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CLINICAL ARTICLE

Giant intracranial aneurysms: natural history and 1-year case fatality after endovascular or surgical treatment

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OBJECTIVE Clinical evidence on giant intracranial aneurysms (GIAs), intracranial aneurysms with a diameter of at least 25 mm, is limited. The authors aimed to investigate the natural history, case fatality, and treatment outcomes of ruptured and unruptured GIAs.

METHODS In this international observational registry study, patients with a ruptured or unruptured GIA received conservative management (CM), surgical management (SM), or endovascular management (EM). The authors investigated rupture rates and case fatality.

RESULTS The retrospective cohort comprised 219 patients with GIAs (21.9% ruptured GIAs and 78.1% unruptured GIAs) whose index hospitalization occurred between January 2006 and November 2016. The index hospitalization in the prospective cohort (362 patients with GIAs [17.1% ruptured and 82.9% unruptured]) occurred between December 2008 and February 2017. In the retrospective cohort, the risk ratio for death at a mean follow-up of 4.8 years (SD 2.2 years) after CM, compared with EM and SM, was 1.63 (95% CI 1.23–2.16) in ruptured GIAs and 3.96 (95% CI 2.57–6.11) in unruptured GIAs. In the prospective cohort, the 1-year case fatality in ruptured GIAs/unruptured GIAs was 100%/22.0% during CM, 36.0%/3.0% after SM, and 39.0%/12.0% after EM. Corresponding 1-year rupture rates in unruptured GIAs were 25.0% during CM, 1.2% after SM, and 2.5% after EM. In unruptured GIAs, the HR for death within the 1st year in patients with posterior circulation GIAs was 6.7 (95% CI 1.5–30.4, $p < 0.01$), with patients with a GIA at the supraclinoid internal carotid artery as reference. Different sizes of unruptured GIAs were not associated with 1-year case fatality.

CONCLUSIONS Rupture rates for unruptured GIAs were high, and the natural history and treatment outcomes for ruptured GIAs were poor. Patients undergoing SM or EM showed lower case fatality and rupture rates than those undergoing CM. This difference in outcome may in part be influenced by patients in the CM group having been found poor candidates for SM or EM.

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KEYWORDS giant intracranial aneurysm; subarachnoid hemorrhage; aneurysm rupture; vascular disorders

ABBREVIATIONS CM = conservative management; CND = cranial nerve deficit; EM = endovascular management; GCS = Glasgow Coma Scale; GIA = giant intracranial aneurysm; ISAT = International Subarachnoid Aneurysm Trial; ISUIA = International Study of Unruptured Intracranial Aneurysms; mRS = modified Rankin Scale; SAH = subarachnoid hemorrhage; SM = surgical management; UCAS Japan = Unruptured Cerebral Aneurysm Study of Japan; UIATS = Unruptured Intracranial Aneurysm Treatment Score; WFNS = World Federation of Neurosurgical Societies.

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The case fatality of unruptured intracranial aneurysms is predominantly determined by the occurrence of an aneurysm rupture.[10] Various risk factors for aneurysm rupture exist, including hypertension, age, aneurysm size, aneurysm location, and previous subarachnoid hemorrhage (SAH).[5] Since aneurysm size has been shown to be the most dominant risk factor for rupture, unruptured intracranial aneurysms at highest risk of rupture are those categorized as unruptured giant intracranial aneurysms (GIAs). This group comprises all unruptured intracranial aneurysms with diameters of at least 25 mm.[10] Since unruptured GIAs only account for about 5% of all unruptured intracranial aneurysms, limited data are available on long-term rupture rates and treatment outcomes.[3,6–10] Due to this lack of evidence, decisions on unruptured GIA management remain subject to debate.

We describe the results of an international multicenter registry aiming to document the natural history, as observed in patients selected for conservative management (CM) without aneurysmal repair, and outcomes of surgical management (SM) or endovascular management (EM) for both ruptured and unruptured GIAs. For the prospective cohort, we report baseline characteristics as well as rupture rates and case fatality up to 1 year after inclusion. For the retrospective cohort, we present baseline characteristics and case fatality over the entire follow-up period.

Methods

Patients

The Giant Intracranial Aneurysm Registry is a prospective and retrospective observational study with 32 participating centers in Europe, Japan, and the US. The registry is listed at clinicaltrials.gov (registration no. NCT02066493), and its study protocol was previously published.[2] For all patients participating in the prospective arm of the GIA registry, written consent was obtained according to the demands of each study center's institutional review board. The only inclusion criterion for participation in the GIA registry was the diagnosis of an intracranial aneurysm with a diameter of at least 25 mm by means of digital subtraction angiography, CT, or MRI, independent of aneurysm shape or whether the GIA was ruptured or unruptured. We excluded patients younger than 18 years.

