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DISSERTATION

New developments in giant intracranial aneurysm diagnostics

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1 Abbreviations

ACA	Anterior communicating artery
CI	confidence interval
IA	intracranial aneurysm
ICA	internal carotid artery
IQR	interquartile range
GIA	giant intracranial aneurysm
MCA	middle cerebral artery
MLS	mid-line shift
MRI	magnet resonance imaging
LVV	lateral ventricle volume
PAE	perianeurysmal edema
PT	partial thrombosis
r_s	Spearman correlation coefficient
SD	standard deviation
T2WI	T2-weighted image

2 Summary

2.1 Abstract

Hintergrund: Intrakranielle Riesenaneurysmen (GIA) unterscheiden sich klinisch und morphologisch deutlich von kleineren Aneurysmen und stellen daher in ihrer Diagnostik und Therapie eine besondere Herausforderung dar. Hauptziel der Arbeit ist es, neue Ansätze in der bildgebenden Diagnostik darzustellen und diese zu untersuchen. Im Besonderen beschreibt die Arbeit verschiedene Methoden zur Quantifizierung von GIA sowie das Auftreten von perianeurymalem Ödem (PAE) und partieller Thrombosierung (PT). Zusätzlich wurden die Änderung des GIA-Volumens und des von ihm ausgehenden Masseneffekts nach operativer Therapie analysiert.

Methoden: Präoperative MRTs von 69 GIA wurden retrospektiv untersucht in Bezug auf die Lokalisation, den maximalen GIA-Durchmesser, das Volumen sowie das Auftreten und Volumen von PAE und PT. Zusätzlich wurde der klinische Einfluss der GIA-Größe analysiert. In einem zweiten Schritt wurde in prä- sowie postoperativen MRTs von 19 anterioren GIA das GIA-Volumen, das Seitenventrikelvolumen (LVV) sowie die Mittellinienverlagerung (MLS) bestimmt.

Ergebnisse: Die Messungen des GIA-Durchmessers und die GIA-Volumetrie erzeugten voneinander unterschiedliche Ergebnisse. Eine Korrelation beider Messtechniken zeigte sich nur bei anterioren GIA. Nicht die GIA-Größe, sondern nur die GIA-Lokalisation korrelierte mit dem neurologischen Zustand des Patienten. PAE zeigte sich in einem Drittel aller GIA. Das GIA-Volumen, ebenso wie PT, waren assoziiert mit dem Auftreten und der Größe von PAE. In den 19 anterioren GIA zeigte sich postoperativ im MRT eine signifikante Reduktion des GIA-Volumens sowie eine Vergrößerung des LVV und ein Rückgang des MLS. Die postoperative GIA-Volumenreduktion korrelierte mit der Veränderung des LVV und nicht mit dem MLS.

Schlussfolgerung: Unsere Daten deuten darauf hin, dass GIA-Lokalisation, Form und Masseneffekt wichtiger für den präoperativen klinischen Zustand sind als GIA-Größe. Jedoch hat das GIA-Volumen, genauso wie PT, einen ausschlaggebenden Einfluss auf

das Auftreten von PAE. Indirekte operative GIA-Therapie führt zu einer Reduktion sowohl des GIA-Volumens als auch des Masseneffekts auf das angrenzende Hirngewebe.

Abstract

Background: Giant intracranial aneurysms (GIA) differ substantially from smaller IA not only concerning their management but also concerning their diagnostics. The main objective of the studies summarized below is to develop and compare new diagnostic and monitoring techniques in GIA using magnet resonance imaging (MRI). In particular, we describe different modes of GIA quantification and the occurrence of perianeurysmal edema (PAE) and partial thrombosis (PT). In addition, we aim to delineate changes in GIA volume and mass effect on the brain after surgical GIA treatment that is not directed at immediate aneurysm occlusion.

