Title	Symptomatic low-grade carotid stenosis with intraplaque hemorrhage and expansive arterial remodeling is associated with a high relapse rate refractory to medical treatment.
Author(s)	Yoshida, Kazumichi; Sadamasa, Nobutake; Narumi, Osamu; Chin, Masaki; Yamagata, Sen; Miyamoto, Susumu
Citation	Neurosurgery (2012), 70(5): 1143-1151
Issue Date	2012-05
URL	http://hdl.handle.net/2433/174710
Right	© 2011 by the Congress of Neurological Surgeons
Type	Journal Article
Textversion	author

Symptomatic low-grade carotid stenosis with intraplaque hemorrhage and expansive arterial remodeling is associated with a high relapse rate refractory to medical treatment

Kazumichi Yoshida, M.D., Ph.D.,[1] **Nobutake Sadamasa, M.D., Ph.D.,**[2] **Osamu Narumi, M.D., Ph.D.,**[2] **Masaki Chin, M.D.,**[3] **Sen Yamagata, M.D., Ph.D.,**[2] **and Susumu Miyamoto, M.D., Ph.D.**[1]

[1]Department of Neurosurgery, Kyoto University School of Medicine, Kyoto, Japan

[2]Department of Neurosurgery, Kurashiki Central Hospital, Okayama, Japan

[3]Department of Neurosurgery, Shizuoka General Hospital, Shizuoka, Japan

All correspondence should be addressed to: Kazumichi Yoshida

Department of Neurosurgery

Kyoto University Graduate School of Medicine

54 Kawahara-cho Shogoin Sakyo-ku, Kyoto, 606-8507 Japan

TEL: +81-75-751-3459   FAX: +81-75-752-9501

E-mail address: kazuy@kuhp.kyoto-u.ac.jp

Abstract

Background: Carotid plaque characteristics considerably influence future risk of stroke. However, the severity of stenosis does not accurately reflect plaque burden in patients with expansive arterial remodeling.

Objective: The present study aimed to determine the therapeutic outcome of symptomatic carotid low-grade stenosis with vulnerable plaque based on MRI characterization.

Methods: We studied 25 (male, n = 23; age, 74.2 ± 5.6 years) of 29 consecutive patients with symptomatic carotid low-grade stenosis (< 50%) and both high-signal plaque and expansive remodeling on T1-weighted MR images. The remaining four were excluded due to impending stroke. A single antithrombotic and statin were administered and recurrent ischemic stroke was treated with dual antithrombotics. We considered carotid endarterectomy (CEA) when recurrence was refractory to aggressive medical treatment.

Results: During a 31.3 ± 16.4 month follow-up, 11 of the 25 patients developed a total of 30 recurrent ischemic events (46.0% per patient-year). The patients' characteristics did not significantly differ between the groups with and without recurrence (n = 11 and n = 14, respectively). Seven of 11 patients in the recurrence group who were treated with CEA remained free of ischemic events during a postoperative follow-up of 19.1 ± 14.6 months.

Conclusion: Symptomatic low-grade carotid stenosis with vulnerable plaque confirmed by MRI was associated with a high rate of stroke recurrence that was refractory to aggressive medical treatment. However, CEA was safe and effective for such patients. Plaque characterization by MRI has potential for more accurate stroke risk stratification in the management of carotid low-grade stenosis.

1 Key words: atherosclerosis, carotid artery disease, carotid endarterectomy, magnetic

2 resonance imaging, vulnerable plaque

3

4 Short Title: Carotid stenosis with vulnerable plaque

5

Introduction

Several large multicenter trials have established that carotid endarterectomy (CEA) significantly reduces stroke risk compared with medical treatment in patients with moderate to high-grade stenosis, but has no apparent benefit for those with low-grade stenosis.[1-4] The assessment of stroke risk from carotid atherosclerosis and determination of the need for surgical intervention in these randomized trials have been based on angiographic or ultrasonographic evaluations of stenosis rates.[5]

Accumulating evidence from recent vascular biology studies indicates that plaque stability depending on several factors such as plaque components, volume and morphological characteristics has a large impact on the risk of ischemic events from atherosclerotic disease.[6-9] Therefore, the importance of evaluating not only the severity of stenosis but also the vessel wall itself has been widely recognized for the management of carotid stenosis. While carotid plaque is generally assessed by ultrasonography, MRI has been gaining importance in the evaluation of carotid atherosclerosis with recent technological developments in MRI equipment and imaging sequencing. Many investigations have demonstrated that carotid MRI can accurately, non-invasively and objectively provide a considerable amount of information about carotid atherosclerosis.[10-13] Moreover, several reports have revealed an important characteristic of plaque associated with a high risk of stroke on MR images.[14-17]

Luminography does not necessarily reflect a significant burden of atherosclerotic plaque due to expansive arterial remodeling in some patients with carotid stenosis.[18,19] Some might be at high risk for stroke even if angiography reveals only mild stenosis. Therefore, meticulous risk assessment for ischemic events based on plaque evaluation in addition to stenosis rates is significant, particularly for patients with low-grade

3

stenosis. However, few reports have assessed risk for mild stenosis based on plaque characterization.[20]

The present study retrospectively assesses the therapeutic outcomes of symptomatic carotid low-grade stenosis using MRI plaque evaluation at a single center.

Methods

Patients

We initially identified 29 consecutive patients with symptomatic carotid low-grade stenosis ($< 50\%$) accompanied by both high-signal plaque and expansive remodeling on T1-weighted MR images and a history of presenting at our institution between January 2004 and May 2009. We excluded four with impending stroke and finally studied data from 25 patients (male, n = 23; age, 74.2 ± 5.6 years).

