Prediction of carotid artery in-stentrestenosis by quantitative assessment ofvulnerable plaque using computed tomography

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Prediction of carotid artery in-stent restenosis by quantitative assessment of vulnerable plaque using computed tomography.

Authors:

Kouichi Misaki, MD,[a] Naoyuki Uchiyama, MD,[a] Masanao Mohri, MD,[a] Mitsutoshi Nakada, MD,[a] Fumiaki Ueda, MD,[b] Yutaka Hayashi, MD,[a] *Kanazawa, Japan*

Affiliations:

From the Department of Neurosurgery, Division of Neuroscience, [a] and Department of Radiology, Division of Cardiovascular Medicine,[b] Graduate School of Medical Science, Kanazawa University, Japan

Corresponding author

Kouichi Misaki

Department of Neurosurgery, Division of Neuroscience, Graduate School of Medical Science, Kanazawa University, 13-1 Takara-machi, Kanazawa, Ishikawa 920-8641,

Japan

Phone: +81-76-265-2384, Fax: +81-76-234-4262

E-mail: misaki@med.kanazawa-u.ac.jp

Key word: carotid plaque, carotid artery stenting, in-stent restenosis, multidetector computed tomography

Abstract

Background and purpose: To assess the relationship between plaque volume evaluated by multidetector computed tomographic angiography (MDCT) and in-stent restenosis (ISR) after carotid artery stenting (CAS).

Materials and Methods: From a retrospectively maintained database, data were collected for 52 patients with carotid artery stenosis treated with CAS between 2007 and 2012. We defined ISR of ≥50% as a peak systolic velocity ≥ 200 cm/s on echo-duplex scan. Carotid plaques were subdivided into 4 components according to radiodensity in Hounsfield units (HU) as follows: <0, 0–60, 60–130, and >600 HU. Risk factors that influenced ISR were compared using univariate and multivariate Cox regression analyses.

Results: During a median follow-up period of 36 months, ISR of ≥50% was detected in 5 patients (9.6%). In the univariate Cox proportional hazard regression analysis, renal insufficiency, coronary artery disease, total plaque volume, and plaque volumes with radiodensities <0 and ≥600 HU increased the risk for ISR (P < .10). When the significant risk factors determined from the univariate analysis were subjected to a multivariate analysis, only the volumes of the plaque components with radiodensities <0 HU independently predicted the development of ISR (hazard ratio, 1.041; 95%

confidence interval, 1.006–1.078; *P* = .021).

Conclusion: Our data suggest that the high volume of the plaque components with radiodensities <0 HU was independently associated with the increased risk of ISR after CAS. Quantitative and qualitative tissue characterizations of carotid plaques using MDCT might be a useful predictive tool of the development of ISR.

Abbreviation key list

CAS; carotid artery stenting, CEA; carotid endarterectomy, CI; confidence interval , HU; Hounsfield units, ISR; in-stent restenosis, MDCT; multidetector computed tomographic angiography, PSV; peak systolic velocity, ROI; region of interest

Intruduction

Carotid artery stenting (CAS) has been developed as a potential therapeutic alternative to carotid endarterectomy (CEA) for the treatment of atherosclerotic lesions of the carotid artery. The number of patients who developed in-stent restenosis (ISR) has increased with the increase in the number of CAS patients who have undergone long-term monitoring. The neointimal formation occurs in the surface of the stent within almost one year after CAS, and the ISR is reportedly caused by the further progression of arteriosclerosis within the stent after neointimal formation.(1),(2),(3) Persistence of inflammatory stimuli and subsequent cellular proliferation within vulnerable plaque is considered to play an important role in occurrence of the ISR after CAS, and preoperative evaluation of vulnerable plaque may be useful for the prediction of the development of ISR due to in-stent arteriosclerosis. We previously reported the utility of multidetector computed tomography (MDCT) in diagnosis of vulnerable

plaque, in this article the plaque components with radiodensities <0 Hounsfield units (HU) on MDCT, which are consistent with lipid core, are associated with the number of distal embolisms after CAS.(4) These lipid components may also be associated with ISR because vulnerable plaque is considered to cause the intense arteriosclerosis in the stent.(2),(3) In this study, we describe the usefulness of MDCT plaque diagnosis as a preoperative predictor of restenosis after CAS.

