4%	0.941

17.8.9 ***TABLE 8A***. *Outcomes of Endovascular Treatment by Aneurysm Location*

Endovascular Treatment of PICA-Aneurysms	***Proximal***			***Distal***			*P*
	Overall % (95%CI)	*Raw Proportion*	I^2	*Overall % (95%CI)*	*Raw Proportion*	I^2	
Pre-treatment Morbidity (SAH H&H III-V)	48.7% (26.3%; 71.4%)	81 / 177	88.2%	56.8% (29.9%; 81.9%)	7 / 12	0.0%	0.645
Procedure-related Morbidity	12.7% (6.2%; 20.9%)	26 / 249	63.0%	7.3% (0.0%; 19.5%)	2 / 42	29.4%	0.391
Perioperative Mortality	12.7% (6.4%; 20.7%)	30 / 231	57.4%	4.1% (0.0%; 11.8%)	1 / 34	0.0%	0.071
Procedure-related Mortality	3.4% (1.0%; 7.1%)	8 / 249	34.6%	2.9% (0.0%; 8.9%)	0 / 42	0.0%	0.851
Rupture During Treatment	6.0% (2.5%; 10.6%)	17 / 249	38.2%	2.9% (0.0%; 9.7%)	0 / 34	0.0%	0.350
Neurological Morbidity at Last Follow-up	10.3% (6.1%; 15.2%)	22 / 228	20.0%	17.1% (5.1%; 33.6%)	8 / 42	21.3%	0.367
Neurological Mortality at Last Follow-up	13.7% (7.0%; 22.0%)	32 / 231	58.4%	4.1% (0.0%; 11.8%)	1 / 34	0.0%	0.050
Complete Aneurysm Occlusion at Last Follow-up	82.6% (70.6%; 92.0%)	139 / 177	68.5%	92.5% (75.6%; 100%)	12 / 12	0.0%	0.230
Aneurysm Recurrence	5.7% (3.1%; 8.9%)	12 / 249	0.0%	8.9% (2.0%; 19.3%)	3 / 42	0.0%	0.490
Aneurysm Rebleed	2.5% (0.9%; 4.9%)	5 / 249	0.0%	2.9% (0.0%; 8.9%)	0 / 42	0.0%	0.875
Perioperative Stroke	9.9% (4.8%; 16.3%)	21 / 249	51.0%	13.5% (4.8%; 25.3%)	5 / 42	0.0%	0.539
Acute Hydrocephalus	26.0% (0.0%; 66.3%)	13 / 60	88.3%	33.3% (6.4%; 66.7%)	3 / 9	0.0%	0.749
Shunt needed	7.9% (0.0%; 21.5%)	5 / 65	63.3%	13.0% (0.0%; 56.1%)	1 / 11	57.1%	0.740
CN Palsies at Last Follow-up	4.8% (0.0%; 12.8%)	5 / 120	63.4%	5.1% (0.0%; 22.3%)	0 / 10	0.0%	0.957
Parent Vessel Occlusion	8.6% (3.0%; 16.5%)	23 / 231	65.1%	41.3% (17.6%; 67.2%)	12 / 34	36.2%	0.013
Technical Success	97.6% (95.3%; 99.2%)	244 / 249	0.0%	91.1% (80.7%; 98.0%)	39 / 42	0.0%	0.150
Favorable Neurological Outcome at Last Follow-up	78.8% (67.9%; 88.0%)	167 / 210	65.5%	62.4% (43.7%; 79.5%)	16 / 26	0.0%	0.117

18. PART B: CURRENT TRENDS AND RESULTS OF SURGICAL AND ENDOVASCULAR TREATMENT MODALITIES – WHAT FACTORS HAS A KEY ROLE IN NEUROLOGICAL OUTCOME?

18.1 METHODS

Following institutional review board approvals, all patients with PICA-aneurysms included in a prospective database of intracranial aneurysms (at Mayo Clinic, Rochester, MN, U.S., at Medical University Innsbruck, Austria as well as at Masaryk Hospital, Ústí nad Labem, Czech Republic) from 2000 to 2015 were included in this study. Information collected in this database included patient demographics and baseline clinical characteristics, aneurysm characteristics, treatment characteristics, and treatment outcomes. Patient demographic data collected included age, sex, baseline symptoms, and baseline neurologic status. Aneurysm characteristics included location and size. Treatment characteristics included type of microsurgery and its surgical approach, in case of endovascular treatment type of device/coils used, number of flow diverters used, and use of stent or balloon assistance.