Expansive remodeling was diagnosed using carotid MRI and the criteria of Hardie et al.[21]

Symptomatic patients were defined as those who presented with transient ischemic attack (TIA), ischemic stroke, or amaurosis fugax in the territory of the ipsilateral carotid artery at the time of admission. If necessary, patients underwent Holter monitoring, transesophageal echocardiography or aortic MRI and were checked by cardiologists. We excluded patients when cardiogenic or aortogenic embolism remained as the possible etiology.

Our institutional Ethics Committee approved the study, and all patients provided written informed consent to analyze their records and publish the findings.

Imaging

The severity of carotid artery stenosis was evaluated by digital subtraction

4

angiography (DSA), computed tomography angiography (CTA), or magnetic resonance angiography (MRA) using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria.[3] All patients who were scheduled for CEA were also examined by DSA.

Atherosclerotic plaque associated with intraplaque hemorrhage (IPH) was diagnosed when axial T1-weighted 3D gradient-echo black blood (BB)-MRI images revealed high signals relative to the sternocleidomastoid muscle.[22] Using axial MR images of areas with the highest rate of stenosis, relative overall plaque MR signal intensity (roSI) was measured and compared with plaque MRI signals as described.[23]

Plaque in the patients who underwent CEA was characterized in more detail by obtaining several additional MR images as follows. Plaque components were precisely evaluated using 2D spin-echo BB-MRI,[23] plaque distribution was evaluated using long-axis 3D inversion-recovery turbo field echo BB-MRI,[24] and fibrous cap rupture or erosion was detected using 3D time of flight (TOF) MRI.[25]

The parameters of each MR imaging sequences were as follows.

Axial black-blood T1-weighted images (3D gradient-echo): field of view, 220 mm; matrix size, 179×256; TR/TE, 30/5.8 msec; flip angle, 20°.

Axial black-blood T1-weighted images (2D double IR-TSE): field of view, 150 mm; matrix size, 256×256; TR/TE, 700-1000 (1 cardiac cycle)/12 msec; flip angle, 110°; slice thickness, 3.0 mm.

Long-axis T1-weighted images (3D IR turbo field echo): field of view, 150 mm; matrix size, 320×512; TR/TE/TI, 10/2.7/500 msec; flip angle, 35°; slice thickness, 1.6 mm.

Treatment

Medical treatment was started essentially with a single antithrombotic drug selected from among aspirin, ticlopidine, clopidogrel and cilostazol. Concomitant hypertension, hyperlipidemia or diabetes was also treated if necessary. Angiotensin II receptor blockers and statins were preferentially administered to control hypertension and hyperlipidemia, respectively. Dual antithrombotic therapy was administered if patients developed recurrent ischemic stroke or had other ischemic vascular diseases. Ischemic symptom recurrence was defined as TIA, MRI-confirmed infarct or amaurosis fugax in the territory of the ipsilateral carotid artery.

We examined the implementation of CEA when patients presented with more than two recurrences despite maximal medical therapy, had no other general problems and consented to surgical intervention. Carotid endarterectomy proceeded under general anesthesia and with intra-operative monitoring of somatosensory evoked potentials (SEP) and near-infrared spectroscopy (NIRS). An internal shunt was selectively applied when the SEP amplitude fell by > 50% or the value of NIRS dropped by > 20%. Patients continued medical treatment with a single antithrombotic after undergoing CEA.

Statistical analysis

We investigated the number of recurrences during follow-up under medical treatment (period between starting medical treatment and surgical intervention for patients who underwent CEA). Differences in risk factors, medical regimen, roSI on BB-MRI, and duration of follow-up were analyzed between groups with and without recurrence. We also analyzed excised specimens, perioperative complications and postoperative recurrence after CEA.

Numerical data are expressed as means ± standard deviation. Statistical significance

was calculated using Student's *t* test or Fisher's exact test and probability values of < 0.05 were considered significant. All data were statistically analyzed using SPSS 12.0 for Windows.

Results

During a follow-up period of 31.3 ± 16.4 months while under medical management, 11 (44%) of 25 patients developed a total of 30 ischemic recurrences (mean, 2.73 ± 1.85 each). The annual recurrence rate under medical management was thus 46.0% per patient-year. None of age, gender, hypertension, hyperlipidemia, diabetes, ischemic heart disease, atrial fibrillation, medical regimen, roSI and duration of follow-up significantly differed between the groups with (n = 11) and without (n = 14) recurrence (Table 1).

Seven of 11 patients with recurrence underwent CEA 12.1 ± 10.4 days after the last ischemic attack. The duration between the initial event and CEA was 35.4 ± 16.9 months and the number of recurrences before CEA was 3.29 ± 2.06. The findings of DSA revealed a stenosis rate of 27.1 ± 9.9% and obvious ulceration in two patients. Distinctly high signals of plaque were found on BB-MRI of all patients and the roSI was 1.84 ± 0.21. Preoperative TOF-MRI assessment of fibrous cap predicted ruptured or thin fibrous cap in four patients and the quality of MR images from one patient was too low to evaluate. Internal shunts were used in two of the CEA procedures. Histological assessment of excised plaques confirmed massive and fresh IPH in all specimens. Five and two plaques had ruptured and eroded fibrous caps, respectively. Postoperative diffusion weighted images confirmed the absence of perioperative complications such as new infarcts in all patients, whereas a neck hematoma and transient hoarseness

1 occurred in one patient each.

2 No ischemic events, including those in the contralateral hemisphere, were confirmed

3 during the postoperative follow-up period of 19.1 ± 14.6 months (Table 2).

