Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2016;41:187–198
DOI: 10.1159/000443485

Received: May 7, 2015
Accepted: December 14, 2015
Published online: January 15, 2016

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

Julius Dengler[a, b] Nicolai Maldaner[a] Sven Gläsker[i] Matthias Endres[b–e] Martin Wagner[f, g] Uwe Malzahn[f, h] Peter U. Heuschmann[f–h] Peter Vajkoczy[a] on behalf of the Giant Intracranial Aneurysm Study Group

[a]Department of Neurosurgery, [b]Center for Stroke Research Berlin, [c]Department of Neurology, [d]German Center for Cardiovascular Research (DZHK), and [e]German Center for Neurodegenerative Diseases (DZNE), Charité – Universitaetsmedizin Berlin, Berlin, [f]Institute of Clinical Epidemiology and Biometry and [g]Comprehensive Heart Failure Center, University of Würzburg, and [h]Clinical Trial Center Würzburg, University Hospital Würzburg, Würzburg, and [i]Department of Neurosurgery, University Hospital Freiburg, Freiburg, Germany

Key Words
Giant intracranial aneurysm · Endovascular treatment · Surgical aneurysm treatment

Abstract
Background: Designing treatment strategies for unruptured giant intracranial aneurysms (GIA) is difficult as evidence of large clinical trials is lacking. We examined the outcome following surgical or endovascular GIA treatment focusing on patient age, GIA location and unruptured GIA. ***Methods:*** Medline and Embase were searched for studies reporting on GIA treatment outcome published after January 2000. We calculated the proportion of good outcome (PGO) for all included GIA and for unruptured GIA by meta-analysis using a random effects model. ***Results:*** We included 54 studies containing 64 study populations with 1,269 GIA at a median follow-up time (FU-T) of 26.4 months (95% CI 10.8–42.0). PGO was 80.9% (77.4–84.4) in the analysis of all GIA compared to 81.2% (75.3–86.1) in the separate analysis of unruptured GIA. For each year added to patient age, PGO decreased by 0.8%, both for all GIA and unruptured GIA. For all GIA, surgical treatment resulted in a PGO of 80.3% (95% CI 76.0–84.6) compared to 84.2% (78.5–89.8, p = 0.27) after endovascular treatment. In unruptured GIA, PGO was 79.7% (95% CI 71.5–87.8) after surgical treatment and 84.9% (79.1–90.7, p = 0.54) after endovascular treatment. PGO was lower in high quality studies and in studies presenting aggregate instead of individual patient data. In unruptured GIA, the OR for good treatment outcome was 5.2 (95% CI 2.0–13.0) at the internal carotid artery compared to 0.1 (0.1–0.3, p < 0.1) in the posterior circulation. Patient sex, FU-T and prevalence of ruptured GIA were not associated with PGO. ***Conclusions:*** We found that the chances of good outcome after surgical or endovascular GIA treatment mainly depend on patient age and aneurysm location rather than on the type of treatment conducted. Our analysis may inform future research on GIA.

KARGER

© 2016 S. Karger AG, Basel
1015–9770/16/0414–0187$39.50/0

E-Mail karger@karger.com
www.karger.com/ced

Julius Dengler, MD
Department of Neurosurgery
Charité, Campus Virchow Klinikum, Augustenburger Platz 1
DE–13353 Berlin (Germany)
E-Mail julius.dengler@charite.de

Introduction

Increasing intracranial aneurysm (IA) size is one of the main risk factors for aneurysm rupture with subsequent morbidity and mortality [1–5]. Guidelines therefore recommend conservative treatment for unruptured small IA, with cutoffs ranging between 7 and 13 mm in diameter and surgical or endovascular treatment for larger aneurysms [2, 3, 6–8]. Surgical and endovascular treatment have become common for unruptured large IA and are also increasingly conducted in unruptured giant IA (GIA), which are defined as the largest IA with a diameter ≥25 mm and are known for rupture rates exceeding 10% per year [1, 9]. While the treatment of unruptured large IA is widely accepted, the treatment of unruptured GIA remains controversial due to reports on poor outcome and overall cost ineffectiveness [1, 10].

Accurate estimates on surgical or endovascular GIA treatment outcome are difficult to establish mainly due to the low prevalence of the disease since GIA only make up about 2–5% of all IAs [1, 3]. Multicenter prospective approaches have so far only been able to examine GIA treatment outcome as a marginal byproduct of cohorts that predominantly contain data on non-giant IAs [1].

Since GIA are associated with the worst outcome and the highest cost of all IAs, there is a need for robust scientific evidence exclusively focusing on this subgroup of IAs. We conducted a systematic review and meta-analysis of recent literature on surgical or endovascular GIA treatment outcome. The main aim was to examine GIA treatment outcome with emphasis on patient age, GIA location, the type of treatment and unruptured GIA.

Methods

Search Strategy and Selection Criteria

The analysis was designed according to the PRISMA statement [11]. We searched Medline and Embase for studies reporting on outcome of surgical or endovascular GIA treatment. The search was conducted on March 5, 2014, and included studies published between January 2000 and present to reflect the current state of GIA therapy. We used the MeSH term 'intracranial aneurysm*' with subheadings 'therapy', 'surgery', 'mortality' and 'disease management'. We added the following keywords:

- [AND] giant OR fusiform OR saccular OR large OR ruptured OR unruptured OR complex
- [AND] management OR treatment OR endovascular OR surgical OR clip* OR coil* OR stent* OR outcome OR follow-up OR result

The following inclusion criteria were defined. Publications had to be in English. Patients had to be at least 18 years old. If a study also included pediatric patients (<18 years), only data on adult patients were included. Treatment outcome had to be reported for at least 4 IA patients to avoid case reports of anecdotal character. Data on GIA had to be distinguishable from those on non-giant IA. Treatment outcome had to be reported either by using scoring systems such as modified Rankin score (mRS) or Glasgow outcome score (GOS) or by describing the patient's clinical status in sufficient detail for a clear interpretation. We also screened reference lists of included publications and the personal databases of the principal investigators (J.D. and P.V.). If uncertainties occurred regarding the type of data presentation, we contacted the authors and asked them to provide the data in a way that made inclusion possible. If relevant data, for example, treatment outcome or GIA location, were missing for a case, the entire case was excluded from the analysis. Principal reviewers were J.D. and N.M. They independently searched the literature and screened titles and abstracts. In case of disagreement, the details were discussed until an agreement was reached. Both reviewers then conducted a full text screening of all eligible articles.

Data Extraction

Standardized forms were used by both reviewers to extract the following data: name of study author, year of publication, type of study design, time frame in which the study was conducted, total number of patients, number of patients with GIA, patient age and sex, prevalence of ruptured GIA, GIA location, type of treatment, follow-up time (FU-T), number of cases lost to follow-up, type of outcome description (GOS, mRS or no score), number of cases with good or bad outcome and type of data presentation (aggregate or individual).

Study quality was assessed according to the following categories: outcome described by score (1 point) or neurological symptoms (0 points), study design prospective (1 point) or retrospective (0 points), cases lost to follow-up less than 3% (1 point) or more than 3% (0 points). Studies with 3 points were graded high quality, and studies with less than 3 points lower quality.

Good outcome was classified as GOS 4–5 or mRS 0–2 or improvement or no aggravation of clinical symptoms compared to pre-treatment status [12]. GIA location was categorized as internal carotid artery (ICA, including the posterior communicating artery), middle cerebral artery (MCA), anterior cerebral artery (ACA, including the anterior communicating artery) and posterior circulation (including the vertebral, basilar, cerebellar and posterior cerebral arteries). The type of treatment was divided into surgical, endovascular and combined surgical/endovascular. For quality control, a third reviewer (S.G.) also completed the data extraction form for 10 studies randomly selected from the pool of eligible studies.