Of note, our periprocedural pharmacologic protocol for patients undergoing flow-diverter therapy was uniform throughout the study period. Starting clopidogrel (Plavix), 75 mg, and aspirin, 325 mg, daily for 5 days before the procedure was recommended. Postoperatively, patients were maintained on the same clopidogrel and aspirin dosage for 3 months. After 3 months, clopidogrel was discontinued for patients undergoing on-label treatment. For cases that were not on-label, and especially in high-risk locations, we have continued antiplatelet therapy for a longer time due to a potentially higher risk of thromboembolic events. Usually, patients with aneurysms distal to the origin of the posterior communicating artery or involving the posterior circulation were usually maintained on clopidogrel for a longer time, and the antiplatelet therapy was recommended according to the results of their follow-up conventional angiography. After discontinuation of clopidogrel, low-dose aspirin (81 mg/day) indefinitely was recommended. Loading doses of clopidogrel and aspirin were given on the day before or the day of the procedure for patients who were not electively admitted. Platelet reactivity was not tested in any patient.

18.1.1 OUTCOMES

Treatment outcomes included intraprocedural and periprocedural technical events, clinical events (including aneurysm perforation, thrombosis, neurologic symptoms, medical symptoms, ophthalmologic symptoms, and groin complications), and late technical and clinical events at follow-up. Periprocedural complications were defined as those occurring within 30 days following the procedure, and late events were defined as events occurring after 30 days.

Subarachnoid hemorrhage (SAH) was diagnosed by computed tomography (CT) or lumbar puncture. The location of hemorrhage in the subarachnoid space, brain parenchyma and in ventricles was evaluated using the Fisher Grading Score. In every patient where multiple aneurysms or other associated vascular anomalies such as AVM or multiple aneurysms were present, the origin of the hemorrhage was identified based on pattern and location of the hemorrhage on CT and/or the irregularity of the aneurysm. If the patient's clinical condition indicated increased intracranial pressure (ICP) and hydrocephalus occurred on the CT scan, placement of an external ventricular drain (EVD) was performed. Pertinent neurological and angiographic findings at all three centers were assessed and discussed by a multidisciplinary team in order to select the best therapeutic strategy with maximizing patient benefits and reducing the periprocedural complications in each case.

Aneurysms were cathegorized according to Drake's classification[359] as proximal and distal. We collected data regarding aneurysm characteristics and morphology.

Depending on the policy of each individual institution further clinical and radiographic follow-up data were obtained at variable periods of follow-up. In detail, clinical follow-up was collected within the first 30 days (Mayo Clinic & Medical University Innsbruck), at the time of radiographic follow-up at 6 and 12 months and 3 years. At Mayo Clinic, clinical follow-up was obtained by a specialized nurse not directly involved with the original procedure, commonly. At the time of follow-up, patients were asked to rate themselves on the basis of the modified Rankin Scale. Patients were also asked to specify the reason for any score higher than zero. A baseline assessment, following the same methodology, was also obtained at the first encounter before aneurysm treatment. Generally, for patients with flow diverters, radiologic follow-up with conventional angiography was recommended at 6, 12, and 36 months, and for patients with coiling or clipping, conventional angiography or MRA was recommended 6 or 12 months after the original

procedure, depending on aneurysm characteristics and initial radiographic outcome. Afterward, imaging follow-up for patients with coiling or clipping was individualized according to various patient and aneurysm factors. Aneurysm occlusion on follow-up angiography, MRA, and/or CTA was categorized as "complete" (no filling of the aneurysm sac), "near-complete" (>90% occlusion), and "incomplete" (<90% occlusion).

We studied the following outcomes: 1) the presence of perioperative complications, 2) mid- and long-term complications, 3) target aneurysm rupture, 4) retreatment rates, 5) major recurrence rates, and 6) long-term neurologic outcome. Long-term neurologic outcome was assessed by using standard neurological examinations, the Glasgow Outcome Scale (GOS) or else the modified Rankin Scale and with the methodology detailed above. We also determined whether neurologic disability was secondary to the aneurysm or other symptoms (i.e. back pain, intercurrent nonrelated illness, and so forth). "Neurologic morbidity" was defined as any neurologic deficit that appeared either due to target aneurysms or their surgical or endovascular treatment. "Neurologic mortality" was defined as any death of the patient related to target aneurysms and/or their treatment complications.

18.1.2 STATISTICAL ANALYSIS

Baseline characteristics and outcomes were compared between the groups. Descriptive statistics are presented as means and proportions. Means are presented with standard deviations. All statistical analysis was performed using IBM SPSS Statistics 22.0. Quantitative variables were compared using Mann-Whitney-Wilcoxon test and Kruskal-Wallis test. Categorical variables were compared using Fisher exact 2-tailed test, the Pearson χ^2 test, or the test for linear trends, whereas the continuous variables were compared between group by means of the Mann-Whitney-Wilcoxon test, Kruskal-Wallis test or a Student's T test. Univariate associations between continuous variables were tested using Spearman rank correlation coefficients (r_s). One-way analysis of variance (ANOVA) was also performed. Statistical significance was defined as a P-value <0.05.