Procedures

All patients were included at index hospitalization. In patients with ruptured GIAs and those with unruptured GIAs without aneurysm repair, "index hospitalization" was defined as the first presentation to one of the registry centers, including outpatient visits. In patients with an unruptured GIA in the EM or SM groups, index hospitalization was defined as the stay in which aneurysm repair was carried out. Clinical and radiological data were documented at index hospitalization, discharge, and 1 year after discharge at each study center. According to the type of treatment chosen by the local neurovascular team in charge, patients were assigned to one of 3 different cohorts: CM, SM, or EM. In case of combined EM/SM treatment, the patients were assigned according to the initial treatment technique. In the retrospective cohort, there were 4 of 219 (1.8%) combined treatment cases, all of which were unruptured and had initial EM. In the prospective cohort, we recorded 15 of 367 (4.1%) combined treatment cases, all of which were also unruptured and underwent initial EM. The modified Rankin Scale (mRS) score, the Glasgow Coma Scale (GCS) score, and, in case of SAH, the World Federation of Neurosurgical Societies (WFNS) grade were assessed. Furthermore, cranial nerve deficits (CNDs), motor deficits, and aphasia were documented. Various risk factors and previous EM or SM were recorded as well. All follow-up examinations reassessed the neurological condition and documented whether a rupture of the GIA had occurred over time. Here, we report the initial results on 1-year outcomes and rupture rates.

Statistical Analysis

All included data were extracted from the database on February 5, 2017. We identified 362 prospective and 219 retrospective inclusions. Completed 1-year follow-up rates were 78.0% in the prospective cohort, since not all patients had reached their 1-year follow-up examination. One-year rupture rates with subsequent SAH were examined in 2 steps: first for the entire cohort of unruptured GIAs, and second after excluding unruptured GIAs located at the cavernous segment of the internal carotid artery, which are predominantly extradural and therefore less likely to cause SAH.

Baseline characteristics were compared between groups using the chi-square test, Fisher's exact test, t-test, or Mann-Whitney U-test, as appropriate. Kaplan-Meier estimates and log-rank statistics were used for assessing risk of death or rupture at 1 year; survival time was measured from date of inclusion to date of death within 365 days after inclusion; patients with no record of death up to 365 days were censored at their last date of documented contact (in or out of hospital) if it was before 365 days after inclusion or at day 365. After adjusting for between-group differences at baseline, factors associated with 1-year case fatality in unruptured GIAs were examined using univariable and multivariable Cox regression analyses. Variables in univariable analysis that were statistically significant on a 0.1 level were included in multivariable analysis; variables were eliminated via backward elimination procedure; hazard ratios, 95% confidence intervals, and p values of statistically nonsignificant variables were given just before removal. All analyses were conducted using IBM SPSS Statistics for Windows (version 24, IBM Corp.), and the level of significance was 0.05.

Results

Retrospective Cohort: Baseline Characteristics and 1-Year Case Fatality

The 219 patients in the retrospective cohort had their index hospitalization between January 5, 2006, and November 7, 2016, at 28 centers. At baseline, 171 GIAs (78.1%) were unruptured and 48 (21.9%) were ruptured. Baseline characteristics of patients in the retrospective cohort are listed in Table 1, both for ruptured and unruptured GIAs. At a mean follow-up of 4.8 years (SD 2.2 years), data were available for 191 cases (87.2%); case fatality in ruptured