Statistical Analysis

The primary end point was the proportion of good outcome (PGO) interpreted as probability value and displayed as percentage with corresponding 95% CI. The PGO was calculated as the number of GIA cases with good outcome divided by the total number of included GIA cases. Meta-analysis was conducted using a random effects model including a grand mean for PGO, the deviation of the study's true PGO from the grand mean and the deviation of the study's observed PGO from the study's true PGO (sampling error). Using this model, the mean PGO was estimated by a weighted mean over the single studies with assigned weights as inverse of the sum of within-study variance and estimated hetero-

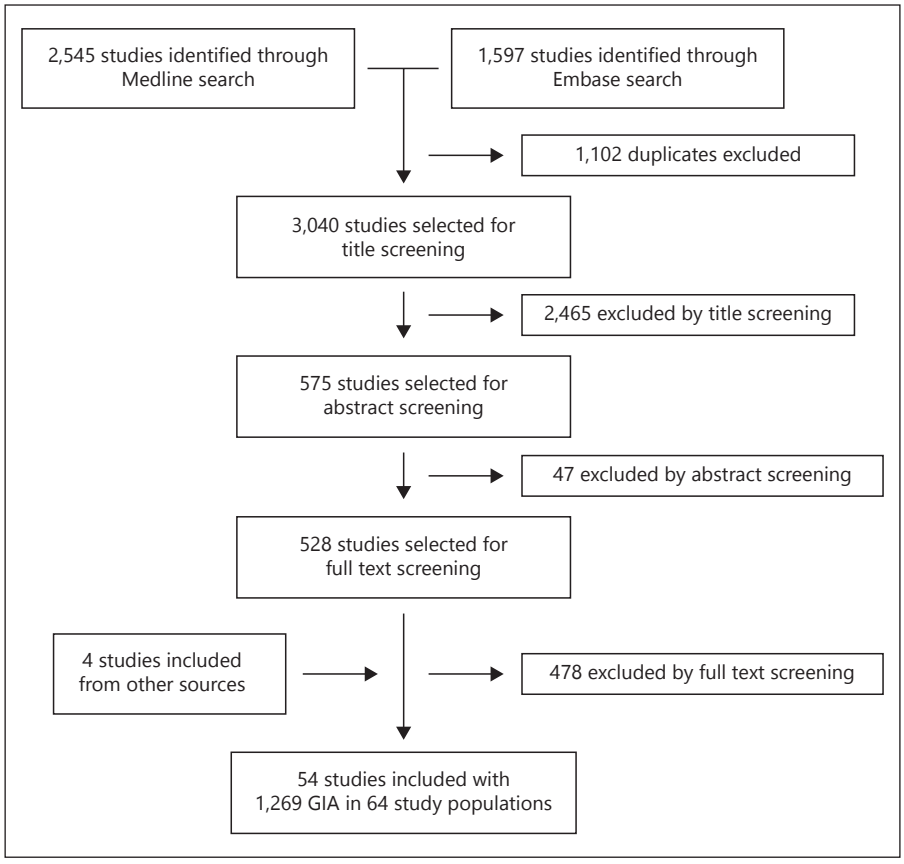

Fig. 1. Literature search.

geneity variance. The variance of the distribution of the deviations of the study's true PGOs from the grand mean was denoted by τ^2 (heterogeneity variance), which was calculated using the DerSimonian method [13]. The heterogeneity of proportions was analyzed using a Q-statistic test, measuring weighted squared deviations. We used the I^2-statistic to estimate the proportion of the observed variance in PGO. Sub-group meta-analyses were conducted for the following categories: patient age and sex, type of treatment, study quality, type of outcome description, mean FU-T (shorter than or equal to and longer than the median of all mean FU-Ts), prevalence of ruptured GIA (0, <33.3 or ≥33.3%) and type of patient data presentation (aggregate or individual). Meta-regression was conducted to explore the heterogeneity of PGO in more detail and adjust PGO by including mean age as covariate for 4 models using patient sex, type of treatment, prevalence of ruptured GIA and the type of patient data presentation as factors.

For the separate evaluation of individual patient data, we used univariate cross table analysis and subsequent hierarchical logistic regression analysis to examine the relationship between the odds for good outcome and the variables GIA location, patient age and type of treatment. Patient age was divided into 4 quartiles: <45, 45–54, 55–63, and >63 years. We used multilevel models with the covariates patient age and type of treatment to calculate adjusted OR for good outcome for each GIA location taking into account clustering of patients within different study populations. We applied a mixed effects model including the random study effect as a G-side effect.

Since outcome data for ruptured and unruptured GIA were not separable in all studies, we used 3 different approaches for data analysis. The first approach examined the PGO for the entire data stock by meta-analysis, including both ruptured and unruptured GIA. The second approach exclusively examined unruptured GIA presented as aggregate or individual patient data, again using meta-analysis. For this, we excluded all ruptured GIA cases from studies presenting individual patient data and all studies presenting aggregate patient data that did not differentiate between outcome data for ruptured and unruptured GIA. The third approach exclusively analyzed unruptured GIA presented as individual patient data applying hierarchical logistic regression within a multilevel model.

For statistical analysis, we used SAS 9.2 (SAS Institute Inc., Cary, N.C., USA) and OpenMeta[Analyst] for Windows 7 (Brown University, Providence, R.I., USA) [14].

Results

The inclusion criteria were met by 54 studies with 64 study populations and 1,269 GIA (fig. 1) [1, 15–67]. Patient data description was aggregate in 15 study populations (854 GIA) [1, 15–26] and individual in 49 study populations (415 GIA) [27–67]. Table 1 displays the