Methods: MRIs of 69 GIA were retrospectively analyzed regarding GIA location, diameter and volume as well as the occurrence and volume of PAE and PT. Furthermore, the clinical impact of these parameters was evaluated. In a second step, we measured changes in GIA volume, lateral ventricle volume (LVV) and mid-line shift (MLS) by using pre- and postoperative MRIs of 19 anterior circulation GIA.

Results: Comparing GIA sizes produced different results depending on whether GIA diameter or volume was measured. A correlation between these two modes of measurement was only observed in anterior circulation GIA. Only GIA location but not GIA size correlated with the patient's clinical condition. PAE was observed only in one third of all cases. Both GIA volume and PT were associated with the occurrence and size of PAE. Our cohort of 19 anterior circulation GIA showed a significant decrease in postoperative GIA volume as well as an increase in LVV and a reduction in MLS. The decrease in GIA volume correlated with the increase in ipsilateral LVV but not with the change in MLS.

Conclusion: Our data suggest that GIA size is clinically less relevant than examining GIA location, shape and mass effect. However, GIA volume as well as PT have a distinct influence on the occurrence of PAE. Since cavernous ICA aneurysms showed no PAE at all one may speculate that the dura mater could serve as a barrier protecting the brain from PAE formation. We showed that indirect surgical GIA therapy leads to a significant decrease in postoperative GIA volume and mass effect exerted on the brain.

2.2 Introduction

Giant Intracranial Aneurysms (GIA) are defined as intracranial aneurysms (IA) measuring ≥ 25 mm in diameter.[1] They account for 5% of all IA and are known to have rupture rates exceeding 10% per year.[2] But while for small and medium sized aneurysms the knowledge in diagnostics and monitoring has considerably increased over the last few decades, GIA have been somewhat left out, with most authors ignoring the clinical and morphological peculiarities of those lesions.[3]

Due to their sheer size, GIA exert considerable mass effect on the brain. Depending on the function of the compressed brain area they can cause severe neurological deficits.[4] We already know that increasing IA size is a main risk factor for mortality and morbidity driven by higher rupture rates.[2] However, since GIA are a very heterogeneous subgroup defined only by their largest diameter, two GIA with the same diameter can have different three-dimensional shapes and effect on surrounding brain matter. Therefore, GIA seem to have more in common with brain tumors than with vascular pathologies. While a growing amount of evidence suggests that IA volume might be an independent risk factor for poor outcome, a systematic comparative analysis of volumetry and measuring diameters is still lacking.[5,6]

Mass effect exerted by GIA is also believed to be aggravated by perianeurysmal edema (PAE) adjacent to the GIA.[7,8] PAE along with partial thrombosis (PT) are further morphological characteristics that are frequently seen in GIA patients on preclinical magnetic resonance imaging (MRI).[9] While PAE is well studied in pathologies such as brain tumors and intracerebral hemorrhage, in GIA our knowledge of PAE is limited.[10,11] Neither has there been a systematic analysis of the origin of PAE and its association with PT in GIA, nor of the prognostic value of PAE.

However, GIA differ from small aneurysms not only in morphological characteristics but also concerning their surgical treatment. Since large aneurysms frequently incorporate thrombus and neighboring vessels, direct surgical clipping or endovascular coiling is often not feasible or associated with a high risk of hemorrhage or stroke. Alternatively, neurosurgeons can establish a cerebrovascular bypass in combination with proximal

and/or distal GIA occlusion.[12,13] This indirect surgical method allows for an alteration of blood flow while leaving the GIA body practically untouched. The concept behind this operation is to reduce hemodynamic stress on the GIA in order to support GIA shrinkage over time, resulting in a decrease in mass effect.[14] Although some authors question the ability of GIA to shrink over time there has been no systematic analysis on GIA volume changes after this indirect treatment.[15] Nor has there been an analysis of postoperative changes in mass effect. These changes can be monitored, as has been done in intracerebral hemorrhage, by measuring mid-line shift (MLS) or by volumetry, using the lateral ventricle volume (LVV) as an indicator of brain compression.[16,17]