TABLE 1. Baseline characteristics in the retrospective cohort

	Ruptured GIA						Unruptured GIA					
	Total (n = 48)	CM (n = 9)	SM (n = 20)	EM (n = 19)	p Value*	p Value†	Total (n = 171)	CM (n = 25)	SM (n = 35)	EM (n = 111)	p Value*	p Value†
Median age, yrs	54.5 (45.5–61.8)	63.0 (45.5–69.5)	52.0 (47.3–60.3)	57.0 (40.0–61.0)	0.12	0.55	59.0 (50.0–67.0)	63.0 (51.5–75.0)	53.0 (45.0–64.0)	60.0 (53.0–67.0)	0.075	0.012
No. of women	33 (68.8)	6 (66.7)	15 (75.0)	12 (63.2)	>0.9	0.501	100 (58.5)	10 (40.0)	16 (45.7)	74 (66.7)	0.050	0.030
Aneurysm size, mm					0.380	0.186					0.084	0.689
25–29	32 (66.7)	5 (55.6)	11 (55.0)	16 (84.2)			79 (46.2)	7 (28.0)	16 (45.7)	56 (50.5)		
30–34	8 (16.7)	1 (11.1)	6 (30.0)	1 (5.3)			45 (26.3)	6 (24.0)	11 (31.4)	28 (25.2)		
35–39	4 (8.3)	2 (22.2)	1 (5.0)	1 (5.3)			19 (11.1)	5 (20.0)	2 (5.7)	12 (10.8)		
≥40	4 (8.3)	1 (11.1)	2 (10.0)	1 (5.3)			28 (16.4)	7 (28.0)	6 (17.1)	15 (13.5)		
Median diameter, mm	28.0 (26.0–30.0)	29.0 (27.5–38.0)	29.0 (26.0–30.8)	26.0 (26.0–28.0)	0.142	0.095	30.0 (26.0–35.0)	34.0 (28.5–40.5)	30.0 (26.0–34.0)	29.0 (27.5–34.0)	0.008	0.772
Aneurysm location					0.704	0.030					0.013	<0.001
ICA	18 (37.5)	2 (22.2)	7 (35.0)	9 (47.4)			93 (54.4)	11 (44.0)	13 (37.1)	69 (62.2)		
ACA	6 (12.5)	1 (11.1)	4 (20.0)	1 (5.3)			10 (5.8)	5 (20.0)	3 (8.6)	2 (1.8)		
MCA	17 (35.4)	4 (44.4)	9 (45.0)	4 (21.1)			24 (14.0)	3 (12.0)	13 (37.1)	8 (7.2)		
Posterior circulation	7 (14.6)	2 (22.2)	0 (0.0)	5 (26.3)			44 (25.7)	6 (24.0)	6 (17.1)	32 (28.8)		
Symptoms												
Median GCS score	6 (3–14)	6 (3–13.5)	5.5 (3–14)	7 (5–14)	0.872	0.365	15 (15–15)	15 (15–15)	15 (15–15)	15 (15–15)	0.336	0.142
Median mRS score	5 (2–5)	5 (3–5)	5 (3–5)	5 (2–5)	0.784	0.627	2 (1–3)	1 (1–3)	1 (0–2)	3 (1–4)	0.292	<0.001
CND	24 (70.6)	4 (80.0)	11 (73.3)	9 (64.3)	>0.9	0.765	115 (83.3)	14 (82.4)	17 (68.0)	84 (87.5)	>0.9	0.066
Motor deficit	25 (73.5)	5 (100.0)	10 (66.7)	10 (71.4)	0.293	0.334	36 (25.9)	5 (27.8)	5 (20.0)	26 (27.1)	0.782	0.757
Aphasia	20 (60.6)	4 (80.0)	6 (40.0)	10 (71.4)	0.379	0.133	16 (9.4)	3 (16.7)	3 (8.6)	10 (10.4)	0.437	0.745

ACA = anterior cerebral artery; ICA = internal carotid artery; MCA = middle cerebral artery.

Values are presented as the number of patients (%) unless indicated otherwise. Median values are reported as the median (IQR). Analyses were restricted to patients without missing values in the respective variable.

* Comparison between CM and SM and EM combined.

† Comparison between the SM and EM group.

GIA was 100% (8/8) in the CM group, 64.7% (11/17) in the SM group, and 57.1% (8/14) in the EM group. In patients with an unruptured GIA, case fatality was 75.0% (15/20) in the CM group, 14.3% (4/28) in the SM group, and 20.2% (21/104) in the EM group. The resulting risk ratio for death after CM, compared with EM and SM, was 1.63 (95% CI 1.23–2.16) in ruptured GIAs and 3.96 (95% CI 2.57–6.11) in unruptured GIAs.

Prospective Cohort

Index hospitalization for the 362 patients in the prospective cohort occurred between December 5, 2008, and February 5, 2017, at 32 centers. At baseline, 300 GIAs (82.9%) were unruptured and 62 (17.1%) were ruptured.

Ruptured GIAs: Baseline Characteristics and 1-Year Case Fatality

Baseline characteristics of patients with ruptured GIAs are shown in Table 2. In the ruptured GIA cohort, 27.4% received CM, 33.9% SM, and 38.7% EM. Factors associated with 1-year case fatality in ruptured GIAs are shown in Table 3. In the CM group, we observed a case fatality of 100%, which was significantly higher than that observed in patients in the SM group (36%, 95% CI 14%–58%) or EM group (39%, 95% CI 19%–59%) ($p < 0.001$). Other factors associated with case fatality were high WFNS grade, low GCS score, high mRS score, or cranial nerve deficit at admission.