Table 1. Characteristics of 54 studies reporting on GIA treatment outcome

Study	Mid-year of study	Study design	Type of treatment	Number of GIA included	Sex, female, %	Mean age, years	Reported on:	
							prevalence of ruptured GIA	individual patient data
ISUIA [1]	1995	P	S/E	124	N/A	54.5	Yes	No
Nanda et al. [15]	2000	R	S	57	71	50.6	Yes	No
Sughrue et al. [16]	2003	R	S	140	64	54.0	Yes	No
Kolasa et al. [17]	1997	R	S/E	20	85	50.0	No	No
Sharma et al. [18]	2001	R	S	177	N/A	N/A	Yes	No
Lozier et al. [19]	1993	P	S	16	63	54.9	Yes	No
Osawa et al. [20]	1993	R	S	12	N/A	N/A	Yes	No
Qi et al. [21]	2001	R	S	155	48	39.3	Yes	No
Li et al. [22]	2007	R	S	4	N/A	No	No	No
Cantore et al. [23]	1997	R	S	99	55	48.0	Yes	No
Nakase et al. [24]	1999	R	S	26	88	54.5	Yes	No
Romani et al. [25]	2002	R	S	8	N/A	N/A	No	No
Orz et al. [26]	1991	R	S	16	N/A	N/A	Yes	No
Jahromi et al. [27]	2004	P	E	39	77	60.9	Yes	Yes
Lubicz et al. [28]	1997	R	E	12	25	50.8	Yes	Yes
Li et al. [29]	2001	R	E	16	56	48.1	Yes	Yes
Ciceri et al. [30]	1995	R	E	4	50	48.0	Yes	Yes
Uda et al. [31]	1994	R	E	4	67	53.5	Yes	Yes
Kalani et al. [32]	1997	R	S/C	12	27	43.7	Yes	Yes
Hauck et al. [33]	2004	R	E	10	80	62.1	Yes	Yes
de Barros et al. [34]	2008	R	E	6	14	58.9	Yes	Yes
Ha and Jang [35]	2004	R	E	9	78	59.2	Yes	Yes
Waldron et al. [36]	2004	R	S	6	33	59.2	Yes	Yes
Seo et al. [37]	2002	R	S	4	25	36.5	Yes	Yes
Sluzewski et al. [38]	1997	R	E	13	56	52.4	Yes	Yes
Zhang et al. [39]	1998	P	S	7	57	52.9	Yes	Yes
Sekhar et al. [40]	1997	R	S	8	88	56.5	Yes	Yes
Raphaeli et al. [41]	2007	R	E	5	40	58.0	Yes	Yes
Biondi et al. [42]	2001	R	E	6	67	43.3	Yes	Yes
Meckel et al. [43]	2010	R	E	8	63	55.1	Yes	Yes
Lubicz et al. [44]	2009	P	E	4	75	61.5	Yes	Yes
Iihara et al. [45]	2003	R	S/E/C	9	30	52.2	Yes	Yes
Clarençon et al. [46]	2002	R	E	12	29	43.1	Yes	Yes
Siddiqui et al. [47]	2010	R	E	7	43	55.4	Yes	Yes
Nakajima et al. [48]	2007	R	S	11	64	47.5	Yes	Yes
Skrap et al. [49]	2005	R	S	15	80	51.6	Yes	Yes
Kubo et al. [50]	2000	R	S	11	91	60.2	Yes	Yes
Miyamoto et al. [51]	2006	R	S/C	6	50	45.7	Yes	Yes
Lownie et al. [52]	1985	R	S/E	13	21	52.8	Yes	Yes
Van Doormaal et al. [53]	2001	R	S	32	75	54.1	Yes	Yes
Nakajima et al. [54]	2007	R	S	5	40	55.4	Yes	Yes
Lv et al. [55]	2006	R	E	32	68	48.5	Yes	Yes
Pumar et al. [56]	2009	R	E	6	N/A	N/A	Yes	Yes
Velat et al. [57]	1999	P	S	6	91	62.8	Yes	Yes
Biondi et al. [58]	2003	R	E	4	50	55.5	Yes	Yes
Kellner et al. [59]	1998	R	S	6	67	43.5	Yes	Yes
Kalani et al. [60]	2002	R	S/C	8	13	52.6	Yes	Yes
Lubicz et al. [61]	1997	R	E	17	59	40.0	Yes	Yes
Ponce et al. [62]	2000	R	S	8	44	61.3	Yes	Yes
Shi et al. [63]	1998	R	C/E	9	22	56.4	Yes	Yes
Ewald et al. [64]	N/A	R	S/C	8	N/A	N/A	Yes	Yes
Hallacq et al. [65]	1994	R	E	5	40	43.6	Yes	Yes
Tan et al. [66]	2006	R	E	5	20	48.4	Yes	Yes
Weber et al. [67]	2002	R	E	7	100	50.6	Yes	Yes

P = Prospective; R = retrospective; S = surgical; E = endovascular; C = combined; N/A = not available.

study characteristics. We included 27 study populations with endovascular treatment (297 GIA) [1, 17, 27–31, 33–35, 38, 41–47, 52, 55, 56, 58, 61, 63, 65–67], 31 study populations with surgical treatment (955 GIA) [1, 15–26, 32, 36, 37, 39, 40, 45, 48–54, 57, 59, 60, 62, 64] and 6 study populations with combined treatment (17 GIA) [32, 45, 51, 60, 63, 64]. The patients' clinical status was measured by GOS in 26 study populations (844 GIA) [15–18, 20–22, 37–41], by mRS in 25 study populations (217 GIA) [1, 19, 42–60] and by description of neurological symptoms in 13 study populations (208 GIA) [23–26, 61–67]. Data of 6 study populations (190 GIA) were rated high quality [1, 19, 27, 39, 44] while those of the remaining 58 study cohorts (1,079 GIA) were rated lower quality. Information on whether GIA were ruptured or unruptured was available in 60 study populations (1,202 GIA) [1, 15, 16, 18–21, 23, 24, 26–67]. The prevalence of ruptured GIA was ≥33.3% in 15 study populations (511 GIA) [15, 18, 20, 21, 28, 31, 34–38, 42, 52, 53, 57], <33.3% in 18 study populations (396 GIA) [16, 19, 23, 27, 29, 32, 39, 43, 48, 50, 51, 55, 58, 61, 63–66] and 0% in 27 study populations (295 GIA) [1, 24, 26, 30, 32, 33, 40, 41, 44–47, 49, 51, 52, 54, 56, 59, 60, 62–64, 67]. The weighted median FU-T was 26.4 months (95% CI 10.8–42.0).

Overall PGO for all GIA of all study populations was 80.9% (95% CI 77.4–84.4) (fig. 2). There was a significant association between PGO and patient age ($p < 0.01$). For any year added to mean patient age, PGO decreased by 0.8%. This relationship existed in all 3 treatment groups. We adjusted all further analyses for patient age. Table 2 displays the PGO for the type of treatment, study quality, type of outcome description, FU-T, type of patient data description and prevalence of ruptured GIA.

With the surgical study populations as the reference group, there was no significant difference in PGO between surgical (80.3%, 95% CI 76.0–84.6) and endovascular study populations (84.2%, 95% CI 78.5–89.8, $p = 0.27$). The PGO for combined treatment study populations differed significantly (49.9%, 95% CI 28.4–71.5%, $p = 0.01$). However, the total number of patients with combined treatment was comparably low ($n = 17$).

When high quality study populations were defined as the reference group, their PGO (70.0%, 95% CI 60.9–79.2) was significantly lower than that of studies of lower quality (83.6%, 95% CI 77.7–90.0, $p = 0.01$). We also identified a significant difference in PGO depending on whether results were presented as aggregate patient data (75.3%, 95% CI 69.3–81.3) or as individual patient data (83.8, 95% CI 79.6–88.1, $p < 0.01$). PGO was not associated with patient sex, type of outcome description, FU-T or prevalence of ruptured GIA. We found substantial overall heterogeneity ($I^2 = 48\%$) in the analysis of PGO, which suggests relevant differences in study populations. For the separate analysis of treatment outcome of unruptured GIA, we included 455 unruptured GIA from 51 study populations [1, 22, 27–67], presented as aggregate patient data in 3 study populations (128 GIA) [1, 22] and as individual patient data in 48 study populations (327 GIA) [27–67]. Endovascular treatment was conducted in 26 study populations (246 GIA) [1, 27–31, 33–35, 38, 41–47, 52, 55, 56, 58, 61, 63, 65–67], surgical treatment in 20 study populations (196 GIA) [1, 22, 32, 36, 37, 39, 40, 45, 48–54, 57, 59, 60, 62, 64] and combined treatment in 5 study populations (13 GIA) [32, 45, 51, 60, 63]. For all unruptured GIA taken together, the PGO was 81.2% (95% CI 75.3–86.1). Patient age was significantly associated with PGO, which decreased by 0.8% per year added to patient age ($p = 0.01$). Table 2 displays the PGO for unruptured GIA. After adjusting for patient age, we identified no difference in PGO between surgical (79.7%, 95% CI 71.5–87.8, reference group) and endovascular study populations (84.9%, 95% CI 79.1–90.7, $p = 0.54$). For the small group of unruptured GIA with combined treatment (13 GIA), PGO was significantly lower (50.3%, 95% CI 25.6–75.0, $p = 0.02$). High quality study populations displayed lower PGO (68.1%, 95% CI 58.7–77.4) than study populations of lower quality (84.3%, 95% CI 76.5–92.8, $p = 0 \cdot 01$). We also found lower PGO in study populations with aggregate patient data (62.5%, 95% CI 54.2–70.9) than in study populations with individual patient data (84.1%, 95% CI 79.7–88.7, $p < 0.01$). There was no association between PGO and patient sex, type of outcome description or FU-T.