4

5 **Illustrative case (Patient No. 5)**

6 This 73-year-old man with a history of minor stroke presented with right arm

7 weakness at another hospital during July 2006. He remained under treatment with an

8 antithrombotic until October 2007 when he was admitted to our hospital with TIA

9 manifesting as right arm weakness and sensory disturbance. While left carotid

10 angiography revealed only 26% stenosis with slight luminal irregularity (Fig. 1A), axial

11 and long-axis BB-MRI clearly showed appreciable high-signal plaque in the form of

12 expansive remodeling at the carotid bifurcation indicating fresh IPH (Fig. 1B and C).

13 Neither atherosclerotic plaque along the ascending aorta on aortic MRI nor intracardiac

14 thrombus on transesophageal echocardiography was detected. Hyperlipidemia was

15 confirmed by laboratory data upon admission.

16 These findings indicated a diagnosis of recurrent ischemic events due to

17 artery-to-artery embolism originating from the carotid low-grade stenosis with unstable

18 plaque. The patient was administered with dual antithrombotics and statin. He was

19 readmitted to our hospital during July 2008 with right arm and leg weakness. Diffusion

20 weighted images demonstrated fresh multiple minor infarcts in the left hemisphere,

21 whereas left carotid angiography identified no appreciable elevation in the rate of

22 stenosis.

23 Because not even maximal medical therapy could prevent recurrent ischemic events,

24 the patient provided written informed consent to undergo CEA on the seventh day from

1 the last event. The postoperative course was uneventful and no new infarct was

2 demonstrated on diffusion weighted images obtained two days postoperatively.

3 Macroscopic observation of an excised specimen identified a disrupted fibrous cap (Fig.

4 1D) and histological assessment also revealed a ruptured fibrous cap and massive IPH.

5 The patient was treated only with aspirin after CEA and he has remained stroke-free at

6 14 months of follow-up.

7

8 **Discussion**

9 Carotid atherosclerosis has been widely evaluated by ultrasonography, as it is

10 noninvasive and can provide information about luminal stenosis and, to some extent,

11 plaque characteristics.[26, 27] However, limitations are associated with assessing the

12 carotid artery using this modality since discriminating IPH from a lipid core in

13 atherosclerotic plaque is less robust. Furthermore, plaque with dense calcification,

14 stenosis at higher locations and patients with a short neck cannot be fully imaged using

15 US and interpretation of the results is extremely operator-dependent.[28-30]

16 Since the quality of MR equipment has progressed and technical improvements have

17 been made in MR sequences, many studies have recently demonstrated the value of

18 high-resolution MRI for assessment of carotid plaque components, volume and

19 morphology.[10-13, 23, 31, 32] That IPH, which plays a potent role in plaque vulnerability, can

20 be visualized as intense signals on T1-weighted MR images is generally accepted and

21 intense signals are generated more frequently by symptomatic, than asymptomatic

22 carotid plaque.[10, 15, 33] The MR signal of IPH is obviously high during the acute phase

23 and declines over time.[34] Prospective studies of carotid atherosclerosis have revealed

24 that stenosis with IPH detected by MRI confers higher risk for ischemic events than that

9

without IPH in either symptomatic[35] or asymptomatic patients.[17] Considering the many reports describing MRI plaque evaluation of patients with carotid stenosis, regarding plaques with high-signal on T1-weighted MR images as being unstable and at high risk for ischemic stroke seems appropriate.

Few studies have examined the outcomes of medical treatment for symptomatic low-grade carotid stenosis. The European Surgery Carotid Trial (ECST) reported only a 1.3% rate of ipsilateral ischemic strokes lasting beyond seven days in patients with symptomatic mild (0-29%) carotid stenosis during three years of follow-up (0.43% per year) when stroke recurrence assessment was based on merely stenosis rate evaluation.[36] Among patients with < 50% stenosis in the NASCET study, the 5-year rate of any ipsilateral stroke was 18.7% in the medically treated group (3.74% per year).[3] Fritz et al. reported an 8.6% rate of ischemic events including TIA and stroke during two years of follow-up (4.3% per year) in 35 medically treated symptomatic patients with low grade stenosis (< 50%) or ulcerated plaques.[37] Although the rate of recurrent ischemic events has some variation among these studies, probably because of differences in the definition of ischemic events or rate of stenosis, they nevertheless concluded that patients with symptomatic low-grade stenosis did not benefit from CEA because the outcome of medical treatment was favorable.

To the best of our knowledge, only Altaf et al.[20] prospectively analyzed recurrence risk based on MRI plaque evaluation in addition to rates of stenosis among patients with symptomatic carotid low-grade stenosis. They showed that the rates of recurrent ischemic events in patients with symptomatic mild stenosis (30-49%) treated medically during a median follow-up period of 28 months were 25% and 10% in plaques with IPH detected or not by MRI, respectively. They concluded that carotid plaques with intense

1 signals on T1-weighted MR images are at higher risk for ischemic recurrence even

2 when the rate of stenosis is not significant.

3   The present retrospective analysis found ischemic recurrence in 44% of medically

4 treated patients who had high-signal plaque and expansive remodeling on T1-weighted

5 carotid MR images, and an annual recurrence rate reached 46.0% per patient-year. A

6 detailed comparative discussion is limited because reports on outcomes of medical

7 treatment for symptomatic mild stenosis based on MRI plaque evaluation are scarce.

8 Nonetheless, we can offer some explanations for the remarkably high rate of ischemic

9 recurrence in this study. Recurrence in our report included both stroke and TIA. The

10 recurrence rate excluding TIA in this study was still high at 36.8% per patient-year.

