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Treatment Outcomes with Selective Coil Embolization for Large or Giant Aneurysms : Prognostic Implications of Incomplete Occlusion

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Objective : The objectives of this study were to evaluate the immediate and long-term efficacy and safety of coil embolization for large or giant aneurysms.

Methods : One hundred and fifty large or giant aneurysm cases treated with endovascular coil embolization between January 2005 and February 2014 at a single institute were included in this study. Medical records and imaging findings were reviewed. Statistical analysis was performed to evaluate prognostic factors associated with major recurrence (major recanalization or rupture) and delayed thromboembolism after selective coil embolization.

Results : Procedure-related symptomatic complications occurred in five (3.3%) patients. The mean clinical and radiological follow-up periods were 38 months (range, 2–110) and 26 months (range, 6–108), respectively. During the follow-up period, the estimated recurrence rate was 4.6% per year. Multivariate analysis using Cox regression showed the degree of occlusion to be the only factor associated with recurrence (p=0.008, hazard ratio 3.15, 95% confidence interval 1.34–7.41). The patient's history of rupture in addition to the size and location of the aneurysm were not associated with recurrence in this study. Delayed infarction occurred in eight cases, and all were incompletely occluded.

Conclusion : Although immediate postprocedural safety profiles were reasonable, longterm results showed recanalization and thromboembolic events to occur continuously, especially in patients with incomplete occlusion. In addition, incomplete occlusion was associated with delayed thromboembolic complications. Patients with incomplete occlusions should be followed carefully for delayed recurrence or delayed thromboembolic events.

Key Words : Endovascular procedures · Giant intracranial aneurysm · Treatment failure · Recurrence.

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INTRODUCTION

Endovascular coil embolization is a well-established treatment method for intracranial aneurysms[18]. Recent evidences suggested that endovascular treatment is not inferior to surgical treatment[8]. The growing use of endovascular treatment has also been fueled by patient preference and the development of new devices[1,10].

Despite these advancements, several limitations and major concerns remain. First, procedural rupture and thromboembolic complications are associated with selective coil embolization, and potentially catastrophic complications are possible[12,27]. Second, endovascular treatments showed inferiority in terms of durability[19]. Potential predictors of recanalization include subarachnoid hemorrhage, aneurysm size, degree of initial packing, location, and configuration of the aneurysm. However, studies showed variable outcomes regarding the utility of the above factors as predictors[4,6,18,26]. To the best of our knowledge, only a few studies have explored treatment outcomes of large or giant aneurysms due to a paucity of cases, despite the fact that large size is the most important risk factor for recurrence[4,7,22]. Thus, prognosis of large or giant aneurysm after selective coil embolization remains unclear. Flow diversion was suggested as a new treatment method for large or giant aneurysms, but immediate and long-term outcomes have not been fully elucidated[24]. Furthermore, delayed thromboembolic complications in embolized large or giant aneurysms have not been investigated, despite being relatively common[12].

In this study, we retrospectively reviewed our data, focusing on recurrence and delayed thromboembolism to identify the actuarial rate of these delayed complications and to identify potential risk factors.

MATERIALS AND METHODS

Patients

This study was approved by the institutional review board of our institution, and patient consent was waived because of the retrospective study design Between January 2005 and February 2014, 1479 intracranial aneurysms in 1334 consecutive patients were treated at our institution. Inclusion criteria were aneurysms >10 mm in diameter and treatment with selective coil embolization. Exclusion criteria were small aneurysms and aneurysms other than berry aneurysms (n=1302), such as dissecting aneurysms, fusiform aneurysms, and traumatic pseudo aneurysms. We also excluded patients who were treated by parent artery occlusion (n=12) and those who were lost to follow-up within 3 months after treatment (n=15). One hundred and fifty cases from our single-institutional registry were included this study. Medical records, including procedural notes, digital subtracted angiography (DSA), pre and post-procedural imaging, and records noting variables such as age, gender, aneurysm configuration (daughter sac, thrombosed aneurysm, and incorporating artery), location and size of the aneurysm, method of treatment, and occlusion status were reviewed. We also reviewed periprocedural events, such as procedural rupture or thromboembolic events.