To examine the PGO of unruptured GIA in more detail, we conducted an analysis of only individual patient data on unruptured GIA. For this, we included 324 unruptured GIA from 48 study populations [27–67]. Treatment was endovascular in 192 GIA (25 study populations) [27–31, 33–35, 38, 41–47, 52, 55, 56, 58, 61, 63, 65–67], surgical in 119 GIA (18 study populations) [32, 36, 37, 39, 40, 45, 48–54, 57, 59, 60, 62, 64] and combined in 13 GIA (5 study populations) [32, 45, 51, 60, 63, 64]. Median FU-T was 16.0 months (95% CI 14.0–20.0). One hundred fifty-three unruptured GIA (47.2%) were located at the ICA, 43 (13.3%) at the MCA, 17 (5.2%) at the ACA and 111 (34.3%) in the posterior circulation. The distribution of the types of GIA treatment (endovascular/surgical/combined) was 68.5/31.5/0% at the ICA, 12.8/71.8/15.4% at the MCA, 31.3/68.7/0% at the ACA and 66.0/27.4/6.6% in the posterior circulation. Table 3

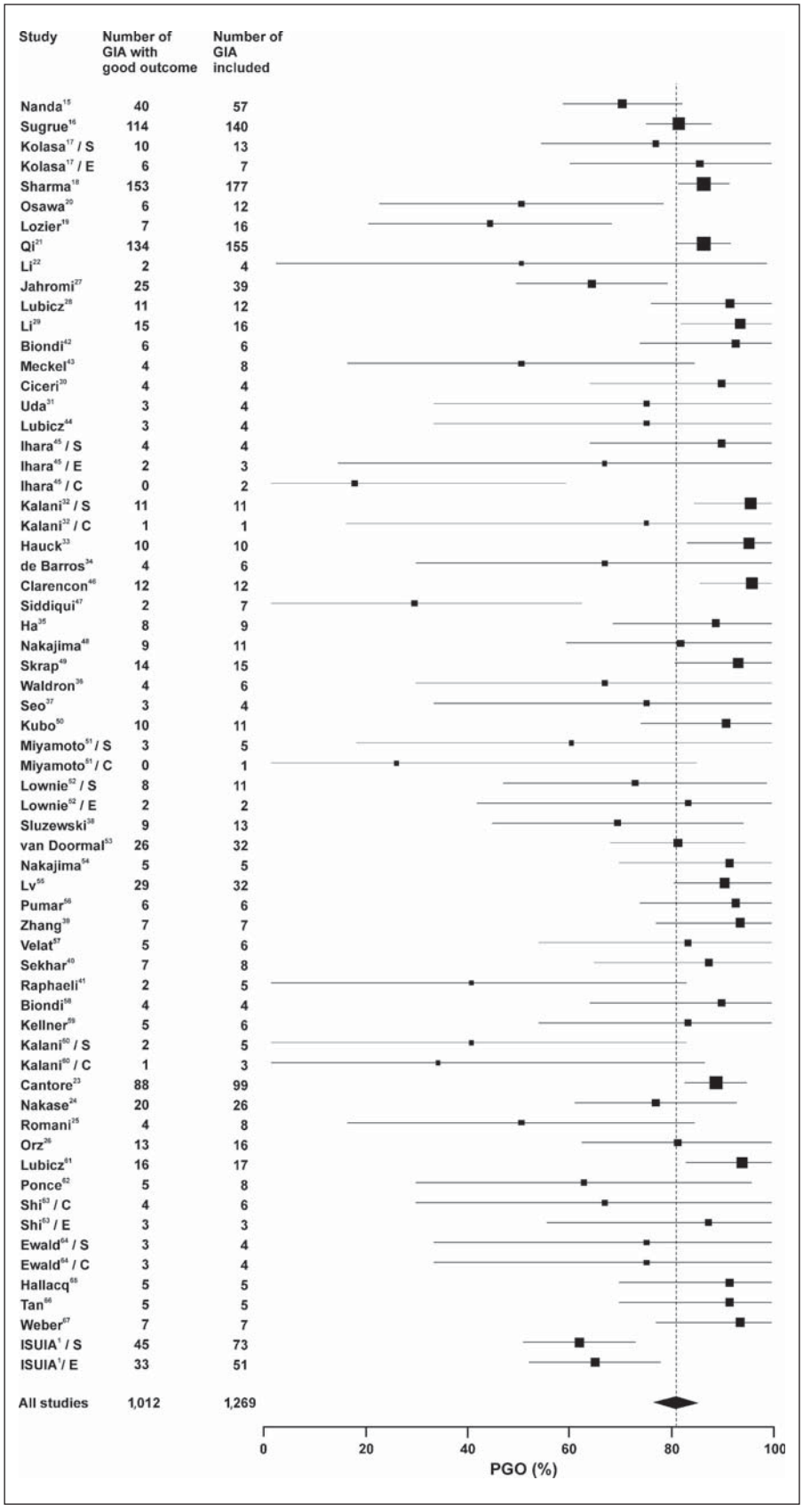

Fig. 2. PGO of all study cohorts. S = Surgical treatment; E = endovascular treatment; C = combined treatment.

Table 2. PGO for all 64 study populations and for unruptured GIA

	All GIA (64 study populations, 1,269 GIA)		Unruptured GIA (51 study populations, 455 GIA)	
	PGO	p value	PGO	p value
Entire study cohort	80.9 (77.4–84.4)	–	81.2 (75.3–86.1)	–
Type of treatment				
Surgical treatment	80.3 (76.0–84.6)	ref.	79.7 (71.5–87.8)	ref.
Endovascular treatment	84.2 (78.5–89.8)	0.27	84.9 (79.1–90.7)	0.54
Combined treatment	49.9 (28.4–71.5)	0.01	50.3 (25.6–75.0)	0.02
Study quality				
High	70.0 (60.9–79.2)	ref.	68.1 (58.7–77.4)	ref.
Lower	83.6 (77.7–90.0)	0.01	84.3 (76.5–92.8)	0.01
Outcome described by				
GOS	83.2 (78.8–87.6)	ref.	81.0 (73.0–89.0)	ref.
mRS	77.6 (70.0–85.2)	0.40	78.8 (70.7–86.8)	0.50
Neurological symptoms	86.8 (81.8–91.7)	0.34	91.5 (84.7–98.4)	0.86
FU-T				
<Median FU-T	80.2 (73.9–86.5)	ref.	80.0 (72.6–87.5)	ref.
≥Median FU-T	86.8 (82.6–91.1)	0.26	84.1 (76.8–91.4)	0.52
Patient data presentation				
Aggregate	75.3 (69.3–81.3)	ref.	62.5 (54.2–70.9)	ref.
Individual	83.8 (79.6–88.1)	<0.01	84.1 (79.7–88.7)	<0.01
Prevalence of ruptured GIA, %				
0	79.6 (72.1–87.1)	ref.		
<33	84.9 (79.4–90.4)	0.29		
≥33	82.4 (77.7–87.0)	0.18		

Data are adjusted for mean patient age and presented in % with 95% CI. FU-T = Follow-up time; ref. = reference group.