We therefore designed two multi-center studies using MRI and clinical data from patients with unruptured GIA to pursue the following goals:

(1) Compare GIA quantification by means of measuring diameter and volume with regard to the vessel of GIA origin, location of mass effect and clinical findings.[18]
(2) Study the prevalence of PAE in relation to GIA location, size, PT and clinical condition.[19]
(3) Answer the question if GIA treated by surgical therapy other than direct clipping display a significant decrease in aneurysm volume after surgery and to analyze whether changes in GIA volume correlate with those in MLS and LVV.[14]

2.3 Methods

All data summarized below were taken from the original published articles according to the thesis regulation of the Charité Berlin.

2.3.1 GIA quantification and association with PAE and PT

This study is based on a retrospective analysis of the Giant Intracranial Aneurysm Registry (GIA Registry) imaging library.[20] Inclusion criteria were the diagnosis of an unruptured GIA, defined as an intracranial aneurysm with a diameter of ≥25 mm, and the presence of an MRI examination before treatment initiation.

All cases were examined by two blinded examiners (N.M. and J.D.) using T2-weighted images (T2WIs). GIA were characterized by their vessel of origin and according to their location of mass effect. Mass effect was defined as any displacement of brain parenchyma from its anatomically normal location.

Volumetric analyses were performed using the software “iPlan Cranial” by manually marking the GIA body and, if present, PAE within each slice of the T2WI. PAE was defined in accordance with previously published work as a region of hyperintensity on T2-weighted images (T2WI) in the vicinity of the GIA. [21,22] In every case the two points furthest apart from each other within the GIA were measured to compare GIA volume to the largest diameter. Thrombosed or calcified parts of the aneurysm wall were identified as a difference between the perfused GIA volume (seen on angiography) and the GIA volume on MRI.

In addition, clinical characteristics of each patient prior to any treatment were extracted from the GIA-Registry's database.

2.3.2 Changes in GIA volume and mass effect after surgical treatment

This analysis is based on images and clinical data extracted from the GIA Registry's prospective database. Inclusion criteria for this study were the diagnosis of an unruptured anterior circulation GIA with two separate MRI examinations, of which one was done less than 3 months before treatment and the other one at least 9 months after treatment. We included only GIA that were not treated by direct clipping but by indirect surgical strategies described below. GIA treated by partial GIA resection or thrombectomy were excluded.

Similar to the study described above two blinded examiners (N.M. and J.D.) examined all cases using T2WIs in axial slices. To assess whether operative treatment led to a change in GIA volume we measured pre- and postoperative GIA volumes as well as LVV as an indicator of changes in mass effect on the brain. To determine MLS the distance between the septum pellucidum and the connecting line between anterior and posterior insertion of the falx cerebri was measured at the level of the third ventricle.[23,24]

Surgical strategies were divided according to the following categories: bypass combined with proximal or distal occlusion or aneurysm trapping; only bypass without aneurysm occlusion or only proximal occlusion without bypass.

2.3.3 Statistical analysis

The Shapiro-Wilk test was used to test variables for normal distribution. Variables with normal distribution are given as means ± standard deviation (SD). Since most of the relevant variables were not distributed normally their values are given as medians with 95% confidence intervals (CI) or interquartile range (IQR) and nonparametric tests were used for further analysis. The Mann-Whitney-U test was applied to compare differences between two independent groups with nonparametric variables, the Wilcoxon signed-rank test was applied to compare differences between dependent variables. To compare three or more unmatched groups the Kruskal-Wallis-Test was used. Interobserver variability was calculated using the two-way random effects model intraclass correlation test. Ordinal regression analysis and binary logistic regression analysis were used to test for association between neurological deficits and diagnostic characteristics of the GIA. Potential correlations were examined by Spearman correlation. All differences with $p < 0.05$ were considered to be of statistical significance.