Materials and methods

Patient selection and data collection. Between January 2007 and August 2012, we performed 52 CAS procedures to treat 52 consecutive patients using preoperative MDCT imaging at Kanazawa University Hospital. Patients were included if MDCT for the target carotid artery was performed preoperatively and follow-up echo-duplex scans were obtained 24 h, 3 months, 6 months, and 12 months after CAS and every year thereafter. Three patients for whom a MDCT study could not be performed because of severe renal failure were excluded. Of 52 lesions, 36 (69.2%) were symptomatic and 16 (30.8%) were asymptomatic. The following patient baseline characteristics were recorded: age, sex, degree of stenosis, hypertension, diabetes mellitus (medication dependent, including oral hypoglycemic agents and insulin), dyslipidemia (medication

dependent or with a serum cholesterol level ≥ 220 mg/dL or serum triglyceride level ≥ 150 mg/dL), renal insufficiency (estimated glomerular filtration rate < 30 mL/min/1.73 m^2), coronary artery disease (history of angina pectoris or myocardial infarction), peripheral vascular disease, contralateral carotid occlusion, prior neck radiotherapy, smoking habit (still smoking or stopped smoking < 6 months before the study), stent type, postdilation, and antiplatelet medication after CAS. Intraoperative and postoperative events were also recorded. Our institutional review board did not require informed consent for participation in this study because our analysis relied on the information obtained as part of the routine clinical care of patients.

Indications for CAS were ICA stenosis > 50% in symptomatic patients and 80% in asymptomatic patients, with one of the following comorbidities: 2 or more coronary vessels with >70% stenosis, bronchopulmonary obstructive disease, post-carotid endarterectomy restenosis, previous radical neck surgery or radiotherapy, surgically inaccessible lesions, and contralateral carotid artery occlusion. ICA stenosis was diagnosed using angiography.

MDCT examination. Scanning was performed on a 64-slice MDCT scanner (GE Medical Systems, Milwaukee, WI) with a standardized protocol (120 kVp; 350 mAs; collimation, 64 × 0.625 mm; table feed, 10.62 mm/rotation; pitch, 0.531). All the

patients received 80 mL of contrast material (370 mg/mL) at an injection rate of 4 mL/s. Saline was not injected after the administration of the contrast material. Synchronization between the passage of contrast material and data acquisition was achieved with a bolus tracking technique. The scan was triggered automatically by means of the threshold, measured in a region of interest (ROI) set in the internal carotid artery. The threshold was set at 100 HU. Image reconstructions were rendered with an intermediate reconstruction algorithm with the following characteristics: field of view, 160 mm; matrix size, 512 × 512; slice thickness, 0.625 mm; and interval, 0.3 mm. Data were transferred to our workstation (GE Advantage Windows version 4.4, GE Medical Systems). Plaque component areas were automatically measured using the Advanced Vessel Analysis software (GE Medical Systems). After manual drawing of the ROI encircling the internal carotid artery, the number of pixels of the different HU values within the ROI was automatically calculated. The lumen area, which is filled with contrast media that has radiodensity of 130-600, was automatically differentiated from the atherosclerotic plaque based on the adjusted cutoff value. The carotid plaque was expediently subdivided into 4 components according to radiodensity as follows: <0, 0–60, 60–130, and >600 HU, as assessed in previous studies (Fig. 1).(4,5) The volumes of the atherosclerotic plaque and its component were calculated by multiplying the

calculated number of pixels, pixel size, and increment. Two observers (K.M. and N.U.), who were blinded to other clinical information, performed the volume measurements.