Table 3. PGO and OR for good outcome after treatment of unruptured GIA with individually described patient data

	PGO	OR (95% CI)	p value
Type of treatment			
Endovascular (192 GIA)	84.4	ref.	0.16
Surgical (119 GIA)	80.7	0.55 (0.12–2.04)	
Combined (13 GIA)	53.8	0.07 (0.01–1.53)	
GIA location			
ICA (including PcomA; 153 GIA)	92.8	ref.	<0.01
ACA (including AcomA; 17 GIA)	82.4	0.41 (0.07–2.62)	
MCA (43 GIA)	83.7	0.85 (0.19–3.87)	
Posterior circulation (111 GIA)	65.8	0.12 (0.05–0.31)	
Patient age, years			
<45 (81 GIA)	90.4	ref.	0.03
45–54 (81 GIA)	85.3	0.62 (0.21–1.83)	
55–63 (81 GIA)	81.3	0.45 (0.16–1.27)	
>63 (81 GIA)	68.5	0.22 (0.08–0.62)	

We included 324 GIA from 48 study populations in this analysis [27–67]. PGO is given as mean %. OR are presented with 95% CI and p value. PcomA = Posterior communicating artery; ref. = reference.

Table 4. OR for good outcome after treatment of unruptured GIA for each GIA location with all other GIA locations as reference group

GIA location	OR (95% CI)	p value
ICA (including PcomA; 153 GIA)	5.15 (2.04–13.00)	<0.01
ACA (including AcomA; 17 GIA)	1.10 (0.07–18.48)	0.92
MCA (43 GIA)	2.28 (0.34–15.31)	0.30
Posterior circulation (111 GIA)	0.14 (0.06–0.33)	<0.01

In this sub-analysis of unruptured GIA with individually described patient data we included 324 GIA from 48 study populations [27–67]. Data are presented with 95% CI and p value. PcomA = Posterior communicating artery.

displays the PGO and OR for good outcome for the type of GIA treatment, GIA location and patient age. Both PGO and OR for good outcome were significantly lower for unruptured GIA in the posterior circulation than for those of all other locations ($p < 0.01$). Again, we found an association between patient age and PGO ($p = 0.03$). After adjusting for patient age and the location of unruptured GIA, there was no difference in PGO between surgical (80.7%, 95% CI 72.9–89.3, reference group), endovascular (84.4%, 95% CI 78.6–90.1) or combined treatment study populations (53.8%, 95% CI 22.5–75.0, $p = 0.16$). To establish OR for good treatment outcome for all locations of unruptured GIA rather than using the ICA as the reference group, we repeated the same model with all other locations of unruptured GIA as the reference group (table 4).

Discussion

Our systematic review and meta-analysis found that the chances of good outcome after surgical or endovascular GIA treatment mainly depend on patient age and GIA location rather than on the type of treatment conducted. Overall PGO ranged above 80%, both for endovascular and surgical study populations. The chances of good outcome following endovascular or surgical GIA treatment decreased with increasing patient age in all GIA and in the subgroup of unruptured GIA. Unruptured GIA of the ICA were more likely to show good treatment outcome than unruptured GIA in the posterior circulation. These findings are in line with data on unruptured non-giant IA [1].

Furthermore, we found that GIA treatment outcome was not influenced by patient sex, the time of follow-up or whether the patients' clinical status was presented based on scores or not. Also, there was no association between pre-treatment aneurysm rupture and GIA treatment outcome. This contradicts findings on non-giant IA [4]. A possible explanation may be that our analysis only included those ruptured GIA that underwent either endovascular or surgical treatment. This means that there are no data on patients with a ruptured GIA that were in too poor of a clinical condition to receive any sort of treatment. It is therefore highly likely that the subgroup of ruptured GIA in our analysis is selected for those patients in relatively good neurological condition and, therefore, may not represent the full spectrum of patients with ruptured GIA.

Our analysis also included a small cohort of unruptured GIA with combined surgical/endovascular treatment ($n = 13$). In this group, treatment outcome was significantly worse. However, these results have to be discussed with caution due to this group's comparably limited case number. Nevertheless, lower chances of good outcome after combined GIA treatment may also indicate that those cases were more complex and that the initial treatment, be it surgical or endovascular, may not have been successful or may have produced complications making a second type of intervention necessary.

GIA treatment outcome was also influenced by certain study characteristics, such as the type of data presentation and study quality. In studies presenting individual patient data, treatment outcome was significantly better than in studies presenting aggregate patient data. This disparity was more pronounced in the analysis of unruptured GIA. Furthermore, studies of lower quality reported significantly better treatment outcome than high quality studies. Since the majority of studies in our analysis was of lower quality, our overall findings may be biased toward a better treatment outcome. This becomes especially evident when comparing our overall results to those of the International Study of Unruptured Intracranial Aneurysms (ISUIA), which is the largest prospective study presenting data on unruptured GIA treatment outcome [1]. We were able to include recently updated ISUIA data after a mean FU-T of 10 years. ISUIA reached a good treatment outcome in 64.7% of GIA after endovascular and 61.6% of GIA after surgical treatment. Apart from ISUIA's relatively high study quality another potential explanation for ISUIA's outcome results ranging below our overall results may be our analysis' shorter mean FU-T of 16 months.

Our analysis is the first to systematically evaluate the current interdisciplinary GIA literature. Nevertheless, it has limitations. The quality of the included studies was predominantly low as all of them were purely observational and non-randomized. Only few studies were of prospective design [1, 19, 27, 39, 44, 57]. Study design-dependent selection bias can therefore not be ruled out. Furthermore, there was substantial variance and heterogeneity in the included studies, which also suggests that our results should be discussed with caution. Additionally, since studies reporting better outcome were shown to be more likely to be published, some publication bias may also confound our overall results [68]. Another limitation is that we allowed different modes of outcome measurement. Even though we found that treatment outcome did not differ between score-based and non–score-based outcome quantification, we cannot exclude that the type of outcome description may have influenced our results. Finally, as all meta-analyses are limited by their search terms, so is ours. Our meta-analysis could have applied more specific search terms describing both surgical and endovascular techniques of treatment.

Conclusions

In light of the dismal natural history of unruptured GIA, the results of our analysis may help elucidate the controversial field of endovascular and surgical GIA treatment and may therefore be of interest for the ongoing discussion on how to treat unruptured GIA. Our findings support the view that when deciding which type of GIA treatment to conduct each case should be discussed interdisciplinarily with special focus on patient age and GIA location. Since our analysis showed that high quality clinical trial evidence on GIA treatment outcome is lacking, we feel that there is a need for a systematic multicenter approach to collect not only clinical but also imaging data on GIA. As a first step toward this goal, the currently ongoing GIA registry was established as an international prospective and retrospective observational trial aiming to serve as a platform for future GIA research [69–71].

Acknowledgments

The authors thank James C. Torner and Robert D. Brown Jr. for providing updated results from ISUIA.

Funding Sources

The establishment of the GIA group has received funding from the German Federal Ministry of Education and Research via a grant from the Center for Stroke Research Berlin (01 E0 0801). None of the grant providers participated in study design, data collection, data analysis, data interpretation or writing the report.

Disclosure Statement

J.D. has received a research grant from the German Federal Ministry of Education and Research via a grant from the Center for Stroke Research Berlin. P.V. has received personal fees from Brainlab and Ulrich medical. M.E. has received research grants from the German Federal Ministry of Education and Research, the German Research Foundation, the European Union, Volkswagen Foundation, Corona Foundation, Bayer, AstraZeneca and Roche, and has received personal fees from Bayer, Pfizer, BMS, Sanofi, MSD, AstraZeneca, Boston Scientific, Ever, Novartis, GSK and the German Center for Neurodegenerative Diseases. N.M., S.G., M.W., U.M. and P.U.H. declare no conflict of interest.