2.4 Results

2.4.1 GIA quantification and association with PAE and PT

MRI data of 69 unruptured GIA in 66 patients, which had been included into the GIA registry at 12 participating centers between January 2009 and November 2013, were analyzed in this study. Patient and GIA characteristics are summarized in Table 1. Interobserver agreement was excellent for GIA volume and diameter as well as for PAE volume with an intraclass correlation coefficient of >0.92 and corresponding p values of <0.05.

Characteristics	Entire Cohort	No PAE	PAE
Patient age, y, mean (SD)	56.4 (14.1)	55.8 (14,7)	57.7 (12,9)
Patient sex (f/m)	38/31	30/16	8/15
Number of GIA	69	46/69 (66.7)	23/69 (33.3)
GIA volume, cm^3, median (IQR)	9.3 (7.3)	8.1 (6.1)	14.1 (17.4)
GIA diameter, mm, median (IQR)	33.6 (9.9)		
Proportion of GIA with PT (%)	47/69 (68.1)	25/46 (52.2)	22/23 (95.7)
GIA location, n (%)			
ACA	6 (9%)	4	2
cavernous ICA	23 (33%)	23	0
supraclinoid ICA	7 (10%)	5	2
MCA	18 (26%)	6	12
posterior circulation	15 (22%)	8	7

Table 1 Patient and aneurysm characteristics

IQR interquartile range, *SD* standard deviation, *GIA* giant intracranial aneurysm, *PAE* perianeurysmal edema, *PT* partial thrombosis, *ACA* anterior cerebral artery, *ICA* internal carotid artery, *MCA* middle cerebral artery

Correlating GIA diameter and volume in relation to GIA vessel origin. Measuring GIA by diameter and volume produced different results when compared by their vessel of origin. Measuring diameter found posterior circulation GIA to be the largest ones (39.2 mm, IQR 37.3– 48.3), while measuring volume found GIA of the MCA to be the largest ones (12.3 cm^3, IQR 7.2–27.8). For the entire patient cohort the Spearman correlation coefficient (r_s) between diameter and volume was 0.72 ($p < 0.001$), describing a moderate correlation. In a subanalysis for each group of vessel origins we found a correlation only in anterior circulation GIA (MCA: $r_s = 0.96$, $p < 0.001$; ACA: $r_s = 1.00$, $p < 0.001$) but not in GIA of the posterior circulation ($r_s = 0.20$, $p = 0.48$). While anterior circulation GIA were predominantly saccular in shape, those of the posterior circulation were mostly fusiform.

Correlating GIA characteristics with the occurrence of PAE and PT. In the entire cohort of 69 unruptured GIA, PAE was observed in 23 GIA, resulting in an overall prevalence of GIA-associated PAE of 33.3%. PT existed in 68.1 % of the entire patient cohort. PT was present in 96% of all GIA with PAE and only in 54% of GIA without PAE. Binary regression analysis showed that GIA volume (OR 1.13, 95% CI 1.02 – 1,25, p=0.02) and the occurrence of PT (OR 9.84, 95% CI 1.16 – 83.73, p=0.04) were

independent predictors of PAE formation. GIA with PAE were larger than GIA without PAE (p=0.001) and GIA volume correlated with PAE volume (r_s = 0.51, p=0.01). None of the 23 cavernous ICA GIA showed any sign of PAE.

Clinical findings. We didn't find any association between the patient's clinical condition and GIA diameter (p=0.77), GIA volume (p=0.38) or the presence of PAE (p=0.30). However, we found a significant association between mRS and GIA location. GIA of the posterior circulation showed significantly higher mRS values than GIA of all other locations. Odds ratios for higher mRS in posterior circulation GIA ranged between 8.7 and 24.5.

2.4.2 Changes in GIA volume and mass effect after surgical treatment

Nineteen cases of anterior circulation GIA in 16 patients, which had been included into the GIA registry between March 2009 and February 2012, were analyzed in this study. Mean time to follow-up MRI was 466 days (±171). Patient and GIA characteristics are summarized in Table 2. Interobserver agreement was excellent for GIA volume, LVV and MLS each with an intraclass correlation coefficient of >0.91 and corresponding p values of <0.05.