11 Stroke was diagnosed based on diffusion-weighted images regardless of the severity of

12 ischemic symptoms. The chances of an oversight in ischemic events seemed low

13 because patients were regularly followed up at a single institution. More importantly,

14 the fact that our study patients had not only carotid plaque with IPH detected by MRI

15 but also expansive remodeling might explain why our patients were at higher risk for

16 ischemic events than those described by Altaf et al. Expansive plaque remodeling in

17 patients with coronary artery atherosclerosis has been considered a major factor in

18 vulnerable plaque.[18, 19] A study using a murine model of carotid artery lesions found that

19 the macrophages characteristic of vulnerable plaques assist in expansive remodeling by

20 promoting matrix degeneration through matrix metalloproteinase secretion.[38] A recent

21 study of human carotid atherosclerosis using multidetector CT angiography also found

22 that the incidence of expansive remodeling is much higher among symptomatic, than

23 asymptomatic carotid plaques and that the extent of expansive remodeling correlated

24 with atherosclerotic plaque vulnerability.[21]

With respect to the safety of CEA for treating symptomatic carotid stenosis, large clinical trials have shown that the perioperative complication rate does not depend on the rate of carotid stenosis. Rates of death, disabling stroke, or any other stroke producing symptoms for more than seven days in the ECST report were 3.7% (70-99%) and 2.3% (0-29%) for severe and mild stenosis, respectively, with no statistically significant difference.[36] In addition, NASCET did not find a significant difference in the rate of disabling stroke at 30 days between groups with moderate (2.8%) and severe (3.0%) stenosis.[39] The fact that diffusion-weighted MR imaging in the present study confirmed the absence of perioperative ischemic events demonstrated the safety of CEA for patients with symptomatic low-grade stenosis. None of the patients described herein has presented with TIA or any stroke, even though they were treated with only single antiplatelet drugs after CEA for a median postoperative follow-up of 19 months. Therefore, our results might also indicate the relevance of CEA for patients with symptomatic low-grade stenosis accompanied by vulnerable plaque confirmed by MRI, although this assertion is limited by the number of patients studied and the short period of postoperative follow-up.

Carotid endarterectomy was adopted as a therapeutic option for patients who were refractory to multidisciplinary medical treatment in this study. However, we could not find distinctive differences in the patients' characteristics and MRI findings between the recurrence and non-recurrence groups, which remains an issue. To discriminate patients with low-grade carotid stenosis refractory to medical treatment before recurrences or screen extremely vulnerable plaques with diagnostic imaging remains challenging. In addition to IPH and expansive arterial remodeling, fibrous cap rupture is also an important feature of vulnerable plaques. In fact, a prospective study of asymptomatic

carotid stenosis with MRI plaque evaluation has demonstrated that ruptured fibrous caps more significantly influence ischemic events than IPH.[17] Precise assessment of fibrous cap status would thus seem key to discriminating extremely vulnerable plaques. Several studies of MRI plaque characterization have shown that ruptured or thin fibrous caps can be detected as "dark bands" on TOF images[25, 32, 40] and have demonstrated a moderate to good correlation between MRI findings and CEA specimens for diagnosing ruptured caps. However, these reports also pointed out the limitation of fibrous cap estimation by MRI due to poor image quality when the internal carotid artery is obviously angulated or tortuous or when plaques are densely calcified. In fact, 18-34% of the patients who underwent carotid MRI were excluded from analysis of the fibrous cap in these studies. The present study found that the preoperative estimation of fibrous cap from TOF MR images agreed with histological findings of excised plaques in only 4 of 7 patients. Thus, MRI is not yet satisfactory for fibrous cap assessment in the clinical setting. Improved spatial- and contrast-to-noise ratios, better spatial resolution using a higher magnetic field and faster imaging procedures will allow the identification of finer structures within atherosclerotic arterial walls[41] and enable more precise diagnosis of high-risk plaques for recurrent ischemic events.

The preventive effect against ischemic stroke for low-grade vulnerable stenosis between CEA and medical treatment should be compared. While anti-thrombotic drugs have been widely used to prevent strokes,[42] more aggressive medical treatment with dual anti-platelet medication with aspirin and clopidogrel is apparently more effective than aspirin alone.[43] In addition, statins seem to be appreciably effective against many disorders caused by systemic atherosclerosis. The ability of aggressive lipid-lowering therapy with statins to reduce the incidence of ischemic stroke has been verified by

several large randomized studies.[44, 45] In addition, high-resolution MRI studies have

demonstrated that statins suppress, stabilize and reduce carotid atherosclerotic

plaque.[46-48] Thus, the outcome of medical treatment for carotid stenosis should be

significantly improved by early multifaceted medical intervention for patients with

high-risk atherosclerotic disease. Comparing the long-term results between CEA and

aggressive medical treatment is mandatory to validate the use of CEA for low-grade

high-risk stenosis.

One limitation of the present study is that it was a retrospective analysis of a small

patient cohort over a relatively short follow-up period. Importantly, our patients did not

have symptomatic low-grade carotid stenosis but had plaque with positive remodeling

that was evident on high-signal on T1-weighted images. Therefore, the present findings

are not applicable to symptomatic low-grade stenosis in general. Nevertheless, our

findings promote awareness of the limitations of future stroke risk assessment based

solely on the severity of carotid stenosis.

Conclusion

Among patients with symptomatic low-grade carotid stenosis, those with plaque

containing IPH demonstrated by MRI undergoing outward remodeling were associated

with a high rate of stroke recurrence regardless of medical treatment. Carotid

endarterectomy prevented further stroke in patients who were refractory to aggressive

medical therapy and was validated for treating a subset of patients with low-grade, but

high-risk carotid stenosis determined by plaque evaluation.

1 **References**

1. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *JAMA*. 1995;273(18):1421-1428.

2. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet*. 1998;351(9113):1379-1387.

3. Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med*. 1998;339(20):1415-1425.

4. Halliday A, Mansfield A, Marro J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet*. 2004;363(9420):1491-1502.

5. Biller J, Feinberg WM, Castaldo JE, et al. Guidelines for carotid endarterectomy: a statement for healthcare professionals from a Special Writing Group of the Stroke Council, American Heart Association. *Circulation*. 1998;97(5):501-509.