Statements of Authorship

Study design: J.D., M.W., U.M., P.U.H., P.V. Data aquisition: J.D., N.M., S.G. Data analysis: J.D., M.W., U.M., P.U.H. Drafting the manuscript: J.D., U.M., P.U.H., M.E., P.V. Revising the manuscript: all authors.

Giant Intracranial Aneurysm Study Group Members

P. Vajkoczy, N. Maldaner, A. Uebelacker, J. Dengler : *Department of Neurosurgery, Charité – Universitaetsmedizin Berlin*; M. Endres: *Department of Neurology, Charité – Universitaetsmedizin Berlin, Germany*; G. Bohner, E. Wiener, H.C. Bauknecht: *Department of Neuroradiology, Charité – Universitaetsmedizin Berlin, Germany;* P.U. Heuschmann, U. Malzahn: *Institute of Clinical Epidemiology and Biometry, University of Würzburg, Germany*; S.Gläsker, J. Zentner, V. Van Velthoven: *Department of Neurosurgery, University Hospital Freiburg, Germany*; S. Guhl, H.W.S. Schroeder: *Department of Neurosurgery, University of Greifswald, Germany*; M. Strowitzki: *Department of Neurosurgery, Trauma Center Murnau, Murnau, Germany*; N. Etminan, D. Haengghi, S. Eicker, B. Turowski: *Department of Neurosurgery, University of Düsseldorf, Germany*; K.M. Schebesch, A. Brawanski: *Department of Neurosurgery, University of Regensburg, Germany*; K. Wrede, U. Sure: *Department of Neurosurgery, University of Essen, Germany*; N.O. Schmidt, J. Regelsberger, M. Westphal: *Department of Neurosurgery, University Medical Center, Hamburg Eppendorf, Germany*; D. Mielke, V. Rohde: *Department of Neurosurgery, Georg-August-University Goettingen, Germany*; H. Hosch, D. Moskopp: *Department of Neurosurgery Vivantes-Klinikum im Friedrichshain, Berlin, Germany*; A. Joedicke: *Department of Neurosurgery Vivantes-Klinikum Neukoelln, Berlin, Germany*; C. Hohaus, H.J. Meisel: *Department of Neurosurgery, BG-Clinic*

Bergmannstrost, Halle, Germany; M. Wostrack, B. Meyer, J. Lehmberg: *Department of Neurosurgery, Technical University of Munich, Germany*; C. Musahl, N. Hopf: *Department of Neurosurgery, Klinikum Stuttgart, Stuttgart, Germany*; G. Winkler, U. Spetzger: *Department of Neurosurgery, Klinikum Karlsruhe, Germany*; A. Graewe, U. Meier: *Department of Neurosurgery, Unfallkrankenhaus Berlin, Germany*; B. Hong, M. Nakamura, J. Krauss: *Department of Neurosurgery, Hannover Medical School, Hannover, Germany*; A. Grote, M. Simon, J. Schramm: *Department of Neurosurgery, University Hospital Bonn, Bonn, Germany*; A. Kursumovic, S.A. Rath: *Department of Neurosurgery and Interventional Neuroradiology, Donau-Isar-Klinikum, Deggendorf, Germany*; S. Marbacher, A. Fathi, J. Fandino: *Department of Neurosurgery, Kantonsspital Aarau, Aarau, Switzerland*; P. Familiari, A. Raco: *Department of Neurosurgery, University of Rome 'Sapienza', Rome, Italy*; P. Bijlenga, K. Schaller: *Service de Neurochirurgie, Faculté de Médecine de Genève and Hôpitaux Universitaire de Genève, Switzerland*; A. Gruber, W.T. Wang, E. Knosp: *Department of Neurosurgery, Medical University Vienna, Vienna, Austria*; K.T. Hoffmann, E. Boxhammer: *Department of Neuroradiology, University of Leipzig, Leipzig, Germany*; D.A. Rüfenacht, I. Wanke: *Department of Neuroradiology, Klinik Hirslanden, Zurich, Switzerland*; E. Boccardi, M. Piano: *Department of Neuroradiology, Ospedale Niguarda Ca' Granda, Milano, Italy*; M. Niemelä, V. Nurminen, M. Lehecka, J. Hernesniemi: *Department of Neurosurgery, Helsinki University Central Hospital, Helsinki, Finland*; J.K. Burkhardt, O. Bozinov, L. Regli: *Department of Neurosurgery, University Hospital of Zurich, Switzerland*; O.D. Shekhtman, S.S. Eliava: *Burdenko Neurosurgical Institute, Russian Academy of Medical Sciences, Moscow, Russia*; N. Kato, K. Irie, K. Nishimura, S. Kaku, H. Arakawa, I. Yuki, T. Ishibashi, Y. Murayama: *Department of Neurosurgery, Jikei University School of Medicine, Tokyo, Japan*; I. Fiss, T. Kombos: *Department of Spine Surgery and Neurosurgery, Helios Klinikum Hildesheim, Hildesheim, Germany*; M.T. Pedro, R. König, R. Wirtz, C. Brand, V. Hagel: *Department of Neurosurgery, University Hospital of Ulm, Germany*; J. Helthuis, A. van der Zwan, T. van Doormaal: *Department of Neurosurgery, University Medical Center Utrecht, Utrecht, Netherlands*; C. Cognard, M. Gawlitza: *Department of Neuroradiology, Toulouse University Hospital, Toulouse, France*; J. Walter, R. Kalff: *Department of Neurosurgery, University Hospital Jena, Germany*; J. Fiedler: *Department of Neurosurgery, Budweis Hospital, Czech Republic.*

References

1 Wiebers DO, Whisnant JP, Huston J 3rd, Meissner I, Brown RD Jr, Piepgras DG, Forbes GS, Thielen K, Nichols D, O'Fallon WM, Peacock J, Jaeger L, Kassell NF, Kongable-Beckman GL, Torner JC; International Study of Unruptured Intracranial Aneurysms Investigators: Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet 2003;362:103–110.

2 Brown RD Jr, Broderick JP: Unruptured intracranial aneurysms: epidemiology, natural history, management options, and familial screening. Lancet Neurol 2014;13:393–404.

3 Greving JP, Wermer MJ, Brown RD Jr, Morita A, Juvela S, Yonekura M, Ishibashi T, Torner JC, Nakayama T, Rinkel GJ, Algra A: Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. Lancet Neurol 2014;13:59–66.

4 van Gijn J, Kerr RS, Rinkel GJ: Subarachnoid haemorrhage. Lancet 2007;369:306–318.

5 Wermer MJ, van der Schaaf IC, Algra A, Rinkel GJ: Risk of rupture of unruptured intracranial aneurysms in relation to patient and aneurysm characteristics: an updated meta-analysis. Stroke 2007;38:1404–1410.

6 Bederson JB, Awad IA, Wiebers DO, Piepgras D, Haley EC Jr, Brott T, Hademenos G, Chyatte D, Rosenwasser R, Caroselli C: Recommendations for the management of patients with unruptured intracranial aneurysms: a statement for healthcare professionals from the stroke council of the American Heart Association. Stroke 2000;31:2742–2750.

7 Steiner T, Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G; European Stroke Organization: European stroke organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. Cerebrovasc Dis 2013;35:93–112.