Changes in GIA volume, LVV and MLS after treatment. GIA volume was found to be significantly decreased by 55.2% within a mean of 16 months after the operation. In the same time ipsilateral LVV increased by 86.0% while the contralateral LVV showed an increase by only 13.6%. MLS changed from a preoperative mean of 0.1 mm skewed towards the contralateral hemisphere to −0.9 mm after treatment, meaning that it was now directed to the side of the treated GIA, resulting in an overall-change by a median of 10 mm.

Changes in LVV and MLS in relation to the decrease in GIA volume. For the entire cohort of 19 cases we found a moderate correlation (r_s of 0.60, p=0.01) between changes in GIA volume and those in ipsilateral LVV. In contrast, there was no correlation between changes in GIA volume and those in MLS (r_s = 0.41; p = 0.08). When categorizing the cases by their reduction in GIA volume and type of surgical strategy we found that the five GIA with the largest reduction in volume were all treated using a proximal occlusion

strategy, in most cases with the addition of a bypass.

Characteristics	Number of GIA	19
	Number of patients	16
	Patient age, years, mean (SD)	52 (13)
Modified Rankin score (n)	mRS 0	7
	mRS 1	10
	mRS 2	2
GIA location	MCA	8
	ICA	10
	AcomA	1
Brain hemisphere	Left/right	14/5
Surgical treatment	Bypass with proximal occlusion	8
	Bypass with distal occlusion	5
	Bypass with trapping	2
	Only bypass	2
	Only proximal occlusion	2

Table 1 Patient and aneurysm characteristics

SD standard deviation, *GIA* giant intracranial aneurysm, *AcomA* anterior communicating artery, *ICA* internal carotid artery, *MCA* middle cerebral artery

2.5 Discussion

2.5.1 Quantification of GIA

Our analysis of 69 unruptured GIA showed that diameter and volume measurements are not interchangeable modes of GIA quantification.

When pooled by their vessel of origin, ranking GIA by their median size produced different orders depending on the mode of measurement. We explain this discrepancy by a location-dependent difference in GIA shape. Similar to a recently published article about the morphology of GIA we found that the majority of anterior circulation GIA in our cohort was saccular in shape (77%) while posterior circulation GIA were mostly fusiform (62%).[25] In fact, a correlation between both modes of measurement was only found in GIA of the

anterior circulation with predominantly saccular shape while there was no correlation in posterior circulation GIA with mostly fusiform shape. These findings suggest that adding data on GIA shape may be crucial for an interpretation of GIA quantification.

Another important result of our study is that we did not find any association between GIA size and the patients' clinical condition, independent of the mode of measurement. Only GIA location was associated with neurological deficits. Similar to findings in non-giant IA, GIA of the posterior circulation showed significantly higher mRS scores than those at other locations.[2] Our data suggest that the idea of distinguishing different sizes of GIA may be clinically less relevant than examining their location, shape or mass effect.

Nevertheless, a main advantage of measuring a lesion in three dimensions, as it is being done when using volumetry, is that this generates data from the entire body allowing to keep track of lesions with irregular shapes that contain areas which grow more actively than others. A superior prognostic value of volumetry over measuring diameter was shown to be present in brain tumor volumetry.[26,27] With increasing availability of appropriate software, aneurysm volumetry may become part of clinical routine in the future.

2.5.2 PAE and PT in GIA

Although GIA volume didn't prove to be relevant for the patients' pre-therapeutic clinical condition, we found that GIA volume was a significant risk factor for the occurrence of PAE. Furthermore, GIA volume correlated with PAE size. These results are in line with previous reports that describe that mass effects caused by GIA reduce perfusion of surrounding brain parenchyma and thereby cause PAE.[9] A compression of the venous system surrounding the GIA may play a role here. In Stroke patients the compression of major veins was shown to favor edema formation.[28] One may speculate that the relatively high prevalence of PAE in GIA of the MCA may be due to the fact that at this specific location major veins within the sylvian fissure, which drain blood from the temporal and frontal lobes, may be compressed.