Unruptured GIAs: Baseline Characteristics and 1-Year Case Fatality

For patients with unruptured GIAs, baseline characteristics are shown in Table 2. Patients with an unruptured GIA received CM in 22.0%, SM in 30.0%, and EM in 48.0% of cases. Patients in the CM group were more frequently asymptomatic and significantly older than patients in the SM and EM groups. Patients in the EM group, when compared with SM patients, were in poorer condition (worse mRS score) and older.

One-year rupture rates are displayed in Fig. 1A for the total cohort and in Fig. 1B after exclusion of cavernous unruptured GIAs. One-year rupture rates were substantially lower in the EM and SM groups than in the CM group, for which we identified 1-year rupture rates of 21.6% for the entire prospective cohort and 25.3% after exclusion of unruptured GIAs at the cavernous ICA. All patients with rupture of an initially unruptured GIA died within the 1st year of follow-up. One-year rupture rates in relation to GIA location and treatment group are displayed in Table 4.

Factors associated with 1-year case fatality in the unruptured GIA cohort are shown in Table 5. One-year case fatality was 22.0% in the CM group, 3.0% in the SM group, and 12.0% in the EM group. Compared with patients younger than 55 years, those older than 65 years and those older than 74 years showed HR for death within 1 year of 5.1 (95% CI 1.4–19.0) and 7.6 (95% CI 2.0–28.4), respectively. HR for death within 1 year in patients with posterior circulation unruptured GIAs was 6.7 (95% CI 1.5–30.4), with patients with unruptured GIAs located at the supraclinoid ICA as reference. We found no association between different unruptured GIA sizes and case fatality at 1 year ($p = 0.21$).

Discussion

In the prospective cohort of the registry, patients with CM of a ruptured or an unruptured GIA were in poorer condition at 1 year of follow-up than patients with SM or EM. In ruptured GIAs, the natural history was characterized by a 1-year case fatality of 100%, compared with 36% after SM and 39% after EM. In unruptured GIAs, the natural history displayed a 1-year case fatality of 22% for the entire cohort and 1-year rupture rates of 25%. The results after SM or EM of unruptured GIAs were significantly better: after SM, 1-year case fatality was 3% and rupture rates were 1%; the EM group exhibited a 1-year case fatality rate of 12% and rupture rates of 2%. All patients with rupture of an initially unruptured GIA died within the 1st year. Apart from the type of treatment, 1-year case fatality in unruptured GIAs was associated with patient age and GIA location but not with GIA size. The results in our retrospective cohort generally confirmed those of the prospective cohort.

The natural history and treatment outcomes of ruptured GIAs observed in our study are not easily comparable to previous findings by other studies since the GIA registry is the first to present prospective data specifically for GIA. In non-GIAs, the case fatality associated with aneurysm rupture during the course of natural history was estimated to be below 65%.[1] This is in contrast to the 100% case fatality in conservatively treated ruptured GIAs observed in our series and suggests that once an unruptured GIA ruptures, the overall prognosis may be significantly poorer than that observed in ruptured non-GIAs. As far as treatment outcome of ruptured intracranial aneurysms is concerned, the highest impact trial reporting data on case fatality still is the International Subarachnoid Aneurysm Trial (ISAT).[7] With regard to ruptured GIAs, ISAT is limited by the fact that ruptured GIAs were not examined as a separate category and only 7.2% of the examined ruptured intracranial aneurysms in ISAT were larger than 11 mm in size, which means that the proportion of ruptured GIAs was even lower. Based on this cohort of predominantly small- and medium-sized ruptured intracranial aneurysms, ISAT reports a 1-year case fatality of 8.1% after EM and 10.1% after SM, which is significantly lower than the respective case fatality found in our cohort of ruptured GIAs. This disparity suggests that even if SM or EM are conducted in ruptured GIAs, outcomes are significantly poorer than those observed in ruptured non-GIAs. Even though ruptured GIAs are underrepresented in ISAT, some similarities to our findings do exist. Just as in ISAT, we found that 1-year case fatality was significantly associated with WFNS grade and aneurysm location and that aneurysm size did not predict case fatality. However, we were not able to confirm ISAT's finding that patient age is associated with 1-year case fatality. It is important to note that comparing our findings to those of ISAT may be limited in that ISAT was a randomized trial, while the GIA registry is a purely observational study. However, our findings in ruptured GIAs suggest no relevant difference