Regarding characteristics of aneurysm, an incorporating artery was defined as a complete arterial orifice arising from the aneurismal neck. A thrombosed aneurysm was defined as evidence of intra-aneurysmal thrombus on pre-procedural computed tomography or magnetic resonance imaging. Clinical and radiological follow-up periods were calculated from the time of coil embolization to the latest inpatient or outpatient clinic and to the latest magnetic resonance angiography (MRA) or DSA.

The degree of embolization was assessed by two physicians (J.K.I. and C.J.H.). Embolization was considered to be complete if there was no contrast filling the dome, body, or neck of the aneurysm. A neck remnant was defined as residual filling of the aneurysm neck or part of the neck, and contrast agent present in the body or dome of the aneurysm indicated a residual sac. Recurrence was categorized as either minor or major recurrence. Minor recurrence was defined as any increase in aneurysmal neck filling on follow-up angiography (MRA or DSA) that did not require further treatment. Major recurrence was defined as increased aneurysmal filling requiring further treatment such as coil embolization, surgical clipping, or aneurysms that ruptured. Delayed (>1 month) ischemic stroke at corresponding area of parent vessel of aneurysm or progressive stenosis/occlusion of the parent vessel adjacent to aneurysm were considered delayed thromboembolic events.

The primary outcome of this study was major recurrence, and the secondary outcomes were all recurrence including minor recurrence and delayed thromboembolism.

This study was retrospective in design; therefore, follow-up protocols differed between patients. MRA was main follow imaging protocol. MRA including time-of-flight sequence was performed on a 1.5 T or 3 T system with or without contrast enhancement. The first evaluation after treatment was usually performed at six months after coiling. Follow-up evaluations were performed yearly thereafter. If major recurrence was suspected, a subsequent DSA was performed within a month.

In the cases with stent assisted coil embolization, 100 mg aspirin and 75 mg of clopidogrel were prescribed at least seven days prior to the procedure. For stent-assisted procedures in the setting of subarachnoid hemorrhages, patients were loaded with 300 mg aspirin and clopidogrel immediately after the procedure, with or without intravenous tirofiban. Patients were then maintained on daily doses of 75 mg clopidogrel and 100 mg aspirin for six months, followed by 100 mg of aspirin per day indefinitely.

Aneurysm coiling

The decision to treat aneurysms with endovascular therapy was based on agreement between the attending neurosurgeon and the interventional radiologist. The decision was based on aneurysm morphology, aneurysm parent vessel relationship, patient preference, and the patient's surgical comorbidities. In patients with favorable aneurysm geometries, the aim was to selectively and completely coil the aneurysm while preserving the patency of the parent artery. Depending on operator discretion, wide-neck aneurysms were coiled with stents or with balloon assistance. For unruptured aneurysms, coiling was performed with an initial 50 U/Kg heparin bolus and by maintaining the intraoperative activated clotting time at 1.5–2.5 times the baseline rate. Systemic heparinization was not deployed during coil embolization for ruptured aneurysms. Coils (commercially available bare metal or hydrogel coils) were placed until satisfactory obliteration was achieved or until placement of additional coils was not possible.

Statistical analysis

We performed statistical analysis with SPSS version 20.0 (SPSS Inc., chicago, IL, USA). We performed simple comparisons using Chi-square tests, Fisher's exact tests, and Mann-Whitney U tests when applicable. To identify potential risk factors for aneurysm recurrence, we performed the log-rank test for univariate analysis. Actuarial rate was estimated by Kaplan-Meier method. Cox regression analysis was used for multivariate analyses. Parameters with p values <0.1 on univariate analysis were entered into multivariate analysis. Hazard ratio (HR) with 95% confidence intervals (95% CI) were calculated using Cox regression analysis. p<0.05 was considered to be statistically significant.