Another interesting finding is that in GIA of the cavernous ICA we found no PAE at all, although those GIA also caused substantial mass effect on the brain. Therefore, mass

effect or GIA thrombosis may not be the only risk factors for PAE formation. Since GIA of the cavernous ICA were the only GIA in our study that were separated from the brain parenchyma by the dura mater, the dura mater may play a relevant role in protecting the brain from PAE. In intracerebral hemorrhage metabolic factors like thrombin and degradation products of hemoglobin secreted from thrombosed parts of the hemorrhage are known to contribute to perihematomal edema formation.[11] Although this concept might not be completely transferable to GIA, the thrombus within the GIA may also secrete factors inducing PAE. While at all other GIA locations in our study, those factors were able to directly diffuse into the neighboring brain tissue, the dura mater may have acted as a protective layer that prevented such processes. This theory is especially relevant since we were able to identify PT as one of the main risk factors for PAE formation. PT was observed in almost all GIA with PAE and only in about half of GIA without PAE. Again, even though a large part of GIA of the cavernous ICA displayed PT, such thrombus did not seem to have an effect on PAE formation.

In contrast to our assumption that PAE might aggravate the patients' clinical condition, we found no association between the occurrence of PAE and clinical findings. However, since our patient cohort consisted mostly of patients at initial diagnosis one may speculate that PAE may become more clinically relevant as the disease progresses as well as in post-treatment morbidity. PAE may therefore serve as a radiological marker of treatment success over time.

2.5.3 Changes in GIA volume and mass effect after surgical treatment

Our study is the first to show that GIA volume can decrease over time after surgical treatment in cases in which no direct GIA clipping is conducted. In addition, we were able to demonstrate that a decrease in GIA volume over time leads to a decrease in mass effect on the brain.

These findings are important since there is an ongoing discussion on whether GIA have the ability to shrink over time when not directly clipped.[15] By choosing an indirect surgical strategy, as done in our study, the therapist seeks to alter blood flow patterns in a way that allows for new thrombotic processes within the GIA lumen. If such new thrombus then persists over time, natural degradation of parts of the GIA may be initiated, resulting

in decreasing GIA size and mass effect on the brain. Our study was able to show that a decrease in mass effect leads to an enlargement of the formerly compressed lateral ventricles and a reduction of MLS.

Our results demonstrate a direct correlation between a decrease in GIA volume and an increase in ipsilateral LVV. In contrast, the decrease in GIA volume did not correlate with changes in MLS. This may be explained by the fact that GIA shrinkage usually takes place near the lateral border of the lateral ventricle. The LVV may therefore be affected substantially sooner than the midline of the brain and a displacement of the septum pellucidum may only be observed at a far later stage of the disease. Our findings therefore suggest that monitoring postoperative changes in GIA mass effect may be more exact than using the traditional method of describing changes in MLS.

Another advantage of measuring changes in LVV after GIA treatment is that the LVV is usually measurable without being confounded by implant artifacts on MRI. In contrast, if one attempts to directly measure the volume of the GIA itself, there may be relevant artifacts especially on MRI after surgical or endovascular treatment preventing an exact quantification of the treated GIA.

2.5.4 Study limitations

There are certain limitations to our analyses. First of all, case inclusion was not consecutive since we were only able to include those cases from the GIA registry with available MRI data. The number of cases in our studies (n=69 and n=19) may be viewed as rather limited. Due to this limitation we were not able to assess which specific surgical strategy was most effective in reducing GIA volume over time. However, as GIA are a rare phenomenon a multi-center approach was necessary to gather even the limited amount of cases presented here. Furthermore, because of the multi-center study design MRI slice thickness was not standardized resulting in measurements being more precise in some cases than in others.