6. Streifler JY, Eliasziw M, Fox AJ, et al. Angiographic detection of carotid plaque ulceration. Comparison with surgical observations in a multicenter study. North American Symptomatic Carotid Endarterectomy Trial. *Stroke*. 1994;25(6): 1130-1132.

7. Carr S, Farb A, Pearce WH, Virmani R, Yao JS. Atherosclerotic plaque rupture in symptomatic carotid artery stenosis. *J Vasc Surg*. 1996;23(5):755-765;

1   discussion 765-756.

2   8.   Falk E. Stable versus unstable atherosclerosis: clinical aspects. *Am Heart J.*

3   1999;138(5 Pt 2):S421-425.

4   9.   Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient:

5   a call for new definitions and risk assessment strategies: Part I. *Circulation.*

6   2003;108(14):1664-1672.

7   10.   Yuan C, Mitsumori LM, Ferguson MS, et al. In vivo accuracy of multispectral

8   magnetic resonance imaging for identifying lipid-rich necrotic cores and

9   intraplaque hemorrhage in advanced human carotid plaques. *Circulation.*

10   2001;104(17):2051-2056.

11   11.   Cai JM, Hatsukami TS, Ferguson MS, Small R, Polissar NL, Yuan C.

12   Classification of human carotid atherosclerotic lesions with in vivo multicontrast

13   magnetic resonance imaging. *Circulation.* 2002;106(11):1368-1373.

14   12.   Saam T, Ferguson MS, Yarnykh VL, et al. Quantitative evaluation of carotid

15   plaque composition by in vivo MRI. *Arterioscler Thromb Vasc Biol.*

16   2005;25(1):234-239.

17   13.   Takaya N, Cai J, Ferguson MS, et al. Intra- and interreader reproducibility of

18   magnetic resonance imaging for quantifying the lipid-rich necrotic core is

19   improved with gadolinium contrast enhancement. *J Magn Reson Imaging.* 2006;

20   24(1):203-210.

21   14.   Yuan C, Zhang SX, Polissar NL, et al. Identification of fibrous cap rupture with

22   magnetic resonance imaging is highly associated with recent transient ischemic

23   attack or stroke. *Circulation.* 2002;105(2):181-185.

24   15.   Moody AR, Murphy RE, Morgan PS, et al. Characterization of complicated

carotid plaque with magnetic resonance direct thrombus imaging in patients with cerebral ischemia. *Circulation.* 2003;107(24):3047-3052.

16. Saam T, Cai J, Ma L, et al. Comparison of symptomatic and asymptomatic atherosclerotic carotid plaque features with in vivo MR imaging. *Radiology.* 2006;240(2):464-472.

17. Takaya N, Yuan C, Chu B, et al. Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI--initial results. *Stroke.* 2006;37(3):818-823.

18. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med.* 1987;316(22):1371-1375.

19. Pasterkamp G, Galis ZS, de Kleijn DP. Expansive arterial remodeling: location, location, location. *Arterioscler Thromb Vasc Biol.* 2004;24(4):650-657.

20. Altaf N, Daniels L, Morgan PS, et al. Detection of intraplaque hemorrhage by magnetic resonance imaging in symptomatic patients with mild to moderate carotid stenosis predicts recurrent neurological events. *J Vasc Surg.* 2008;47(2):337-342.

21. Hardie AD, Kramer CM, Raghavan P, Baskurt E, Nandalur KR. The impact of expansive arterial remodeling on clinical presentation in carotid artery disease: a multidetector CT angiography study. *AJNR Am J Neuroradiol.* 2007;28(6):1067-1070.

22. Endo H, Yoshida K, Kurosaki Y, et al. [Detection of intraplaque hemorrhage with use of screening black-blood MRI]. *No Shinkei Geka.* 2009;37(3):249-253.

23. Yoshida K, Narumi O, Chin M, et al. Characterization of carotid atherosclerosis

and detection of soft plaque with use of black-blood MR imaging. *AJNR Am J Neuroradiol.* 2008;29(5):868-874.

24. Yoshida K, Endo H, Sadamasa N, et al. Evaluation of carotid artery atherosclerotic plaque distribution by using long-axis high-resolution black-blood magnetic resonance imaging. *J Neurosurg.* 2008;109(6):1042-1048.

25. Hatsukami TS, Ross R, Polissar NL, Yuan C. Visualization of fibrous cap thickness and rupture in human atherosclerotic carotid plaque in vivo with high-resolution magnetic resonance imaging. *Circulation.* 2000;102(9):959-964.

26. Grønholdt ML, Nordestgaard BG, Schroeder TV, Vorstrup S, Sillesen H. Ultrasonic echolucent carotid plaques predict future strokes. *Circulation.* 2001;104(1):68-73.

27. Kalogeropoulos A, Terzis G, Chrysanthopoulou A, Hahalis G, Siablis D, Alexopoulos D. Risk for transient ischemic attacks is mainly determined by intima-media thickness and carotid plaque echogenicity. *Atherosclerosis.* 2007;192(1):190-196.

28. Mikkonen RH, Kreula JM, Virkkunen PJ. Reproducibility of Doppler ultrasound measurements. *Acta Radiol.* 1996;37(4):545-550.

29. Kuntz KM, Polak JF, Whittemore AD, Skillman JJ, Kent KC. Duplex ultrasound criteria for the identification of carotid stenosis should be laboratory specific. *Stroke.* 1997;28(3):597-602.

30. Mathiesen EB, Joakimsen O, Bønaa KH. Intersonographer reproducibility and intermethod variability of ultrasound measurements of carotid artery stenosis: The Tromsø Study. *Cerebrovasc Dis.* 2000;10(3):207-213.