RESULTS

Immediate treatment outcomes

Among 150 aneurysms, 30 were ruptured and 120 were unruptured. Stent-assisted coil embolization (SAC) was used in 54 cases, balloon-assisted coil embolization was used in 19 cases, and simple coil embolization using one or two microcatheters was used in the remaining cases. The patients' baseline characteristics are described in Table 1. Immediate complete occlusion was achieved in 27 cases, neck remnants remained in 88 cases, and residual sacs remained in 35 cases. Procedural rupture occurred in three cases, and procedural thrombus formation occurred in 13 cases. Procedure-related morbidity occurred in five patients (1 rupture, 4 thromboembolisms). The median clinical and radiological follow-up periods were 38 months (range, 2–110) and 26 months (range,

Table 1. Baseline patient characteristics

Characteristics	Value
Gender (male/female)	43/107
Age (years)	58.2±11.3
Aneurysm characteristics	
Ruptured aneurysm	30
Incorporating vessel	59
Thrombosed aneurysm	13
Daughter sac	87
Location	
Distal internal carotid artery	100
Anterior cerebral artery	18
Middle cerebral artery	5
Posterior circulation	27
Size	
10–25 mm	139
>25 mm	11

6–108), respectively.

Primary outcomes

Major recurrence occurred in 23 cases during the follow-up period, including 2 ruptures, 3 symptomatic recurrences, and 18 asymptomatic recurrences. Symptomatic recurrences were associated with mass effect, with one case of stem compression and two cases of cranial nerve palsy. All recurrences were treated with subsequent recoiling. The annual major recurrence rate was 4.6±1.2% per year. The estimated annual rate of major recurrence did not decline during the follow-up period (Fig. 1). Simple comparison test showed that incorporating vessels, daughter sacs, and the degree of occlusion were associated with major recurrence (Table 2). According to univariate and multivariate analysis using log-rank and Cox regression tests, occlusion status was associated with major recurrence (p=0.008, HR 3.15, 95% CI 1.34–7.41) (Table 3, Fig. 2). Thrombosed aneurysms tended to show early recurrence, but this effect was not statistically significant in this data set (Fig. 3). Other variables, such as gender, incorporating vessels, stent usage, daughter sacs, location, size, and rupture were not associated with major recurrence or bleeding (p>0.05). Table 4 showed information of patients with recurrence.

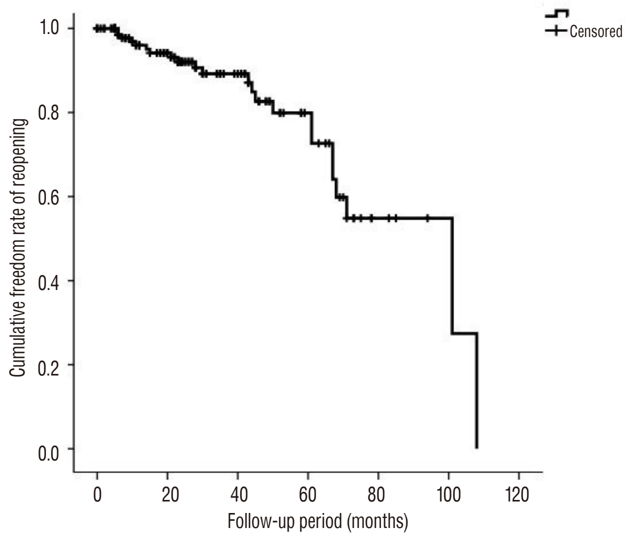

Fig. 1. Estimated major and minor recurrence-free rate.

Secondary outcomes

Recurrences, both major and minor, occurred in 51 cases.

Table 2. Characteristics of patients with and without major recurrence

Characteristics	No major recurrence (n=127)	Major recurrence (n=23)	p-value
Gender (female)	90	17	0.776
Median age (years)	57 (34–79)	60 (40–85)	0.584
Aneurysm characteristics			
Ruptured aneurysm	25	5	0.821
Incorporating vessel	45	14	0.022
Thrombosed aneurysm	11	2	1.000
Daughter sac	79	8	0.014
Location			0.085
Distal internal carotid artery	86	14	
Anterior cerebral artery	17	1	
Middle cerebral artery	5	0	
Posterior circulation	19	8	
Size (>25 mm)	10	1	0.551
Use of stent	54	8	0.782
Occlusion status			0.001
Complete	27	0	
Residual neck	77	11	
Incomplete	23	12	

Values are presented as number (range)

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Table 3. Parameters potentially affecting major recurrence

	Univariate	Multivariate	Hazard ratio	95% confidence interval
Gender (female)	0.423			
Incorporating vessel	0.147			
Daughter sac	0.548			
Thrombosed aneurysm	0.065	0.144	3.03	0.68–13.51
Location	0.130			
Ruptured aneurysm	0.238			
Size (>25 mm)	0.810			
Use of stent	0.563			
Occlusion status	0.028	0.008	3.15	1.34–7.41