2.5.5 Conclusion

The above summarized articles improve our understanding of the diagnostic value of GIA quantification, the occurrence and risk factors of PAE and PT in GIA and the effect of indirect surgical strategies on changes in GIA volume and mass effect on the brain.

We conclude that the idea of distinguishing different sizes of GIA, whether by volume or diameter, may be clinically less relevant than in smaller aneurysms. Decision making on GIA treatment should therefore also consider characteristics such as GIA location, shape and mass effect. However, GIA volume as well as GIA location and PT have a distinct influence on the occurrence of PAE. Since cavernous ICA aneurysms showed no PAE in our patient cohort we speculate that a direct contact between a thrombosed GIA and the brain parenchyma might be decisive for PAE formation. Finally, we conclude that GIA can significantly decrease in size over time after changing the pattern of blood flow within or around a GIA by indirect surgical techniques whenever direct clipping is not possible. The resulting decrease in mass effect reduces stress on neighboring brain structures.

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3 Affidavit

I, Nicolai Maldaner certify under penalty of perjury by my own signature that I have submitted the thesis on the topic “New developments in giant intracranial aneurysm diagnostics”. I wrote this thesis independently and without assistance from third parties, I used no other aids than the listed sources and resources.

All points based literally or in spirit on publications or presentations of other authors are, as such, in proper citations (see "uniform requirements for manuscripts (URM)" the ICMJE www.icmje.org) indicated. The sections on methodology (in particular practical work, laboratory requirements, statistical processing) and results (in particular images, graphics and tables) correspond to the URM (s.o) and are answered by me. My contributions in the selected publications for this dissertation correspond to those that are specified in the following joint declaration with the responsible person and supervisor. All publications resulting from this thesis and which I am author of correspond to the URM (see above) and I am solely responsible.

The importance of this affidavit and the criminal consequences of a false affidavit (section 156,161 of the Criminal Code) are known to me and I understand the rights and responsibilities stated therein.

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Date Signature

4 Declaration of own contributions

Nicolai Maldaner had the following share in the following publications:

Publication 1: Maldaner N, Guhl S, Mielke D, Musahl C, Schmidt NO, Wostrack M, Rüfenacht DA, Vajkoczy P, Dengler J; Changes in volume of giant intracranial aneurysms treated by surgical strategies other than direct clipping. Acta Neurochirurgica; 2015
Contribution in detail: participation in the design of the study; communication with participating study group members; patient inclusion into the GIA registry and obtaining patients' written consent; literature review; acquisition of clinical data; measuring GIA and ventricle volume and mid-line shift using the software "iPlan Cranial"; analysis and interpretation of data using "SPSS"; drafting figures and tables for the publication; presentation of preliminary data in internal lab meetings; poster presentation of preliminary data at the 65th DGNC meeting; participation in drafting the article; participation in responding to reviewer comments and revising the article.

Publication 2: Dengler J, Maldaner N, Bijlenga P, Burkhardt JK, Graewe A, Guhl S, Hong B, Hohaus C, Kursumovic A, Mielke D, Schebesch KM, Wostrack M, Rufenacht D, Vajkoczy P, Schmidt NO; Perianeurysmal edema in giant intracranial aneurysms in relation to aneurysm location, size, and partial thrombosis. Journal of Neurosurgery; 2015
Contribution in detail: participation in conception and design; communication with participating study group members; patient inclusion into the GIA registry and obtaining patients' written consent; literature review; acquisition of clinical data; identification and volumetric analysis of perianeurysmal edema, measuring GIA volume and diameter using the software "iPlan Cranial"; identifying partial thrombosis and location of mass effect; calculation of relative perianeurysmal edema volume; participation in analysis and interpretation of data using "SPSS"; presentation of preliminary data in internal lab meetings; participation in drafting the article; critically revising the article.