18.2 RESULTS

From 2000 to 2015, 94 consecutive patients harboring PICA-aneurysms were referred to three institutions: Medical University Innsbruck, Austria; Mayo Clinic, Rochester, MN, USA; Masaryk Hospital, Ústí nad Labem, Czech Republic. Amidst these 94 patients, 70 presented with SAH and/or intracerebellar hemorrhage, 5 patients developed neurological symptoms of brainstem and lower cranial nerve compression, 12 patients were asymptomatic with incidental PICA-aneurysm and 7 patients had dissecting PICA-aneurysms. Four patients were excluded due to missing informed consent. In addition, 7 patients with dissecting aneurysms were also excluded because of completely different nature as well as treatment approaches in these aneurysms. Finally, 83 patietns were included in the study. PICA-aneurysms were classified into two groups: ruptured (n=67) and unruptured PICA-aneurysms (n=16). Of note, fourteen patients included in this study were already reported as part of a single center experience.[375]

18.2.1 RUPTURED PICA ANEURYSMS

18.2.1.1 PATIENTS

There were 67 patients harboring ruptured PICA-aneurysm. One patient with an AVM presented with multiple distal feeding pedicle PICA-aneurysms. The clinical condition of patients with ruptured aneurysms was assessed using the H&H score, 26 patients were classified as H&H IV-V (38.8%) and 41 patients (61.2%) as H&H I-III. Pre-treatment PICA-aneurysm rerupture occurred in 7 cases (10.4%) resulting in a rapid decline of neurological state in 6 patients (9.0%). Of note, two patients (3.0%) admitted in deep coma (H&H V) with massive cerebral edema on initial CT scan, did not improve after intensive systemic and neurological reanimation and died without any further treatment of the aneurysm. Data with patient characteristics are listed in **Table 1B**. Aneurysm characteristics including initial H&H score, Fisher score, and rebleeding before treatment are summarized in **Table 2B**.

18.2.1.2 INITIAL RADIOGRAPHIC FINDINGS

As mentioned above, two patients (3.0%) with H&H V did not improve despite all required intensive measures and died without any further treatment. Additionally, radiologic data were not available for two patients (3.0%).

A total of 67 patients with ruptured PICA-aneurysms presented with a SAH. Of these, Fisher grade 4 was noted in 53 cases (76.1%). Three patients (4.5%) had an intraparenchymal hematoma. Acute hydrocephalus occurred in 51 cases (76.1%) leading to an initial placement of EVD in 43 patients (64.2%). As a consequence, 18 patients (26.9%) developed shunt-dependent hydrocephalus. Data including aneurysm characteristics are listed in **Table 2B**.

A total of 27 patients (40.3%) were diagnosed with other intracerebral vascular malformations such as coexisting aneurysms, cavernomas, dural arteriovenous fistulas or AVMs. Multiple aneurysms were found in 12 patients (17.9%). Six patients (9.0%) presented with associated AVMs; four of them were localized in the posterior fossa. The data are summarized in **Table 2B**.

Of note, at Mayo Clinic, it is preferred to use DSA as a diagnostic tool in order to identify the intracerebral anomaly and discover the source of hemorrhage as the endovascular approach is here a first-line treatment for intracranial aneurysms. This was the case of 25 patients (96.1%) from 26 treated patients with symptomatic aneurysms. In Innsbruck and Ústí nad Labem CTA is the standard aneurysm-diagnostic tool. We perform DSA if endovascular treatment is considered, if CTA is negative, or if a suspicion arises of a small aneurysm, or in case of a need to analyze flow dynamics. In these cases, DSA is the next step in the diagnostic process.

18.2.1.3 THERAPY

Overall, 34 patients (52.3%) underwent endovascular procedures and microsurgery was initially performed in 29 patients (47.7%) with two additional patients after failed primary intented endovascular treatment.

Surgical approach was planned and tailored based on size, shape, rupture status, and clinical condition of the patient. While planning the surgical trajectory, the location of the

aneurysm based upon the segmental anatomy of PICA, its relationship to the anatomical midline (10 mm or less being considered significant), brainstem and cerebellum, and the variability in the vessel's origin was carefully assessed.