CAS procedure. Dual (aspirin 100 mg and clopidogrel 75 mg) or triple antiplatelets (aspirin 100 mg, clopidogrel 75 mg, and cilostazol 200 mg) were administered for a minimum of 7 days prior to the procedure. The patients were placed under local anesthesia, and a bolus injection of heparin (70 IU/kg) was given immediately before the intervention to increase the activated clotting time to a minimum of 300 s. A 6-F, 90-cm catheter sheath was inserted from the femoral artery to the ipsilateral common carotid artery proximal to the stenosis. We used Angioguard (Johnson & Johnson, Cordis, Minneapolis, MN) or FilterWire (Boston Scientific, Natick, MA, USA) as the embolic protection device for all the patients. All but 4 patients underwent predilation of the internal carotid lesions. The predilation was performed using a 3.5-mm balloon catheter protected with the embolic protection device. A self-expandable stent, either Precise (Johnson & Johnson, Cordis) or Wallstent RP (Boston Scientific), was used in all the patients. Postdilation was performed with a 4.5- or 5-mm balloon catheter; the inflation pressure was 8 atm. In cases with insufficient stent expansion, the balloon was additionally inflated up to 10 atm.

Follow-up. The patients underwent an echo-duplex scan, and neurological

examinations of all the patients were performed at 24 h, 3 months, 6 months, and 12 months after CAS and yearly thereafter. ISR was defined as an arterial narrowing of 50% or more, which was reported to be equivalent to a peak systolic velocity (PSV) ≥ 200 cm/s.(6),(7)

Statistical analysis. Time to restenosis was analyzed using survival analysis methods. Survival curves were estimated using the Kaplan-Meier method. Univariate and multivariate Cox proportional hazard regression models were used to determine risk factors of the development of restenosis. The risk factors investigated included sex, degree of stenosis, symptomatic lesion, hypertension, diabetes mellitus, dyslipidemia, renal insufficiency, coronary artery disease, peripheral vascular disease, contralateral carotid occlusion, prior neck radiation, smoking, stent type, postdilation, postprocedural medications (aspirin, clopidogrel, and cilostazol), PSV assessed by echo-duplex scan, and plaque volume. For each risk factor, hazard ratio and the associated 95% confidence interval (CI) from the univariate analysis were calculated. Multivariate analysis was conducted for the risk factors with significant *P* values (<.10) in the univariate analysis. All the analyses were conducted using the SPSS version 19 statistical software (SPSS Inc., Chicago, IL).

Results

The baseline characteristics of the patients are shown in Table 1. Of the 52 patients, 44 (84.6%) were men and 8 (15.4%) were women. Their mean age was 69.8 ± 7.7 years (range, 52–84 years). The clinical data included symptomatic stenosis in 36 (69.2%) patients, hypertension in 38 (73.1%), diabetes mellitus in 24 (46.2%), dyslipidemia in 22 (42.3%), renal insufficiency in 5 (9.6%), coronary artery disease in 14 (26.9%), peripheral vascular disease in 5 (9.6%), contralateral carotid occlusion in 3 (5.8%), prior neck radiation in 2 (3.8%), and smoking in 36 (69.2%).

All the CAS procedures performed were successful, and excellent lesion dilation was achieved. The deployed stent was Precise (Johnson & Johnson, Cordis) in 38 (73.1%) and Wallstent RP (Boston Scientific) in 14 patients (26.9%). None of the patients needed more than 1 stent. Postdilation was performed in 41 patients (78.8%) using a 4.5- or 5-mm balloon catheter. The overall periprocedural complication rate was 3.8% (2 cases, 1 minor stroke and 1 hyperperfusion syndrome). No fatal complications or major stroke events were encountered.

During the median follow-up period of 36 months (interquartile range, 24.0–42.0), an ISR ≥ 50% was detected in 5 patients (9.6%). None of the patients with ISR had a neurological event ipsilateral to the restenosed vessel and needed retreatment.

Plaque volume could be calculated for all the 52 patients (Table 1). The total plaque volumes (mean ± standard deviation) in all the patients, in those with restenosis, and in those without restenosis were 671 ± 426, 1101 ± 310, and 625 ± 413 mm^3, respectively. The volumes of the plaque components with radiodensities < 0, 0–60, 60–130, and >600 HU were respectively 11 ± 26, 280 ± 206, 340 ± 247, and 40 ± 70 mm^3 for all the patients; 30 ± 29, 415 ± 239, 530 ± 221, and 126 ± 99 mm^3 for those with restenosis; 9 ± 25, 265 ± 200, 320 ± 243, and 31 ± 61 mm^3 for those without restenosis (Table 1).