TABLE 2. Baseline characteristics in the prospective cohort

	Ruptured GIA						Unruptured GIA					
	Total (n = 62)	CM (n = 17)	SM (n = 21)	EM (n = 24)	p Value*	p Value†	Total (n = 300)	CM (n = 66)	SM (n = 90)	EM (n = 144)	p Value*	p Value†
Median age, yrs	55.0 (45.8–70)	58.0 (47.5–74.5)	47.0 (42.5–59.5)	60.5 (51.0–73.5)	0.55	0.002	61.0 (51.0–70.0)	69.5 (60.8–76.3)	56.0 (43.8–64.0)	60.5 (51.3–68.8)	<0.001	0.002
No. of women	33 (53.2)	11 (64.7)	7 (33.3)	15 (62.5)	0.27	0.051	178 (59.3)	37 (56.1)	47 (52.2)	94 (65.3)	0.54	0.047
Aneurysm size, mm					0.94	0.66					0.79	<0.001
25–29	39 (62.9)	11 (64.7)	14 (66.7)	14 (58.3)			142 (47.3)	28 (42.4)	29 (32.2)	85 (59.0)		
30–34	10 (16.1)	2 (11.8)	4 (19.0)	4 (16.7)			63 (21.0)	14 (21.2)	27 (30.0)	22 (15.3)		
35–39	7 (11.3)	2 (11.8)	1 (4.8)	4 (16.7)			33 (11.0)	8 (12.1)	9 (10.0)	16 (11.1)		
≥40	6 (9.7)	2 (11.8)	2 (9.5)	2 (8.3)			62 (20.7)	16 (24.2)	25 (27.8)	21 (14.6)		
Median diameter, mm	28.0 (25.8–32.3)	28.0 (25.5–33.5)	27.0 (25.0–31.5)	29.0 (26.0–34.0)	0.89	0.20	30.0 (26–37)	30.5 (27.0–38.5)	31.0 (27.8–40.8)	29.0 (26.0–35.0)	0.28	0.001
Aneurysm location					0.39	0.014					0.23	<0.001
ICA (cavernous)	1 (1.6)	0 (0.0)	0 (0.0)	1 (4.2)			69 (23.0)	12 (18.2)	9 (10.0)	48 (33.3)		
ICA (supraclinoid)	19 (30.6)	3 (17.6)	8 (38.1)	8 (33.3)			79 (26.3)	17 (25.8)	22 (24.4)	40 (27.8)		
ACA	7 (11.3)	1 (5.9)	4 (19.0)	2 (8.3)			13 (4.3)	1 (1.5)	7 (7.8)	5 (3.5)		
MCA	21 (33.9)	7 (41.2)	9 (42.9)	5 (20.8)			65 (21.7)	13 (19.7)	39 (43.3)	13 (9.0)		
Posterior circulation	14 (22.6)	6 (35.3)	0 (0.0)	8 (33.3)			74 (24.7)	23 (34.8)	13 (14.4)	38 (26.4)		
Symptoms												
Median GCS score	8 (3–15)	3 (3–4)	8 (3–15)	14 (7–15)	<0.001	0.07	15 (15–15)	15 (15–15)	15 (15–15)	15 (15–15)	0.14	0.56
Median mRS score	5 (2–5)	5 (5–5)	5 (1–5)	3 (1–5)	<0.001	0.12	1 (0–2)	1 (0–2)	1 (0–1)	1 (1–2)	0.80	0.03
CND	17 (42.5)	11 (78.6)	3 (27.3)	3 (20.0)	0.002	>0.9	133 (66.2)	24 (61.5)	35 (63.6)	74 (69.2)	0.50	0.48
Motor deficit	23 (57.5)	11 (84.6)	6 (54.5)	6 (37.5)	0.016	0.38	43 (22.5)	11 (30.6)	14 (26.4)	18 (17.6)	0.20	0.20
Aphasia	20 (52.6)	10 (83.3)	6 (60.0)	4 (25.0)	0.015	0.11	12 (6.2)	3 (8.3)	5 (9.1)	4 (3.9)	0.47	0.28
WFNS grade for ruptured GIA					0.001	0.032						
I	12 (19.4)	1 (5.9)	2 (9.5)	9 (37.5)								
II	8 (12.9)	0 (0.0)	2 (9.5)	6 (25.0)								
III	3 (4.8)	0 (0.0)	1 (4.8)	2 (8.3)								
IV	12 (19.4)	1 (5.9)	8 (38.1)	3 (12.5)								
V	27 (43.5)	15 (88.2)	8 (38.1)	4 (16.7)								

Values are presented as the number of patients (%) unless indicated otherwise. Median values are reported as the median (IQR). Analyses were restricted to patients without missing values in the respective variable.