31. Yuan C, Kerwin WS, Ferguson MS, et al. Contrast-enhanced high resolution

MRI for atherosclerotic carotid artery tissue characterization. J *Magn Reson Imaging.* 2002;15(1):62-67.

32. Cai J, Hatsukami TS, Ferguson MS, et al. In vivo quantitative measurement of intact fibrous cap and lipid-rich necrotic core size in atherosclerotic carotid plaque: comparison of high-resolution, contrast-enhanced magnetic resonance imaging and histology. *Circulation.* 2005;112(22):3437-3444.

33. Cappendijk VC, Cleutjens KB, Heeneman S, et al. In vivo detection of hemorrhage in human atherosclerotic plaques with magnetic resonance imaging. *J Magn Reson Imaging.* 2004;20(1):105-110.

34. Chu B, Kampschulte A, Ferguson MS, et al. Hemorrhage in the atherosclerotic carotid plaque: a high-resolution MRI study. *Stroke.* 2004;35(5):1079-1084.

35. Altaf N, MacSweeney ST, Gladman J, Auer DP. Carotid intraplaque hemorrhage predicts recurrent symptoms in patients with high-grade carotid stenosis. *Stroke.* 2007;38(5):1633-1635.

36. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. European Carotid Surgery Trialists' Collaborative Group. *Lancet.* 1991;337(8752):1235-1243.

37. Fritz VU, Levien LJ. Therapy for isolated, low and high grade symptomatic carotid artery stenosis. *Ann Vasc Surg.* 1988;2(4):367-372.

38. Ivan E, Khatri JJ, Johnson C, et al. Expansive arterial remodeling is associated with increased neointimal macrophage foam cell content: the murine model of macrophage-rich carotid artery lesions. *Circulation.* 2002;105(22):2686-2691.

39. Ferguson GG, Eliasziw M, Barr HW, et al. The North American Symptomatic Carotid Endarterectomy Trial : surgical results in 1415 patients. *Stroke.*

1.   1999;30(9):1751-1758.

2.   40.   Trivedi RA, U-King-Im J, Graves MJ, et al. Multi-sequence in vivo MRI can

3.   quantify fibrous cap and lipid core components in human carotid atherosclerotic

4.   plaques. *Eur J Vasc Endovasc Surg.* 2004;28(2):207-213.

5.   41.   Yarnykh VL, Terashima M, Hayes CE, et al. Multicontrast black-blood MRI of

6.   carotid arteries: comparison between 1.5 and 3 tesla magnetic field strengths. *J*

7.   *Magn Reson Imaging.* 2006;23(5):691-698.

8.   42.   Collaborative overview of randomised trials of antiplatelet therapy-I: Prevention

9.   of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in

10.   various categories of patients. Antiplatelet Trialists' Collaboration. *BMJ.*

11.   1994;308(6921):81-106.

12.   43.   Markus HS, Droste DW, Kaps M, et al. Dual antiplatelet therapy with

13.   clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler

14.   embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli

15.   in Symptomatic Carotid Stenosis (CARESS) trial. *Circulation.*

16.   2005;111(17):2233-2240.

17.   44.   Group HPSC: MRC/BHF Heart Protection Study of cholesterol lowering with

18.   simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled

19.   trial. *Lancet.* 2002;360(9326):7-22.

20.   45.   Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of

21.   cholesterol-lowering treatment: prospective meta-analysis of data from 90,056

22.   participants in 14 randomised trials of statins. *Lancet.*

23.   2005;366(9493):1267-1278.

24.   46.   Corti R, Fuster V, Fayad ZA, et al. Effects of aggressive versus conventional

1   lipid-lowering therapy by simvastatin on human atherosclerotic lesions: a

2   prospective, randomized, double-blind trial with high-resolution magnetic

3   resonance imaging. *J Am Coll Cardiol.* 2005;46(1):106-112.

4   47.   Saam T, Yuan C, Chu B, et al. Predictors of carotid atherosclerotic plaque

5   progression as measured by noninvasive magnetic resonance imaging.

6   *Atherosclerosis.* 2007;194(2):e34-42.

7   48.   Underhill HR, Yuan C, Zhao XQ, et al. Effect of rosuvastatin therapy on

8   carotid plaque morphology and composition in moderately hypercholesterolemic

9   patients: a high-resolution magnetic resonance imaging trial. *Am Heart J.*

10   2008;155(3):584.e581-588, 2008.

11

Figure legends

Figure 1. Angiographic and MR images of left carotid artery obtained from Patient 5.

A. Preoperative digital subtraction angiography (DSA) image acquired after two strokes that were refractory to medical treatment. Bulb shows slight luminal irregularity but only 26% stenosis based on North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria.

B. Long-axis T1-weighted black-blood MR image of carotid bifurcation shows large amount of plaque without significant narrowing of internal carotid artery (ICA lumen; expansive arterial remodeling).

C. T1-weighted black-blood MR image perpendicular to long axis of ICA at bifurcation also indicates expansive remodeling. *ICA lumen. SCM, sternocleidomastoid muscle.

D. Excised carotid plaque has yellowish luminal surface at carotid bifurcation and extensively thinned and partially disrupted fibrous cap on luminal surface of the ICA. CCA, common carotid artery.