Publication 3: Dengler J, Maldaner N, Bijlenga P, Burkhardt JK, Graewe A, Guhl S, Nakamura M, Hohaus C, Kursumovic A, Schmidt NO, Schebesch KM, Wostrack M, Vajkoczy P, Mielke D; Quantifying unruptured giant intracranial aneurysms by measuring diameter and volume - a comparative analysis of 69 cases. Acta Neurochirurgica; 2015

Contribution in detail: participation in conception and design; communication with participating study group members; patient inclusion into the GIA registry and obtaining patients' written consent; literature review; acquisition of clinical data; measuring GIA volume and diameter using the software "iPlan Cranial"; identification of GIA origin and GIA shape; location of mass effect; participation in analysis and interpretation of data using "SPSS"; presentation of preliminary data in internal lab meetings; participation in drafting the article; critically revising the article.

Signature, date and stamp of the supervising University teacher

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Signature of the doctoral candidate

5 Print copies of selected publications

Perianeurysmal edema in giant intracranial aneurysms in relation to aneurysm location, size, and partial thrombosis.

https://dx.doi.org/10.3171/2014.10.JNS141560

Quantifying unruptured giant intracranial aneurysms by measuring diameter and volume - a comparative analysis of 69 cases.

https://dx.doi.org/10.1007/s00701-014-2292-5

Changes in volume of giant intracranial aneurysms treated by surgical strategies other than direct clipping.

https://dx.doi.org/10.1007/s00701-015-2448-y

6 Curriculum vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

7 Complete list of publications

Publications

1. Dengler J, Maldaner N, Gläsker S, Endres M, Wagner M, Malzahn U, Heuschmann PU, Vajkoczy. Outcome of Surgical or Endovascular Treatment of Giant Intracranial Aneurysms, with Emphasis on Age, Aneurysm Location, and Unruptured Aneuryms - A Systematic Review and Meta-Analysis. Cerebrovasc Dis. 2016;41(3-4):187-198.

2. Wostrack M, Mielke D, Kato N, Guhl S, Schmidt NO, Maldaner N, Vajkoczy P, Dengler J. Interobserver variability in the characterization of giant intracranial aneurysms with special emphasis on aneurysm diameter and shape. Acta Neurochir (Wien) 2015;157(11):1859–65.

3. Familiari P*/ Maldaner N.*, Kursumovic A, Rath SA, Vajkoczy P, Raco A, Dengler J. Cost Comparison of Surgical and Endovascular Treatment of Unruptured Giant Intracranial Aneurysms. Neurosurgery 2015;77(5),733-41. *shared first author

4. Maldaner N, Guhl S, Mielke D, Musahl C, Schmidt NO, Wostrack M, Rüfenacht DA, Vajkoczy P, Dengler J. Changes in volume of giant intracranial aneurysms treated by surgical strategies other than direct clipping. Acta Neurochir (Wien) 2015;157(7):1117–23.

5. Dengler J, Maldaner N, Bijlenga P, Burkhardt JK, Graewe A, Guhl S, Hong B, Hohaus C, Kursumovic A, Mielke D, Schebesch KM, Wostrack M, Rufenacht D, Vajkoczy P, Schmidt NO. Perianeurysmal edema in giant intracranial aneurysms in relation to aneurysm location, size, and partial thrombosis. J Neurosurg 2015;123(2):446-52.

6. Dengler J, Maldaner N, Bijlenga P, Burkhardt JK, Graewe A, Guhl S, Nakamura M, Hohaus C, Kursumovic A, Schmidt NO, Schebesch KM, Wostrack M, Vajkoczy F, Mielke D. Quantifying unruptured giant intracranial aneurysms by measuring

diameter and volume--a comparative analysis of 69 cases. Acta Neurochir (Wien) 2015;157(3):361–8.

Poster presentations

- 65. Jahrestagung der deutschen Gesellschaft für Neurochirurgie (DGNC), 12.-14. Mai 2014; Poster P170: Changes in lateral ventricle volume in relation to aneurysm volume after surgical therapy of giant intracranial aneurysms. N. Maldaner, S. Guhl, D. Mielke, C. Musahl, N. Schmidt, M. Wostrack, P. Vajkoczy, J. Dengler

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