The far lateral approach and variations of suboccipital craniotomy in the sitting or lateral position were predominantly used due to aneurysm proximal location in most cases. Direct aneurysm clipping was utilized in 30 patients (96.8%), while in one case (3.2%) it was necessary to excise the aneurysm and reconstruct the parent artery with an end-to-end bypass. In two patients (6.5%), due to malignant edema, it was indispensable to perform partial parenchymal resection to access the aneurysm. The treatment characteristics are listed in **Table 3B**.

18.2.1.3.1 INITIAL ANGIOGRAPHIC RESULTS OF ENDOVASCULAR TREATMENT

Of 34 endovascularly treated patients, parent artery occlusion was performed in five patients (14.7%). Postoperative follow-up immaging revealed patent PICAs in the remaining 29 cases (85.3%) and aneurysm neck remnants (near-complete occusion) in 9 cases (26.5%). In two patients (5.9%), the former intention of endovascular treatment failed and the patients subsequently underwent surgery. The data are summarized in **Table 4B**.

18.2.1.3.2 INITIAL ANGIOGRAPHIC RESULTS OF SURGICAL TREATMENT

Amongst the 31 surgically treated patients, postoperative angiography showed that the PICA was occluded in two cases (6.5%). In one patient (3.2%) the parent artery occlusion occurred inadvertently after direct clipping of the aneurysm while in the other patient (3.2%) both the right and left distal PICA branches were sacrificed during AVM resection. Aneurysm neck remnants (near-complete occlusion) were present in 6 cases (19.4%). The data are summarized in **Table 4B**.

Among the six patients with AVM (9.5%), two had ruptured aneurysms involving the distal PICA segment which was also feeding the AVM. One of these distal aneurysms was resected along with the AVM (and both right and left distal PICA branches were sacrificed), the other distal PICA-aneurysm associated with AVM was coiled and the patient underwent surgery for AVM

resection. One of the six patients with AVM was treated for proximal PICA-aneurysm and the distal cerebellar AVM in the same session.

18.2.1.4 COMPLICATIONS

18.2.1.4.1 COILING-RELATED COMPLICATIONS

Of 34 patients treated endovascularly, 4 patients (11.8%) experienced procedure-related complications. Of these, as the most adverse event with lethal consequences, intraprocedural aneurysm rupture occurred in two patients (5.9%) resulting in rapid neurological decline, hemodynamic failure and death in both cases. One patient (2.9%) suffered hemiparesis and ophthalmoparesis from a pontine infarction. One other patient (2.9%) developed a pseudoaneurysm of the femoral artery which was treated with thrombin injection. In addition to the periprocedural complications, nine patients in the endovascular group (26.5%) also experienced swallowing problems during the hospital stay, however these were felt to be related to the direct effects of the initial hemorrhage. PEG placement was mandatory in seven patients (20.6%) and eight patients (23.5%) required a tracheotomy. In addition, one patient (2.9%) developed bilateral asymmetric fourth cranial nerve palsy with diplopia and the consequent corrective surgery at follow-up afterwards. The data are summarized in **Table 5B**.

18.2.1.4.2 SURGERY-RELATED COMPLICATIONS

Among the 31 operated patients, 6 patients (19.4%) experienced surgery-related complications. Accidental PICA occlusion occurred in one patient (3.2%) resulting in symptomatic cerebellar stroke. 6 patients (19.4%) experienced postoperative lower cranial nerve palsies. Of these, the lower cranial nerve dysfunction resulted in aspiration pneumonia in two patients (6.5%). All six patients (19.4%) required PEG insertion after surgery. Tracheotomy was mandatory in three patients (9.7%). Not surprisingly, with the exception of one distal PICA-aneurysm, all were

localized on the proximal segment of PICA in these patients. The data are summarized in **Table 5B**.

18.2.1.5 CLINICAL AND RADIOGRAPHIC FOLLOW-UP

Clinical outcome and follow-up. Among the 67 patients with ruptured PICA-aneurysms, 32 patients (47.8%) were discharged from the hospital in an excellent clinical condition (GOS 5), 10 patients (14.9%) showed a GOS of 4, 8 patients (11.9%) had a GOS of 3, 10 patients (14.9%) presented with severe deficits and a GOS of 2 and 7 patients (10.4%) died. When considering the neurological outcome at discharge by aneurysm location, 50% patients with ruptured distal PICA-aneurysm presentend with poor clinical outcome at the time of discharge (GOS 1-3) compared to 31.9% of patients with ruptured proximal PICA-aneurysm.

When comparing the clinical outcome at discharge by treatment strategy, neurological morbidity rates were similar between both endovascular and surgical group. 12 patients (35.3%) in the endovascular group showed a poor outcome at discharge (GOS 1-3) when compared to 11 patients (35.5%) in the surgical group. Of note, 15 patients (44%) of patients in the endovascular group and 9 patients (29%) in the microsurgical group had presented with very poor clinical condition at admission having H&H score of IV or V (P=0.009).