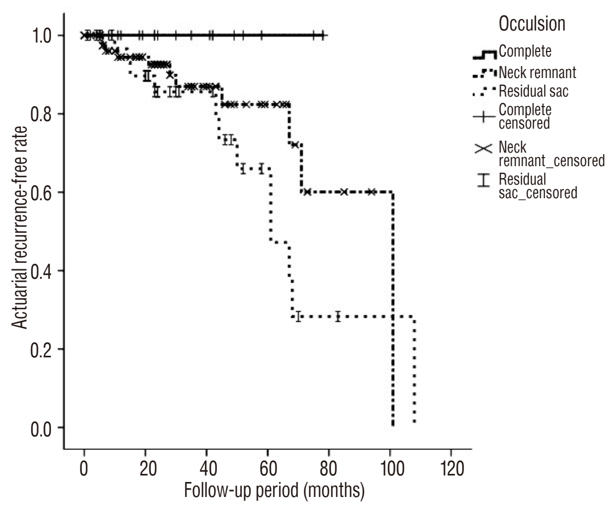

Fig. 2. Actuarial major recurrence rate according to occlusion status.

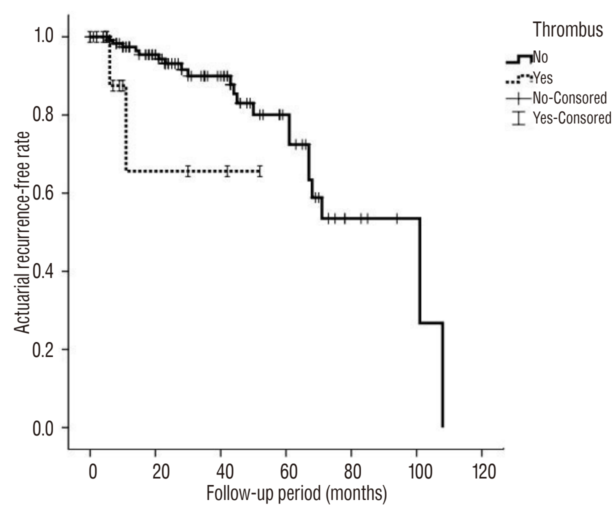

Fig. 3. Actuarial major recurrence rate according to incidence of intra-aneurysmal thrombus.

The actuarial annual overall recurrence rate was estimated to be 8.1±1.3% per year. This rate remained stable at the long-term follow up periods. Delayed thromboembolism occurred in eight patients, and the median time from procedure to delayed thromboembolism was seven months (range, 1–23). All delayed thromboembolic events occurred in the incompletely embolized group, but the differences in delayed thromboembolisms between groups did not show statistically significant (p=0.264, log-rank test). Other variables, including use of stents, gender, incorporating vessels, daughter sacs, aneurysm location, aneurysm size, and rupture status were not associated with delayed thromboembolism in this study (p>0.05). None of the patients showed delayed thromboembolic events after two years (Fig. 4).

Subgroup analysis

Among 54 SAC, 7 were treated with a double-stent overlapping technique with coil embolization to achieve additional flow diversion. Of these seven patients, there were no major recurrance, but two patients had symptomatic thromboembolic events during the clinical follow-up period. However, the association between the double-stent overlapping technique and thromboembolic events was not statistically significant (no stent vs. single stent vs. double stent overlapping, p=0.105, log-rank test).

Among the 35 patients with residual sacs after coil embolization, 28 showed contrast stasis until delayed venous phase at the end of the procedure. Among 28 patients, 24 showed contrast stasis prior to the coil embolization. Ten out of 28 contrast stasis after the coil embolization showed major recurrence during the follow-up period. Newly-developed contrast