8 Etminan N, Beseoglu K, Barrow DL, Bederson J, Brown RD Jr, Connolly ES Jr, Derdeyn CP, Hänggi D, Hasan D, Juvela S, Kasuya H, Kirkpatrick PJ, Knuckey N, Koivisto T, Lanzino G, Lawton MT, LeRoux P, McDougall CG, Mee E, Mocco J, Molyneux A, Morgan MK, Mori K, Morita A, Murayama Y, Nagahiro S, Pasqualin A, Raabe A, Raymond J, Rinkel GJ, Rüfenacht D, Seifert V, Spears J, Steiger HJ, Steinmetz H, Torner JC, Vajkoczy P, Wanke I, Wong GK, Wong JH, Macdonald RL: Multidisciplinary consensus on assessment of unruptured intracranial aneurysms: proposal of an international research group. Stroke 2014;45:1523–1530.

9 Morley TP, Barr HW: Giant intracranial aneurysms: diagnosis, course, and management. Clin Neurosurg 1969;16:73–94.

10 Greving JP, Rinkel GJ, Buskens E, Algra A: Cost-effectiveness of preventive treatment of intracranial aneurysms: new data and uncertainties. Neurology 2009;73:258–265.

11 Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.

12 Weisscher N, Vermeulen M, Roos YB, de Haan RJ: What should be defined as good outcome in stroke trials; a modified Rankin score of 0–1 or 0–2? J Neurol 2008;255:867–874.

13 DerSimonian R, Laird N: Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–188.

14 Wallace BC, Schmid CH, Lau J, Trikalinos TA: Meta-Analyst: software for meta-analysis of binary, continuous and diagnostic data. BMC Med Res Methodol 2009;9:80.

15 Nanda A, Sonig A, Banerjee AD, Javalkar VK: Microsurgical management of giant intracranial aneurysms: a single surgeon experience from Louisiana State University, Shreveport. World Neurosurg 2014;81:752–764.

16 Sughrue ME, Saloner D, Rayz VL, Lawton MT: Giant intracranial aneurysms: evolution of management in a contemporary surgical series. Neurosurgery 2011;69:1261–1270.

17 Kolasa PP, Kaurzel Z, Lewinski A: Treatment of giant paraclinoid aneurysms. Own experience. Neuro Endocrinol Lett 2004;25:287–291.

18 Sharma BS, Gupta A, Ahmad FU, Suri A, Mehta VS: Surgical management of giant intracranial aneurysms. Clin Neurol Neurosurg 2008;110:674–681.

19 Lozier AP, Kim GH, Sciacca RR, Connolly ES Jr, Solomon RA: Microsurgical treatment of basilar apex aneurysms: perioperative and long-term clinical outcome. Neurosurgery 2004;54:286–296.

20 Osawa M, Hongo K, Tanaka Y, Nakamura Y, Kitazawa K, Kobayashi S: Results of direct surgery for aneurysmal subarachnoid haemorrhage: outcome of 2055 patients who underwent direct aneurysm surgery and profile of ruptured intracranial aneurysms. Acta Neurochir (Wien) 2001;143:655–663.

21 Qi W, Wang S, Zhao YL, Yang HB, Zhao JZ: Clinical characteristics and surgical treatment of patients with giant intracranial aneurysms. Chin Med J (Engl) 2008;121:1085–1088.
22 Li J, Lan ZG, Liu Y, He M, You C: Large and giant ventral paraclinoid carotid aneurysms: surgical techniques, complications and outcomes. Clin Neurol Neurosurg 2012;114: 907–913.
23 Cantore G, Santoro A, Guidetti G, Delfinis CP, Colonnese C, Passacantilli E: Surgical treatment of giant intracranial aneurysms: current viewpoint. Neurosurgery 2008;63: 279–289.
24 Nakase H, Shin Y, Kanemoto Y, Ohnishi H, Morimoto T, Sakaki T: Long-term outcome of unruptured giant cerebral aneurysms. Neurol Med Chir (Tokyo) 2006;46:379–384.
25 Romani R, Lehto H, Laakso A, Horcajadas A, Kivisaari R, von und zu Fraunberg M, Niemelä M, Rinne J, Hernesniemi J: Microsurgery for previously coiled aneurysms: experience with 81 patients. Neurosurgery 2011;68:140–153.
26 Orz YI, Hongo K, Tanaka Y, Nagashima H, Osawa M, Kyoshima K, Kobayashi S: Risks of surgery for patients with unruptured intracranial aneurysms. Surg Neurol 2000;53:21–27.
27 Jahromi BS, Mocco J, Bang JA, Gologorsky Y, Siddiqui AH, Horowitz MB, Hopkins LN, Levy EI: Clinical and angiographic outcome after endovascular management of giant intracranial aneurysms. Neurosurgery 2008;63: 662–674; discussion 674–675.
28 Lubicz B, Leclerc X, Gauvrit JY, Lejeune JP, Pruvo JP: Giant vertebrobasilar aneurysms: endovascular treatment and long-term follow-up. Neurosurgery 2004;55:316–323.
29 Li MH, Li YD, Fang C, Gu BX, Cheng YS, Wang YL, Gao BL, Zhao JG, Wang J, Li M: Endovascular treatment of giant or very large intracranial aneurysms with different modalities: an analysis of 20 cases. Neuroradiology 2007;49:819–828.
30 Ciceri EF, Klucznik RP, Grossman RG, Rose JE, Mawad ME: Aneurysms of the posterior cerebral artery: classification and endovascular treatment. AJNR Am J Neuroradiol 2001; 22:27–34.
31 Uda K, Murayama Y, Gobin YP, Duckwiler GR, Viñuela F: Endovascular treatment of basilar artery trunk aneurysms with Guglielmi detachable coils: clinical experience with 41 aneurysms in 39 patients. J Neurosurg 2001;95:624–632.
32 Kalani MY, Zabramski JM, Hu YC, Spetzler RF: Extracranial-intracranial bypass and vessel occlusion for the treatment of unclippable giant middle cerebral artery aneurysms. Neurosurgery 2013;72:428–435.
33 Hauck EF, Welch BG, White JA, Replogle RE, Purdy PD, Pride LG, Samson D: Stent/coil treatment of very large and giant unruptured ophthalmic and cavernous aneurysms. Surg Neurol 2009;71:19–24.
34 de Barros Faria M, Castro RN, Lundquist J, Scrivano E, Ceratto R, Ferrario A, Lylyk P: The role of the pipeline embolization device for the treatment of dissecting intracranial aneurysms. AJNR Am J Neuroradiol 2011;32: 2192–2195.
35 Ha SW, Jang SJ: Clinical analysis of giant intracranial aneurysms with endovascular embolization. J Cerebrovasc Endovasc Neurosurg 2012;14:22–28.
36 Waldron JS, Halbach VV, Lawton MT: Microsurgical management of incompletely coiled and recurrent aneurysms: trends, techniques, and observations on coil extrusion. Neurosurgery 2009;64:301–315.
37 Seo BR, Kim TS, Joo SP, Lee JM, Jang JW, Lee JK, Kim JH, Kim SH: Surgical strategies using cerebral revascularization in complex middle cerebral artery aneurysms. Clin Neurol Neurosurg 2009;111:670–675.
38 Sluzewski M, Menovsky T, van Rooij WJ, Wijnalda D: Coiling of very large or giant cerebral aneurysms: long-term clinical and serial angiographic results. AJNR Am J Neuroradiol 2003;24:257–262.
39 Zhang YJ, Barrow DL, Cawley CM, Dion JE: Neurosurgical management of intracranial aneurysms previously treated with endovascular therapy. Neurosurgery 2003;52:283–293.
40 Sekhar LN, Duff JM, Kalavakonda C, Olding M: Cerebral revascularization using radial artery grafts for the treatment of complex intracranial aneurysms: techniques and outcomes for 17 patients. Neurosurgery 2001;49:646–658.
41 Raphaeli G, Collignon L, De Witte O, Lubicz B: Endovascular treatment of posterior circulation fusiform aneurysms: single-center experience in 31 patients. Neurosurgery 2011; 69:274–283.
42 Biondi A, Jean B, Vivas E, Le Jean L, Boch AL, Chiras J, Van Effenterre R: Giant and large peripheral cerebral aneurysms: etiopathologic considerations, endovascular treatment, and long-term follow-up. AJNR Am J Neuroradiol 2006;27:1685–1692.
43 Meckel S, McAuliffe W, Fiorella D, Taschner CA, Phatouros C, Phillips TJ, Vasak P, Schumacher M, Klisch J: Endovascular treatment of complex aneurysms at the vertebrobasilar junction with flow-diverting stents: initial experience. Neurosurgery 2013;73: 386–394.
44 Lubicz B, Collignon L, Raphaeli G, Pruvo JP, Bruneau M, De Witte O, Leclerc X: Flow-diverter stent for the endovascular treatment of intracranial aneurysms: a prospective study in 29 patients with 34 aneurysms. Stroke 2010; 41:2247–2253.
45 Iihara K, Murao K, Yamada N, Takahashi JC, Nakajima N, Satow T, Hishikawa T, Nagata I, Miyamoto S: Growth potential and response to multimodality treatment of partially thrombosed large or giant aneurysms in the posterior circulation. Neurosurgery 2008;63:832–842.
46 Clarençon F, Bonneville F, Boch AL, Lejean L, Biondi A: Parent artery occlusion is not obsolete in giant aneurysms of the ICA. Experience with very-long-term follow-up. Neuroradiology 2011;53:973–982.
47 Siddiqui AH, Abla AA, Kan P, Dumont TM, Jahshan S, Britz GW, Hopkins LN, Levy EI: Panacea or problem: flow diverters in the treatment of symptomatic large or giant fusiform vertebrobasilar aneurysms. J Neurosurg 2012;116:1258–1266.
48 Nakajima H, Kamiyama H, Nakamura T, Takizawa K, Tokugawa J, Ohata K: Direct surgical treatment of giant middle cerebral artery aneurysms using microvascular reconstruction techniques. Neurol Med Chir (Tokyo) 2012;52:56–61.
49 Skrap M, Petralia B, Toniato G: Temporary balloon occlusion during the surgical treatment of giant paraclinoid and vertebrobasilar aneurysms. Acta Neurochir (Wien) 2010;152: 435–442.
50 Kubo Y, Ogasawara K, Tomitsuka N, Otawara Y, Kakino S, Ogawa A: Revascularization and parent artery occlusion for giant internal carotid artery aneurysms in the intracavernous portion using intraoperative monitoring of cerebral hemodynamics. Neurosurgery 2006; 58:43–50.
51 Miyamoto S, Funaki T, Iihara K, Takahashi JC: Successful obliteration and shrinkage of giant partially thrombosed basilar artery aneurysms through a tailored flow reduction strategy with bypass surgery. J Neurosurg 2011;114:1028–1036.
52 Lownie SP, Drake CG, Peerless SJ, Ferguson GG, Pelz DM: Clinical presentation and management of giant anterior communicating artery region aneurysms. J Neurosurg 2000;92: 267–277.
53 van Doormaal TP, van der Zwan A, Verweij BH, Regli L, Tulleken CA: Giant aneurysm clipping under protection of an excimer laser-assisted non-occlusive anastomosis bypass. Neurosurgery 2010;66:439–447.
54 Nakajima H, Kamiyama H, Nakamura T, Takizawa K, Ohata K: Direct surgical treatment of giant intracranial aneurysms on the anterior communicating artery or anterior cerebral artery. Neurol Med Chir (Tokyo) 2013; 53:153–156.
55 Lv X, Jiang C, Li Y, Yang X, Zhang J, Wu Z: Treatment of giant intracranial aneurysms. Interv Neuroradiol 2009;15:135–144.
56 Pumar JM, Arias-Rivas S, Rodríguez-Yáñez M, Blanco M, Ageitos M, Vazquez-Herrero F, Castiñeira-Mourenza JA, Masso A: Using Leo Plus stent as flow diverter and endoluminal remodeling in endovascular treatment of intracranial fusiform aneurysms. J Neurointerv Surg 2013;5(suppl 3): iii22–iii27.
57 Velat GJ, Zabramski JM, Nakaji P, Spetzler RF: Surgical management of giant posterior communicating artery aneurysms. Neurosurgery 2012;71:43–50.