Clinical and radiographic follow-up examinations were available for 48 of living patients, ranging from 1 month to 10 years. Among the 21 patients (32.3%) who experienced lower cranial nerve palsy after treatment, follow-up information was available in 14 (66.7%). Complete remission was observed in 10 patients (71.4%). In the remaining 4 patients (28.6%), one patient (7.1%) suffered persistent mild dysphagia and vocal cord paralysis with subsequent corrective surgery. One patient (7.1%) showed permanent tenth and twelfth cranial nerve palsy, one patient (7.1%) died due to aspiration pneumonia most likely caused by significant lower cranial nerve palsy and one patient (7.1%) presented with persistent vocal cord paralysis resulting in a hoarse voice. Of 2 patients who developed postoperative motor deficits, the hemiparesis recovered completely only in one patient, while the other remained. Persistent oculomotor impairment with the following exposure keratopathy occurring in one patient (7.1%) led to corrective surgery. Two additional patients (3.0%) suffered from short memory impairment.

Of 6 (19.4%) initially diagnosed aneurysm neck remnants with near-complete occlusion rates after surgery, one remnant (3.2%) remained stable and in three patients (9.7%) the originally diagnosed remnant was not visible on the non-invasive imaging study at one year follow-up. A new fusiform dilatation of the PICA developed in the remaining case (3.2%).
Among patients undergoing endovascular treatment, five patients (14.7%) required retreatment due to growning aneurysm remnants / major recurrences during follow-up. These were treated with flow diverting technique in one patient (2.9%), microsurgery in one patient (2.9%), and additional coil embolization in the remaining 3 patients (8.8%). An asymptomatic progressive occlusion of the PICA was diagnosed in one patient (2.9%) at follow-up after endovascular treatment. The data are summarized in **Table 4B**.

18.2.2 UNRUPTURED PICA ANEURYSMS

18.2.2.1 PATIENTS

Twelve patients with incidental asymptomatic PICA-aneurysms and four patients with presenting with mass effect due to unruptured PICA-aneurysms were included in this series. Patient characteristics are summarized in **Table 1B**.

18.2.2.2 INITIAL RADIOGRAPHIC FINDINGS

Aneurysm characteristics are listed in **Table 2B**. Multiple intracranial aneurysms were present in 4 patients (25.0%). Four aneurysms (25.0%) caused brainstem compression with subsequent neurological deficits and in one patient (6.3%) brainstem edema was also present.

18.2.2.3 THERAPY

Microsurgery was performed in 7 patients (43.8%). In particular, two giant (28.6%) and one large PICA-aneurysm (14.3%) required a complex surgical strategy including trapping and

PICA bypass or VA-PICA anastomosis. 9 patients (56.2%) underwent endovascular treatment. The data are summarized in **Table 3B**.

18.2.2.3.1 ANGIOGRAPHIC RESULTS OF ENDOVASCULAR TREATMENT

Aneurysmal remnants were present in three patients (33.3%) after coil embolization. Two of these remnants (22.2%) were managed conservatively, while the third patient with a developed major recurrence of a giant PICA-aneurysm requiring further treatment. Consequently, an additional endovascular procedure consisting of pipeline embolization was considered. Finally, the patient endovascular PICA occlusion since good collateral flow was present.

18.2.2.3.2 ANGIOGRAPHIC RESULTS OF SURGICAL TREATMENT

Postoperative radiographic studies showed patency of the PICA in all but one patient (14.3%) after surgery.

18.2.2.4 COMPLICATIONS

One patient (14.3%) developed acute transient ophthalmoplegia with resultant diplopia after endovascular treatment. There were no surgery-related complications in the unruptured group.

18.2.2.5 CLINICAL AND RADIOGRAPHIC FOLLOW-UP

All patients with unruptured PICA-aneurysms were discharged in good neurological condition. Fifteen patients (93.8%) were available for follow-up. The above-mentione acute ophthalmoplegia after coiling resolved completety.