Table 4. Information of the patients with major recurrence

Patient number	Age	Gender	Location of aneurysm	Maximal diameter (mm)	Dome-neck ratio	Type of treatment	Initial occlusion	Time to recurrence (months)	Type of recurrence
1	63	Female	P-com	19	1.7	Simple	Residual neck	11	Asymptomatic
2	48	Female	Basilar tip	33	1.0	Simple	Incomplete	0	Rupture
3	63	Female	P1/2	17	1.3	Simple	Incomplete	17	Asymptomatic
4	69	Female	Cavernous ICA	18	1.0	Stent assisted (enterprise)	Incomplete	15	Asymptomatic
5	72	Female	P-com	13	1.0	Simple	Incomplete	44	Asymptomatic
6	53	Female	Paraclinoid ICA	16.7	1.1	Stent assisted (enterprise)	Incomplete	50	Asymptomatic
7	60	Female	Paraclinoid ICA	19.5	1.6	Simple	Incomplete	43	Asymptomatic
8	55	Female	Paraclinoid ICA	20	1.7	Simple	Residual neck	45	Asymptomatic
9	53	Male	Basilar tip	17.3	1.3	Simple	Residual neck	67	Asymptomatic
10	46	Female	Basilar tip	13.5	1.6	Simple	Incomplete	68	Asymptomatic
11	42	Female	Cavernous ICA	20.3	1.0	Stent assisted (neuroform)	Incomplete	61	Asymptomatic
12	70	Female	Basilar tip	11.4	1.0	Simple	Residual neck	7	Symptomatic
13	85	Female	P-com	16	1.0	Simple	Residual neck	21	Asymptomatic
14	72	Female	Cavernous ICA	18	1.0	Stent assisted (enterprise)	Incomplete	30	Asymptomatic
15	65	Female	P-com	12	1.1	Simple	Incomplete	67	Asymptomatic
16	62	Male	A-com	12	1.1	Simple	Incomplete	108	Rupture
17	47	Male	Basilar tip	24.5	1.2	Stent assisted (enterprise)	Residual neck	6	Asymptomatic
18	42	Male	Basilar tip	17.3	1.4	Stent assisted (enterprise)	Residual neck	71	Asymptomatic
19	40	Male	Basilar tip	15.5	1.2	Simple	Residual neck	101	Asymptomatic
20	60	Female	Paraclinoid ICA	15.8	1.0	Simple	3	61	Asymptomatic
21	53	Female	CavernousICA	16.5	1.0	Stent assisted (enterprise)	Residual neck	28	Aymptomatic
22	56	Male	P-com	14.7	1.2	Stent assisted (enterprise)	Residual neck	6	Asymptomatic
23	63	Female	Cavernous ICA	19	1.7	Simple	Residual neck	11	Symptomatic

P-com : posterior communicating artery, ICA : internal carotid artery

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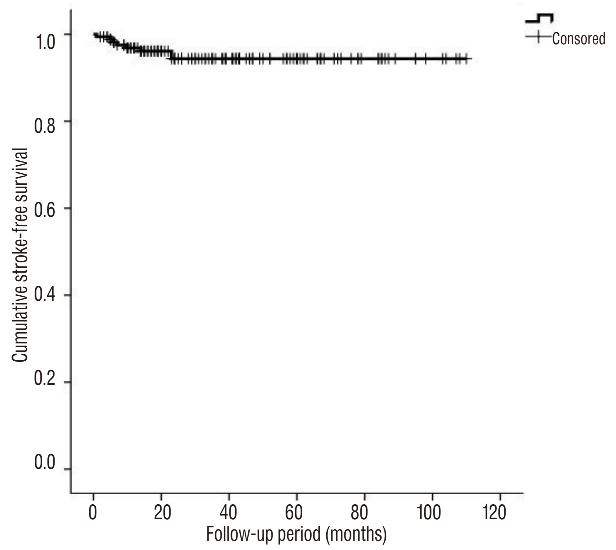

Fig. 4. Actuarial stroke-free survival rate.

stasis occurred in four patients with aneurysms, two of which showed major recurrence during follow-up.

DISCUSSION

Large or giant aneurysms are difficult to treat[4,21,22]. Although numerous efforts have been made to develop effective treatments for these aneurysms, outcomes remain unsatisfactory. In one recent large case series, a 33% re-treatment rate during 26.3 months of clinical follow-up was demonstrated[4,13,23]. Our study had a relatively low recurrence rate when compared to this previous study. However, recurrence was not uncommon, and the annual risk of recurrence did not decrease with the length of follow-up.