* Comparison between CM and SM and EM combined.

† Comparison between the SM and EM groups.

TABLE 3. Factors associated with 1-year case fatality in ruptured GIAs

Category	1-Yr Case Fatality*	95% CI	p Value
Overall	0.55	0.42–0.68	
Treatment			<0.001
SM	0.36	0.14–0.58	
EM	0.39	0.19–0.59	
CM	1	1	
Age, yrs			0.34
<55	0.46	0.28–0.65	
55–64	0.51	0.22–0.80	
65–74	0.66	0.36–0.95	
>74	0.73	0.44–1	
Sex			0.47
Female	0.58	0.41–0.74	
Male	0.53	0.33–0.73	
Aneurysm size, mm			0.40
25–29	0.47	0.31–0.63	
30–34	0.7	0.42–0.98	
35–39	0.71	0.38–1	
>39	0.67	0.17–1	
GCS score			<0.001
3–8	0.77	0.63–0.91	
9–12	0	0–0	
13–15	0.32	0.12–0.51	
mRS score			0.036
0 or 1	0.29	0.05–0.53	
2 or 3	0.44	0.12–0.77	
4 or 5	0.66	0.50–0.81	
Aneurysm location			0.051
ICA (cavernous)	0	0–0	
ICA (supraclinoid)	0.37	0.15–0.59	
ACA & MCA	0.56	0.36–0.76	
Posterior circulation	0.89	0.70–1	
Symptoms at admission			
CND	0.73	0.51–0.96	0.027
No CND	0.41	0.20–0.63	
Motor deficit	0.54	0.33–0.75	0.66
No motor deficit	0.48	0.24–0.73	
Aphasia	0.61	0.39–0.83	0.11
No aphasia	0.36	0.12–0.59	
WFNS grade			<0.001
I	0.39	0.08–0.70	
II	0.25	0–0.55	
III	0.33	0–0.87	
IV	0.25	0–0.49	
V	0.85	0.72–0.99	

* Calculated using the Kaplan-Meier estimate.

in 1-year case fatality after SM or EM, as they both ranged slightly below 40%.

In unruptured GIAs, we found significantly lower case fatality and rupture rates after SM or EM when compared with the natural history. This confirms the notion that CM of unruptured GIAs should remain an exception and is in line with the results of a recent meta-analysis of outcomes of EM or SM in unruptured GIAs, which identified good outcomes in 80% after SM and in 85% after EM.[2]

So far, unruptured GIAs have only played a marginal role in prospective studies on rupture rates and treatment outcomes of unruptured intracranial aneurysms. In the 2 largest prospective studies on unruptured intracranial aneurysms, the International Study of Unruptured Intracranial Aneurysms (ISUIA)[10] and the Unruptured Cerebral Aneurysm Study of Japan (UCAS Japan),[8] unruptured GIAs were merely examined as a by-product of an investigation dominated by small- and medium-sized intracranial aneurysms. In ISUIA, unruptured GIAs accounted for only 3.2% in the CM group, 4.2% in the SM group, and 12.0% in the EM group. In UCAS Japan, only 0.5% of all examined cases were unruptured GIAs. When comparing 1-year rupture rates during the course of the natural history of unruptured GIAs observed in our cohort (25%) to those found in ISUIA (18%) and UCAS Japan (27%), our results confirm that already within the 1st year after diagnosis, GIA rupture is a frequent phenomenon. Just like ISUIA, our study identified aneurysm location in the posterior circulation and older patient age as predictors of rupture. Interestingly, UCAS Japan observed that patient age did not predict rupture, and even though UCAS Japan findings are in agreement that aneurysm location is a predictor of rupture, it found that intracranial aneurysms in the posterior circulation were not at higher risk of rupture, whereas intracranial aneurysms at the anterior cerebral artery and posterior communicating artery were. Our results may be closer to those of ISUIA, since UCAS Japan was conducted in the setting of a purely Japanese epidemiology, which has previously been shown to behave differently from predominantly Caucasian cohorts regarding aneurysm rupture risks.

Since unruptured GIAs in the cavernous segment of the ICA are predominantly located extradurally and therefore are less likely to cause SAH, we separated this specific subgroup of unruptured GIAs when reporting rupture rates. In cavernous unruptured GIAs, we found a 1-year rupture rate of 8.3% during the course of natural history. Even though ISUIA reported similar rupture rates for cavernous GIAs of 6.4%, it is important to note that those are 5-year rupture rates and therefore not directly comparable to our results.