18.3 DISCUSSION

Recent publications have reported various treatment options of PICA-aneurysms in a relatively small number of patients treated at specific institutions.[2, 7, 14, 24, 365] Management and treatment strategies of ruptured or unruptured PICA-aneurysms have been developing based on local experience and treatment policy. This multicenter study of 83 treated PICA-aneurysms demonstrates that in general, neurological outcome at discharge after microsurgical or endovascular treatment for ruptured PICA-aneurysms does not differ. However, the overall results closely correlate with the patient's clinical condition at admission. In patients having poor neurological condition (H&H score IV-V at admission, rupture of a PICA-aneurysm resulted in 65.2% probability of poor neurological outcome (GOS 1-3). Not surprisingly, the most substantial differences between microsurgery and endovascular treatment were the rates of aneurysms remnants / major recurrences requiring retreatment favoring the surgical group. Our findings are in line with prior studies which reported retreatment rates up to 18.8% in endovascularly treated patients.[8, 24, 360] In agreement with previously published series,[2, 24] when considering the patients with ruptured PICA-aneurysms, the aneurysm location along the course of the PICA also had substantial impact on overall neurological outcome (50% of patients with ruptured distal PICA-aneurysms showed a poor neurological outcome versus 31.9% of patients with ruptured proximal PICA-aneurysms).

Results of surgical treatment are affected by the size, morphology, and localizations of PICA-aneurysms. Surgical treatment offers the possibility to decompress surrounding anatomical structures and preserve the PICA or its perforators.[33] Endovascular treatment may be demanding often due to the broad neck of these aneurysms, the fusiform shape as well as the highly variable origin and tortuosity of the PICA. Notwithstanding, numerous recent studies reported successful endovascular treatment of PICA-aneurysms.[20, 156, 204, 210, 211, 225, 243, 267, 314, 315] The overall favorable neurological outcome of endovascular treatment of PICA-aneurysms has been reported to be between 66% and 82% depending on the series.[8, 268, 367] In previously published surgical series,[2, 14, 25, 363-365] neurological outcome of surgically treated PICA-aneurysms was considered be more successful, 80% to 89%. However, some recent studies have corroborate results below 75%.[7, 375] In our study, in defiance of the high rates of in-hospital complications (many related to the original

clinical presentation), overall outcomes at discharge showed no significant difference between the two treatment modalities (favorable neurological outcomes rates of patients with a ruptured aneurysm at discharge were 64.7% in the endovascular group versus 64.5% in the surgical group. Importantly, among patients with ruptured aneurysms a higher percentage of patients presenting with H&H grades IV and V underwent endovascular therapy). These results emphasize the importance of a selective case-by-case approach in the treatment of these aneurysms in order to maximize patient benefits and limit the risk of periprocedural complications.

Irrespective of rapidly developing therapeutic advancements, PICA-aneurysms, especially in cases presenting with intraparenchymal hemorrhage, continue to be associated with high rates of morbidity and mortality often associated with the neurological consequences of the acute hemorrhage upon adjacent neural structures. This is especially true in patients with poor neurological condition at admission. In our study, of 26 patients presenting with initial H&H score of IV-V at admission, 18 patients (69.2%) showed a poor clinical outcome or died (GOS 1-3).

It is essential to note that complications occurring due to the original hemorrhage or related to treatment have at times are of temporary character but require additional aggresive treatment. In our study, a total of 17 patients undergoing endovascular treatment (39.5%) and 14 patients treated surgically (36.8%) required extra interventions to treat periprocedural complications such PEG tube placement, VP shunt insertion, corrective surgery of eyes or vocal cord paralysis or retreatment of major recurrences. Likely, in the Barrow Ruptured Aneurysm Trial (BRAT),[376] patients with PICA-aneurysms showed a high incidence of lower cranial nerve palsies resulting in the need for tracheostomy and/or PEG in 50% of patients. Lower cranial nerve dysfunction may have long-term consequences for patients, but the recovery rates within 6 months are as high as 76%.[7, 236] In our study, lower cranial nerve deficits requiring PEG tube placement occurred in 19.4% of surgically and in 23.5% of endovascularly treated ruptured PICA-aneurysms and of these, 73% of patients with adequate follow-up recovered within 6 months.

18.4 CONCLUSIONS

Our results of 83 treated PICA-aneurysms treated at three large international referral neurovascular centers strongly suggest that overall neurological outcome is associated with the patient neurological condition at admission. Based on individual aneurysm and patient characteristics as well as center preference, both endovascular and surgical treatment are reasonable options for PICA-aneurysms. Both strategies are technically feasible and safe with similar neurological morbidity and mortality rates. Complications of the original hemorrhage and of treatment are not negligible and related to cranial nerve morbidity and hydrocephalus. Not surprisingly, endovascular treatment is associated with a higher risk of recurrence requiring retreatment.

Informed consent was obtained from all individual participants included in the study.