58 Biondi A, Janardhan V, Katz JM, Salvaggio K, Riina HA, Gobin YP: Neuroform stent-assisted coil embolization of wide-neck intracranial aneurysms: strategies in stent deployment and midterm follow-up. Neurosurgery 2007;61:460–468.
59 Kellner CP, Haque RM, Meyers PM, Lavine SD, Connolly ES Jr, Solomon RA: Complex basilar artery aneurysms treated using surgical basilar occlusion: a modern case series. Clinical article. J Neurosurg 2011;115:319–327.
60 Kalani MY, Zabramski JM, Nakaji P, Spetzler RF: Bypass and flow reduction for complex basilar and vertebrobasilar junction aneurysms. Neurosurgery 2013;72:763–775.
61 Lubicz B, Gauvrit JY, Leclerc X, Lejeune JP, Pruvo JP: Giant aneurysms of the internal carotid artery: endovascular treatment and long-term follow-up. Neuroradiology 2003;45:650–655.
62 Ponce FA, Albuquerque FC, McDougall CG, Han PP, Zabramski JM, Spetzler RF: Combined endovascular and microsurgical management of giant and complex unruptured aneurysms. Neurosurg Focus 2004;17:E11.
63 Shi ZS, Ziegler J, Duckwiler GR, Jahan R, Frazee J, Ausman JI, Martin NA, Viñuela F: Management of giant middle cerebral artery aneurysms with incorporated branches: partial endovascular coiling or combined extracranial-intracranial bypass – a team approach. Neurosurgery 2009;65:121–129.
64 Ewald CH, Kühne D, Hassler WE: Bypass-surgery and coil-embolisation in the treatment of cerebral giant aneurysms. Acta Neurochir (Wien) 2000;142:731–737.
65 Hallacq P, Piotin M, Moret J: Endovascular occlusion of the posterior cerebral artery for the treatment of p2 segment aneurysms: retrospective review of a 10-year series. AJNR Am J Neuroradiol 2002;23:1128–1136.
66 Tan HQ, Li MH, Li YD, Fang C, Wang JB, Wang W, Wang J, Zhang PL, Zhu YQ: Endovascular reconstruction with the Willis covered stent for the treatment of large or giant intracranial aneurysms. Cerebrovasc Dis 2011;31:154–162.
67 Weber W, Siekmann R, Kis B, Kuehne D: Treatment and follow-up of 22 unruptured wide-necked intracranial aneurysms of the internal carotid artery with Onyx HD 500. AJNR Am J Neuroradiol 2005;26:1909–1915.
68 Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K: Publication bias in clinical trials due to statistical significance or direction of trial results. Cochrane Database Syst Rev 2009;1:MR000006.
69 Dengler J, Heuschmann PU, Endres M, Meyer B, Rohde V, Rufenacht DA, Vajkoczy P; Giant Intracranial Aneurysm Study Group: The rationale and design of the giant intracranial aneurysm registry: a retrospective and prospective study. Int J Stroke 2011;6:266–270.
70 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; Giant Intracranial Aneurysm Study Group: Perianeurysmal edema in giant intracranial aneurysms in relation to aneurysm location, size, and partial thrombosis. J Neurosurg 2015;123:446–452.
71 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;77:733–743.