Despite the remarkably low proportion of unruptured GIAs in ISUIA and UCAS Japan, these 2 studies account for 88% of all cases that formed the basis for the pooled analysis that created the PHASES (population, hypertension, age, size of aneurysm, earlier SAH from another aneurysm, site of aneurysm) score, which is a dedicated tool to predict intracranial aneurysm rupture.[5] The PHASES score highlights the critical role of aneurysm size as a risk factor for rupture by attributing significantly more points to size > 20 mm as a risk factor than to all other factors,

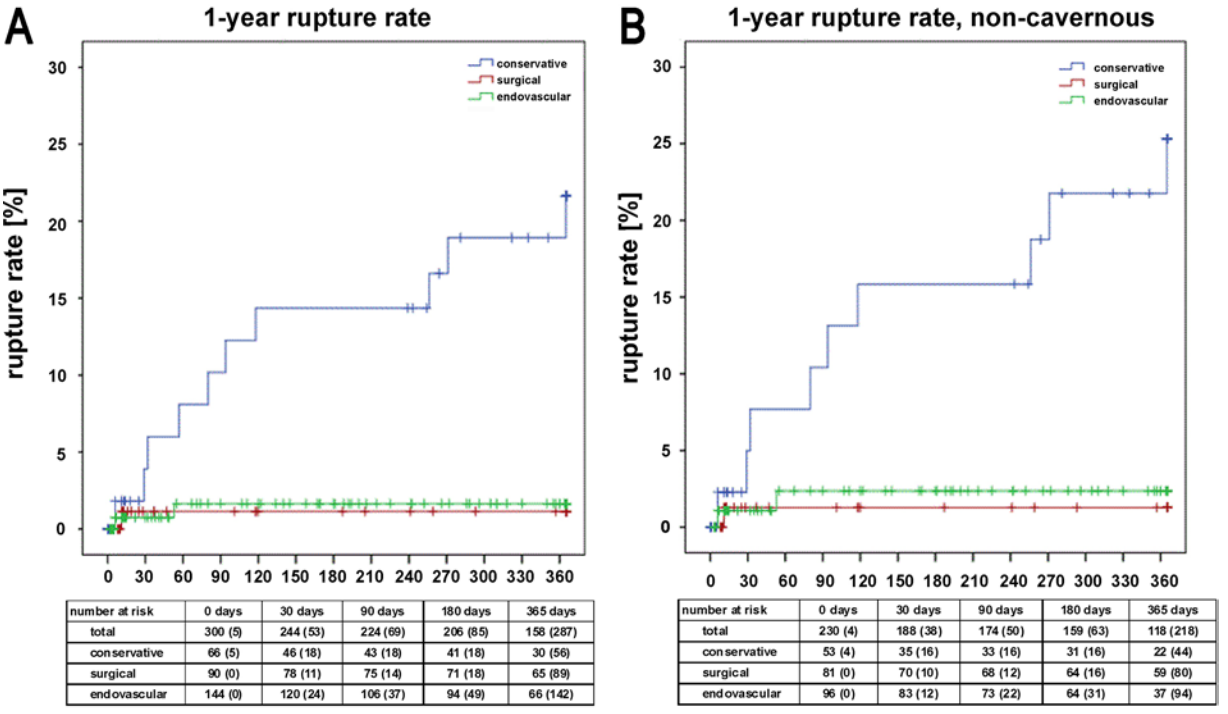

FIG. 1. Rupture rates during the 1st year in the prospective cohort for all unruptured GIAs (**A**) and after exclusion of extradural cavernous carotid unruptured GIAs (**B**). Figure is available in color online only.

namely 2.5 times the amount of posterior circulation location and even 10 times that of hypertension, age > 70 years, or earlier SAH from another aneurysm. Since all previous studies on aneurysm rupture rates and case fatality have stopped short of examining the size of intracranial aneurysms beyond the 25-mm threshold as a potential risk factor for outcome, our study is the first to investigate such giant-size categories. Nevertheless, we found no difference in 1-year case fatality for different size categories beyond 25 mm. This suggests that, at least during the 1st year of follow-up, once giant size is reached by an intracranial aneurysm, any additional growth may not influence case fatality.