Figure 1-A

Figure 1-B

* SCM
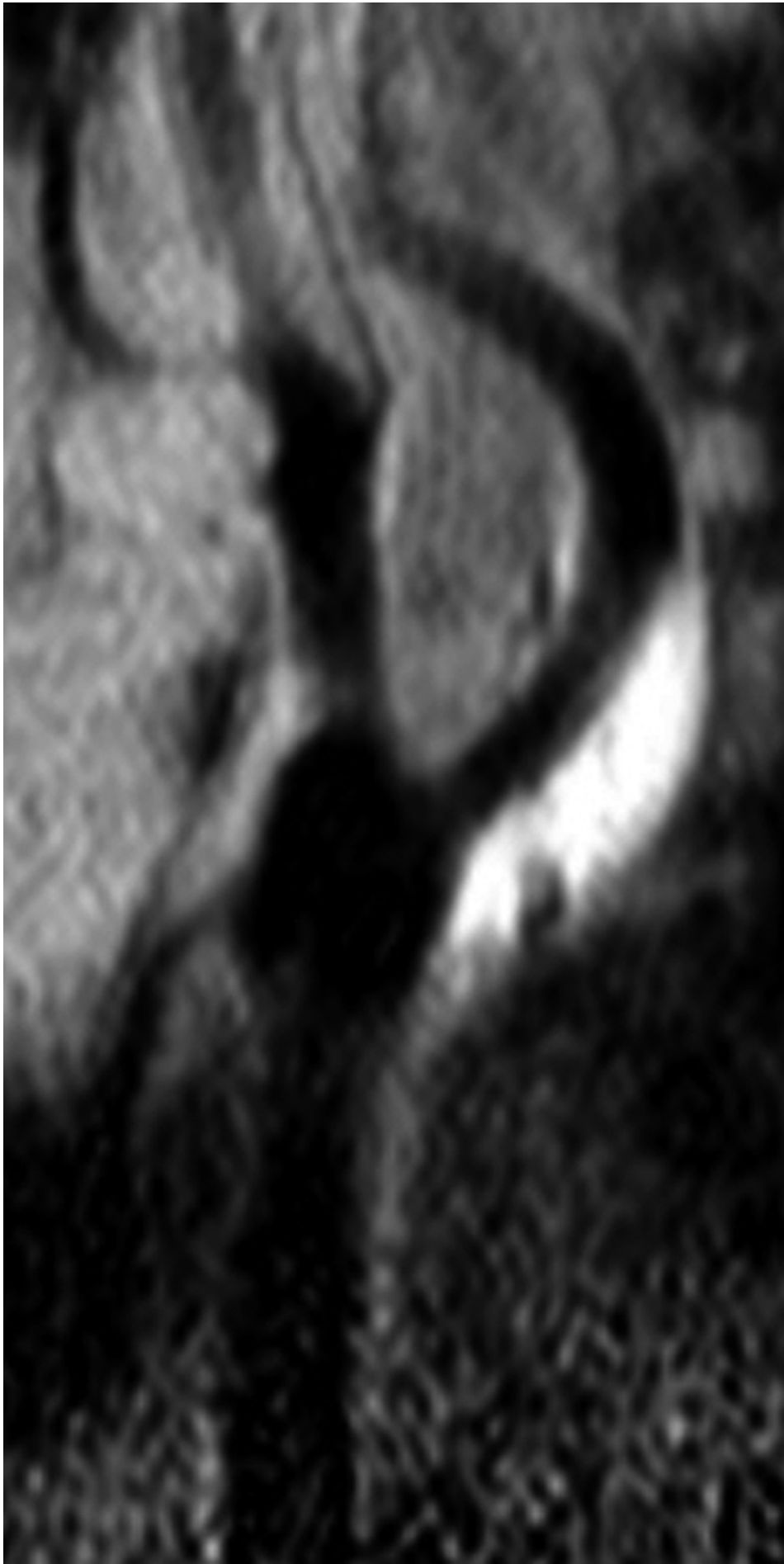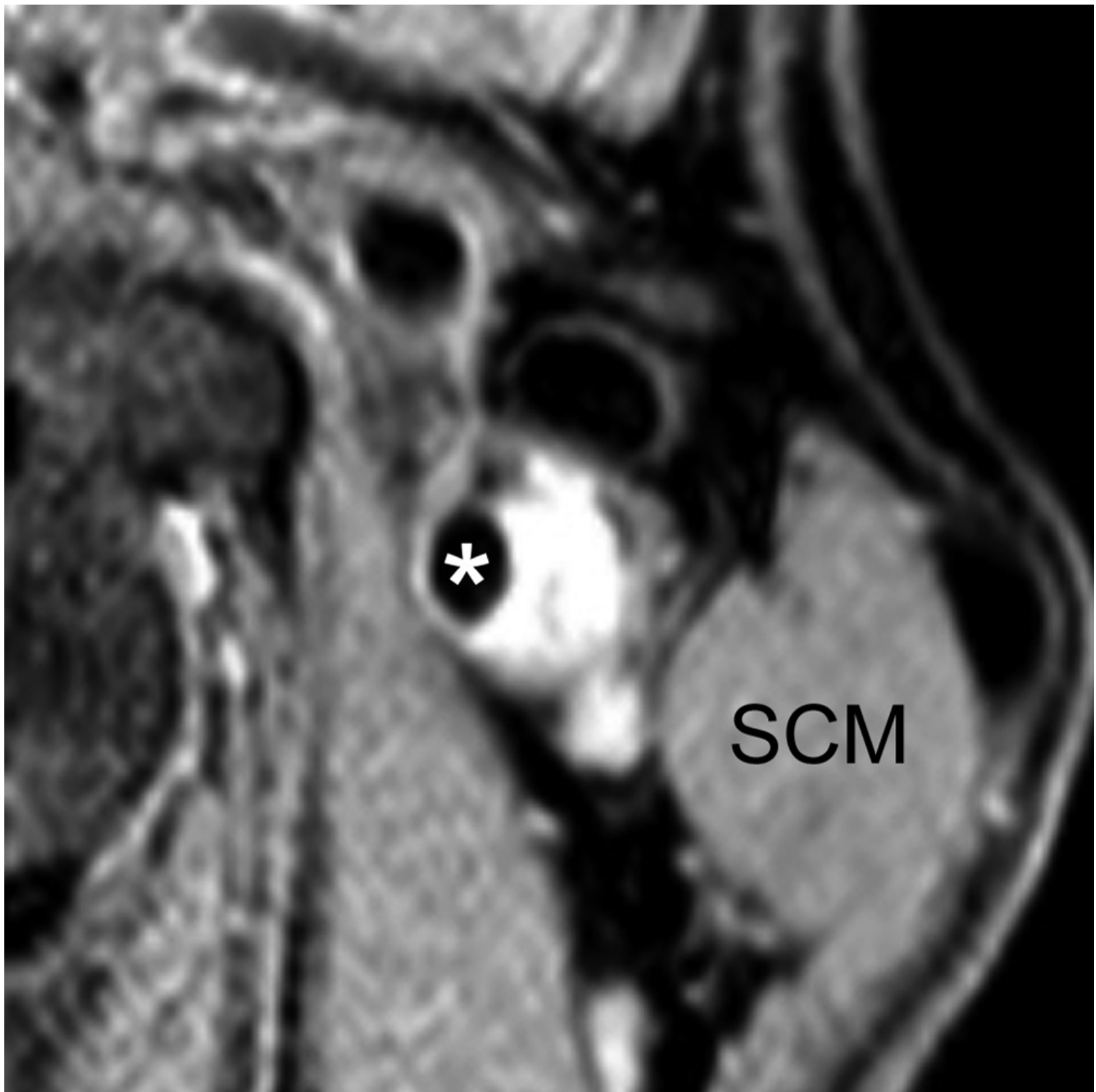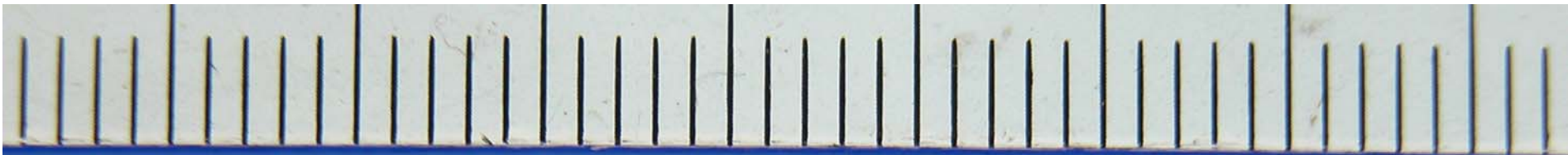
Figure 1-C