Previous studies demonstrated that SAC could lower the recurrence rate after coil embolization for cerebral aneurysms[16,20]. However, our results showed no significant difference between stent use or lack of stent use. Theoretically, stent use could help support the catheter, which could facilitate compact packing and healing[2,16]. Also, the stent allows for some flow diversion. However, according to our results, single stent could not provide adequate catheter stability and facilitated healing in large or giant aneurysm treatment. Also, using a single stent to divert flow in large or giant aneurysms does not adequately reduce recurrence because of the greater inflow through the large necks of these giant aneurysms. Our subgroup analysis showed that selective coil embolization with double stent overlapping prevented recurrence during the follow-up period. These results suggest that minimal flow diversion with stent overlapping may reduce the risk of aneurysm reopening, while a single stent does not reduce this risk[3,14,16]. However, our data showed that high rate (28.6%) of delayed thromboembolic events occurred in the double stent overlapping group despite antiplatelet medication. Although our data did not show association between usage of stent and delayed thromboembolic infarction, stent assited coil embolization could be associated with delayed thromboembolism or instent stenosis[9]. Recent study demonstrated that antiplatelet resistance could be associated with delayed thromboembolism[15]. Therefore optimal antiplatelet should be used after stent assisted coil embolization. These results should be taken into account in future studies of flow-diverting devices.

This study used visual analysis rather than packing density to evaluate the degree of packing. We thought that packing density could not be applied to certain aneurysms, especially large or giant aneurysms, because a large proportion of aneurysms showed daughter sacs. These daughter sacs made adequate contrast filling of the aneurysms difficult, and filling was not always possible in large or giant aneurysms during 3-dimensional rotatory angiograms. Thus, conventional calculation methods (height×width×depth/2) would be more inaccurate when used with large aneurysms compared to small saccular aneurysms[5]. In this study, we used visual analysis, which can vary between observers[17], but visual analysis by multiple interpreters seemed to be a reliable predictor of recurrence in this study.

Contrast stasis has been reported as a benign angiographic finding after coil embolization[11,22]. However, this data suggests that contrast stasis is similar to incomplete coil embolization, which is associated with a high risk of recurrence. Although thrombus formation can occur in some patients with contrast stasis, intraluminal thrombus may also be associated with a high risk of recurrence[25]. In this study, inadequate filling of the aneurysmal sac in large or giant aneurysms was associated with an increased risk of recurrance and delayed stroke. A previous study exploring delayed thromboembolism after stent-assisted coil embolization also showed a high rate of delayed thromboembolism following incomplete aneurysm occlusion[12]. Aneurysmal necks with loose packing could also be a source of delayed thromboembolism in large or giant aneurysms, regardless of stent use. Therefore, additional coil embolization should be used in large or giant aneurysms if possible.

Previous studies have tended to use simple comparisons with chi-square or Fisher's exact tests. However, since the risk of aneurysmal reopening is largely influenced by the length of the follow-up period, time should be included as a variable in statistical analyses[4]. Our data demonstrate that simple comparisons and log rank tests showed differing associations between variables and recurrences. An additional finding in our study is that the annual recurrence rate did not decrease with follow-up time, suggesting that long-term follow-up seems to be essential after coil embolization of large or giant aneurysms. A prospective, long-term follow-up study with large size would be helpful to further assess this issue.

In this study, several limitations should be noted. Major recurrence was defined as any growth of an aneurysm that required additional treatment. This outcome measure is subjective, and inter-observer disagreement may exist. Also, the retrospective design of this study is a major limitation. The retrospective design implies that the study population may be heterogeneous, and follow-up periods and protocols varied. A multicenter, prospective study would be helpful to further explore these questions.

CONCLUSION

In conclusion, incompletely occluded large or giant aneurysms showed a constant reopening rate (4.6% per year) during follow-up periods (mean, 38.3 months) after selective coil embolization. Therefore, long-term follow-up imaging is essential in order to reduce the risk of delayed rupture. Incompletely occluded large or giant aneurysm was also associated with delayed thromboembolism within two years. A large, prospective, long-term study is needed to further verify the role of endovascular treatment and to help overcome the limitations of endovascular treatment for large or giant aneurysms.

PATIENT CONSENT

The patient provided written informed consent for the publication and the use of their images.

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