We found that signs of mass effect caused by the unruptured GIAs barely missed statistical significance in predicting case fatality ($p = 0.054$). Since previous studies on intracranial aneurysm rupture were dominated by small- or medium-sized aneurysms, it is not surprising that, so far, mass effect has only rarely been considered when predicting outcome. Nevertheless, in a recently developed score for treatment decision-making in unruptured intracranial aneurysms, the Unruptured Intracranial Aneurysm Treatment Score (UIATS),[4] signs of mass effect constitute a significant factor. This is because the UIATS does not exclusively rely on published evidence but also incorporates the clinical experience of numerous neurovascular experts.

The main limitation of the GIA registry is its purely observational, nonrandomized design. Even though our findings were adjusted to differences between treatment cohorts at baseline, any specifics of decision-making by the investigators when planning treatment strategies may be insufficiently represented in our data. Furthermore, our findings are not able to determine which exact levels of patient disability are too poor for the patient to undergo EM or SM. Also, patients in the CM group may have undergone a kind of negative selection, potentially having been found poor candidates for SM or EM. This may be especially the case in ruptured GIAs, where patients in the CM group were in significantly poorer condition than

TABLE 4. One-year rupture rates in relation to unruptured GIA locations and treatment groups

Unruptured GIA Location	1-Yr Rupture Rates			
	All Patients (n = 300)	CM (n = 66)	SM (n = 90)	EM (n = 144)
Cavernous ICA	1/69 (1.4%)	1/12 (8.3%)	0/9 (0.0%)	0/48 (0.0%)
Supraclinoid ICA	2/79 (2.5%)	1/17 (5.9%)	1/22 (4.5%)	0/40 (0.0%)
ACA	0/13 (0.0%)	0/1 (0.0%)	0/7 (0.0%)	0/5 (0.0%)
MCA	2/65 (3.1%)	2/13 (15.4%)	0/39 (0.0%)	0/13 (0.0%)
Posterior circulation	8/74 (10.8%)	6/23 (26.1%)	0/13 (0.0%)	2/38 (5.3%)

TABLE 5. Factors associated with 1-year case fatality in unruptured GIAs

Category	1-Yr Case Fatality*	95% CI	p Value
Overall	0.11	0.07–0.15	
Treatment			0.005
SM	0.03	0–0.06	
EM	0.12	0.06–0.18	
CM	0.22	0.10–0.34	
Age, yrs			<0.001
<55	0.04	0–0.09	
55–64	0.06	0–0.11	
65–74	0.15	0.06–0.24	
>74	0.31	0.14–0.49	
Sex			0.09
Female	0.08	0.03–0.13	
Male	0.15	0.08–0.22	
Aneurysm size, mm			0.18
25–29	0.08	0.03–0.13	
30–34	0.12	0.03–0.22	
35–39	0.23	0.06–0.39	
>39	0.09	0–0.18	
GCS score			0.017
3–8	1	1	
9–12	0.25	0–0.68	
13–15	0.10	0.06–0.14	
mRS score			0.047
0 or 1	0.08	0.04–0.13	
2 or 3	0.14	0.04–0.24	
4 or 5	0.30	0.01–0.59	
Aneurysm location			<0.001
ICA (cavernous)	0.04	0–0.09	
ICA (supraclinoid)	0.05	0–0.11	
ACA & MCA	0.03	0–0.07	
Posterior circulation	0.32	0.19–0.44	
Symptoms at admission			
CN palsy	0.08	0.03–0.13	0.001
No CN palsy	0.27	0.15–0.39	
Motor deficit	0.15	0.03–0.27	0.74
No motor deficit	0.13	0.07–0.19	
Aphasia	0.18	0–0.42	0.48
No aphasia	0.13	0.07–0.18	

* Calculated using the Kaplan-Meier estimate.

those in the other management groups. Also, patients in the EM group were significantly older, and their GIA was more frequently located in the posterior circulation, both in ruptured and unruptured GIAs. Even though these factors were adjusted for when comparing case fatality of SM and EM, a certain selection bias remains.

Conclusions

The observed high 1-year case fatality in untreated and even in treated ruptured GIAs stresses the importance of the prevention of GIA rupture. Patients undergoing SM or EM showed lower case fatality and rupture rates than those undergoing CM. Even though some of this difference in outcome between groups may be influenced by patients in the CM group having been found to be poor candidates for SM or EM, GIA rupture rates of 25% already within the 1st year should prompt healthcare professionals to consider SM or EM in patients in good clinical condition.

Appendix

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Disclosures

Dr. Boccardi: consultant for Medtronic, Balt, and MicroVention. Dr. Cognard: consultant for Medtronic, MicroVention, Stryker, and Cerenovus.

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Supplemental Information

Previous Presentations

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