18.5 SUPPLEMENTAL MATERIAL

*18.5.1 **TABLE 1B**. Demographic characteristics*

		Ruptured PICA *(n=67)*	***Unruptured PICA*** *(n=16)*	***P***
Mean Age (range)		57 (29 - 83)	56 (21 - 76)	0.259
N (%) **Female**		18 (71.6%)	13 (81.4%)	0.860
Mean (range) Follow-up (weeks)				
N (%) **Comorbidities**				0.370
	Hypertension	25 (37.3%)	7 (43.8%)	
	Dyslipidemia	8 (11.9%)	3 (18.8%)	
	Oncological Disorder	6 (9.0%)	3 (18.8%)	
	Diabetes Mellitus	7 (10.4%)	-	
	Respiratory Disorder	5 (7.5%)	-	
	Thyroid Gland Disorder	5 (7.5%)	-	
	Heart Disease	5 (7.5%)	-	
	Others	12 (17.9%)	5 (31.3%)	
Number of Aneurysms		67	16	

18.5.2 ***TABLE 2B****. Aneurysm characteristics and initial radiographic findings*

		Ruptured PICA *(n=67)*	***Unruptured PICA*** *(n=16)*
N (%) **Hunt&Hess Grade**			N/A
	I	4 (6.0%)	-
	II	27 (40.3%)	-
	III	10 (14.9%)	-
	IV	6 (9.0%)	-
	V	20 (29.9%)	-
N (%) **Re-hemorrhage Before Treatment**		7 (10.4%)	N/A
N (%) **Fisher Grade**			N/A
	1	1 (1.5%)	-
	2	1 (1.5%)	-
	3	8 (11.9%)	-
	4	53 (79.1%)	-
N (%) **Acute Hydrocephalus**		51 (76.1%)	N/A
	EVD	43 (84.3%)	-
	VP Shunt	18 (35.3%)	-
N (%) **Aneurysm Size (**mm)		67	16
	Very Small (<4mm)	28 (41.8%)	1 (6.3%)
	Small (4-7mm)	16 (23.9%)	8 (50.0%)
	(>7mm)	16 (23.9%)	3 (18.8%)
	Large (15-25mm)	0 (0%)	2 (12.5%)
	Giant (>25mm)	0 (0%)	2 (12.5%)
	Unknown	7 (10.4%)	0 (0%)
N (%) **Aneurysm Location**			
	Proximal	45 (67.2%)	13 (81.3%)
	Distal	22 (32.8%)	3 (18.7%)
N (%) **Aneurysm Lateralization**			
	Left	40 (59.7%)	9 (56.3%)
	Right	27 (40.3%)	7 (43.7%)
N (%) **Morphology**			
	Saccular	49 (73.1%)	9 (56.3%)
	Fusiform	15 (22.3%)	3 (18.9%)
	Unknown	3 (4.5%)	3 (18.9%)
N (%) **Coexisting Vascular Lesions**		27 (40.3%)	10 (62.5%)
	AVM	6 (22.2%)	-
	Associated Intracranial Aneurysm	12 (44.4%)	6 (60.0%)
	Associated Aorta Aneurysm	1 (3.7%)	1 (10.0%)
	Dural Arteriovenous Fistula	1 (3.7%)	-
	Cavernoma	1 (3.7%)	-
	Persistent Trigeminal Artery	-	1 (10.0%)
	Persistent Hypoglossal Artery	-	1 (10.0%)
	Hypoplastic Cerebral Artery	5 (18.5%)	1 (10.0%)
	VA Occlusion	1 (3.7%)	-

18.5.3 ***TABLE 3B****. Treatment characteristics*

	Ruptured PICA			Unruptured PICA		
	Total *(n=65)*	***Proximal*** *(n=44)*	***Distal*** *(n=21)*	***Total*** *(n=16)*	***Proximal*** *(n=13)*	***Distal*** *(n=3)*
N (%) **Endovascular Treatment**	**34 (52.3%)**	**24 (54.5%)**	**10 (47.6%)**	**9 (56.3%)**	**8 (61.5%)**	**1 (33.3%)**
Selective Coiling	27 (79.4%)	21 (87.5%)	7 (70.0%)	7 (77.8%)	6 (75.0%)	1 (100%)
Stent-assisted Coil Embolization	2 (5.9%)	1 (4.2%)	-	-	-	-
Flow Diverter Embolization	-	-	-	1 (11.1%)	1 (12.5%)	-
Parent Vessel Occlusion	5 (14.7%)	2 (8.3%)	3 (30.0%)	1 (11.1%)	1 (12.5%)	-
N (%) **Microsurgical Treatment**	**31 (47.7%)**	**20 (45.5%)**	**11 (52.4%)**	**7 (43.7%)**	**5 (38.5%)**	**2 (66.7%)**
Clipping	27 (87.1%)	17 (85.0%)	10 (90.9%)	4 (57.1%)	3 (60.0%)	1 (50.0%)
Clipping + Wrapping	1 (3.2%)	1 (5.0%)	-	-	-	-
Clipping + Resection	3 (9.7%)	2 (10.0%)	1 (9.1%)	-	-	-
PICA End-to-End Bypass	-	-	-	2 (28.6%)	1 (20.0%)	1 (50.0%)
PICA-VA Anastomosis	-	-	-	1 (14.3%)	1 (20.0%)	-