ICA ←——————————→ CCA

Figure 1-D

Table 1. Characteristics of the patients with symptomatic low-grade carotid stenosis.

	Total (n=25)	Recurrence (n=11)	No recurrence (n=14)	P value
Age (years)	74.2 ± 5.6	73.7 ± 7.2	74.6 ± 4.2	0.716
Gender (male)	23 (92.0%)	10 (90.9%)	13 (92.9%)	0.697
Hypertension	21 (84.0%)	10 (90.9%)	11 (78.6%)	0.396
Hyperlipidemia	18 (72.0%)	9 (81.8%)	9 (64.3%)	0.305
Diabetes	8 (32.0%)	4 (36.4%)	4 (28.6%)	0.504
Ischemic heart disease	10 (40.0%)	4 (36.4%)	6 (42.9%)	0.534
Atrial fibrillation	3 (12.0%)	2 (18.2%)	1 (7.1%)	0.407
Medical treatment				
Statins	17 (68%)	9 (81.8%)	8 (57.1%)	0.19
Dual antiplatelet drugs	15 (60%)	9 (81.8%)	6 (42.9%)	0.058
Warfarin	2 (8%)	2 (18.2%)	0	0.183
roSI of carotid MRI	1.65 ± 030	1.70 ± 0.27	1.61 ± 0.32	0.459
Number of recurrences		2.7 (1-6)	0	
f/u period (months)	31.3 ± 16.4	34.3 ± 16.6	29.0 ± 16.4	

roSI, relative overall signal intensity on axial T1-weighted images of whole carotid plaque except for lumen at maximal stenosis relative to adjacent sternocleidomastoid muscle.;[23] f/u, follow-up.

Table 2. Carotid endarterectomy for symptomatic low-grade carotid stenosis refractory to aggressive medical treatment.

No. of patients	1	2	3	4	5	6	7	Average	SD
Age (years) /gender (M/F)	80/M	68/M	72/M	74/M	73/M	77/M	73/F	73.9	3.8
Duration from initial stroke to CEA (months)	60	18	46	16	24	49	35	35.4	16.9
No. of recurrences	6	6	2	1	2	2	4	3.3	2.1
Rate of stenosis	25	25	47	13.6	26.3	27.8	25.3	27.1	9.9
Ulceration on DSA	+	-	+	-	-	-	-		
roSI on carotid MRI	2.12	1.58	2.08	1.77	1.87	1.88	1.61	1.84	0.21
Histological findings									
Intraplaque hemorrhage	+	+	+	+	+	+	+		
Status of fibrous cap	Ruptured	Eroded	Ruptured	Eroded	Ruptured	Ruptured	Ruptured		
New DWI lesion after CEA	-	-	-	-	-	-	-		
Other complications	Neck swelling	-	Transient hoarseness	-	-	-	-		
mRS on discharge	1	0	1	1	1	1	1		
Ischemic events after CEA	-	-	-	-	-	-	-		
f/u period (months)	47	24	23	17	14	5	4	19.1	14.6

No, number; SD, standard deviation; DSA, digital subtraction angiography; roSI, relative overall signal intensity; MRI, magnetic resonance imaging; DWI, diffusion weighted image; mRS, modified Rankin scale; f/u, follow-up.