18.5.4 ***TABLE 4B****. Technical and angiographic outcomes*

	Endovascular Treatment			Microsurgical Treatment			
Ruptured PICA	***Total*** *(n=34)*	***Proximal*** *(n=24)*	***Distal*** *(n=10)*	***Total*** *(n=31)*	***Proximal*** *(n=20)*	***Distal*** *(n=11)*	**P**
N (%) **Initial Angiographic Occlusion After Treatment**							0.403
Complete	25 (73.5%)	16 (66.7%)	9 (90.0%)	25 (80.6%)	15 (75.0%)	10 (90.9%)	
Near Complete	9 (26.5%)	8 (33.3%)	1 (10.0%)	6 (19.4%)	5 (25.0%)	1 (9.1%)	
Incomplete	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
N (%) **Final Angiographic Occlusion at Last Follow-Up**							0.733
Complete	32 (94.1%)	22 (91.7%)	10 (100%)	28 (90.3%)	19 (95.0%)	10 (90.9%)	
Near Complete	2 (5.9%)	2 (8.3%)	0 (0%)	2 (6.5%)	1 (5.0%)	1 (9.1%)	
Incomplete	0 (0%)	0 (0%)	0 (0%)	1 (3.2%)	0 (0%)	0 (0%)	
Angiographic Follow-up Range (months)			1 - 120				0.009
N (%) **Retreatment**	5 (14.7%)	2 (8.3%)	3 (30.0%)	0 (0%)	0 (0%)	0 (0%)	
Re-coiling	3 (60.0%)	0 (0%)	3 (100%)	-	-	-	
Re-treatment with FD	1 (20.0%)	1 (50.0%)	0 (0%)	-	-	-	
Clipping	1 (20.0%)	1 (50.0%)	0 (0%)	-	-	-	
N (%) **Recurrence**	6 (17.6%)	3 (12.5%)	3 (30.0%)	1 (3.2%)	0 (0%)	1 (9.1%)	0.007

18.5.5 ***TABLE 5B****. Clinical outcomes*

Ruptured PICA	**Endovascular Treatment**			**Microsurgical Treatment**			**P**
	Total *(n=34)*	***Proximal*** *(n=24)*	***Distal*** *(n=10)*	***Total*** *(n=31)*	***Proximal*** *(n=20)*	***Distal*** *(n=11)*	
N (%) **SAH-related Complications with Cranial Nerve Dysfunction**							0.788
Lower Cranial Nerve Palsy	8 (23.5%)	5 (20.8%)	3 (30.0%)	6 (19.4%)	5 (25.0%)	1 (9.1%)	
PEG	7 (20.6%)	4 (16.7%)	3 (30.0%)	6 (19.4%)	5 (25.0%)	1 (9.1%)	0.316
Tracheostomy	8 (23.5%)	4 (16.7%)	3 (30.0%)	3 (9.7%)	3 (15.0%)	-	0.503
Aspiration Pneumonia	-	-	-	2 (6.5%)	2 (10.0%)	0 (0%)	
Other Cranial Nerve Deficit	1 (2.9%)	-	1 (10.0%)	-	-	-	
N (%) **Overall Complications**	**9 (26.5%)**	**6 (25.0%)**	**4 (40.0%)**	**7 (22.6%)**	**6 (30.0%)**	**1 (9.1%)**	
N (%) **Treatment-related Complications**							0.713
Cranial Nerve Deficit	1 (2.9%)	1 (4.2%)	-	6 (19.4%)	5 (25.0%)	1 (9.1%)	
Postprocedural Rerupture	2 (5.9%)	2 (8.3%)	-	-	-	-	
Clinical Stroke	1 (2.9%)	1 (4.2%)	-	2 (6.5%)	1 (5.0%)	1 (9.1%)	
Femoral Artery Pseudoaneurysm	1 (2.9%)	-	1 (10.0%)	-	-	-	
Acute Respiratory Distress Syndrome	-	-	-	1 (3.2%)	1 (5.0%)	-	
Meningitis	-	-	-	4 (12.9%)	3 (15.0%)	1 (9.1%)	
CSF Leak	-	-	-	2 (6.5%)	1 (5.0%)	1 (9.1%)	
N (%) **Overall Complications**	**4 (11.8%)**	**3 (12.5%)**	**1 (10.0%)**	**6 (19.4%)**	**3 (15.0%)**	**3 (27.3%)**	

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