In the univariate analysis, renal insufficiency, coronary artery disease, total plaque volume, and plaque volume with a radiodensity <0 or ≥600 HU were associated with the development of ISR ($P < .10$; Table 2). The unadjusted and adjusted hazard ratios for the ISR among the patients with plaque components with radiodensities <0 HU were 1.020 (95% CI, 1.001–1.040; $P = .036$) and 1.041 (95% CI, 1.006–1.078; $P = .021$), respectively. The receiver-operating characteristic curve of the volumes of the plaque components with radiodensities <0 HU showed a cutoff plaque volume of 7.85 mm^3 for the prediction of carotid artery ISR, with a sensitivity of 80% and specificity of 83%. The area under the curve was 0.85 (Fig. 2). Figure 3 shows the Kaplan-Meier estimated curves for the patients who had plaque volumes > 7.85 mm^3 for components

with radiodensities <0 HU and for those patients whose plaque volumes did not fall within the range. The former patients exhibited lower freedom from restenosis (*P* < .010).

Discussion

This is the first study to investigate the risk of ISR through plaque diagnosis on MDCT. Previously reported risk factors for restenosis include diabetes mellitus,(8) residual stenosis after CAS,(9-11) multiple stent implantation,(10,11) smoking,(8) calcified plaque,(8) previous CEA,(8,12),(13) history of neck cancer,(14) and neck radiotherapy.(13) However, no previous study on risk factors of restenosis has been conducted using quantitative and qualitative plaque analyses. In the present study, the multivariate analysis showed that the total volume of the plaque components with radiodensities <0 HU (lipid core) was significantly correlated with restenosis.

One study that compared between histological diagnosis based on plaque excised during CEA and histological diagnosis based on pretreatment MDCT reported that plaques with radiodensities <60 HU were lipid-rich. We previously reported that even among plaques with radiodensities <60 HU, those with radiodensities <0 HU were strongly correlated with the number of peripheral embolisms after CAS, indicating the

presence of unstable plaques.(4) Plaque components in the coronary artery region that have radiodensities <0 HU are referred to as the “lipid pool”(15,16) and are associated with no-flow conditions after percutaneous coronary intervention. Therefore, they can be regarded as components indicative of the presence of unstable plaques.(17) Plaque components with radiodensities <0 HU only comprise part of the total plaque volume in both the coronary and carotid arteries.(4,15) In this study, we found that they accounted for less than one-tenth of the total amount of plaque. In the event of intraplaque hemorrhage, the effect of the ensuing hematoma may mean that even if a lipid pool is present, its radiodensity may not be <0 HU. The reason as to why the nature of plaque is indicated by this minor component requires further investigation.

During the first 12 months after CAS, neointimal proliferation, which consists of transformed smooth muscle cells and fibrotic maturation of the matrix substances, is observed inside the stent struts. ISR after CAS is believed to occur owing to the subsequent further progression of arteriosclerosis in the neointima.(1)-(3)(18) The association we found in this study between components with radiodensities <0 HU, which indicate the presence of unstable plaques, and restenosis strongly suggests the progression of arteriosclerosis inside the stent. In 4 of the 5 patients in whom restenosis occurred, stenosis progressed after at least a year had passed since CAS, a course

consistent with changes following neointimal formation.

Although one investigation found that restenosis commonly consists of concentric calcified plaques, it did not evaluate the amount or severity of calcification.(8) MDCT provides outstanding spatial resolution and is particularly useful for quantifying the extent of calcified lesions.(4),(5,19)(20)(21) In the present study, the univariate analysis showed that a large volume of calcified plaque with a radiodensity ≥600 HU was associated with restenosis. In terms of the mechanism whereby calcified plaque causes restenosis, some authors have reported that calcification may prevent the full dilatation of stents.(9),(11) In this study, the peak velocity measured by carotid artery ultrasonography on the day after the treatment made no difference in restenosis, suggesting that inadequate dilation could not have been the cause (Table 1).

Other factors that are reportedly correlated with restenosis include previous CEA,(8,12),(13) history of neck cancer,(14) and neck radiotherapy.(13) However, in our study we did not find any significant difference for any of these factors, probably owing to the small number of patients. Therefore, further studies of more cases are required.

Limitations of the study. The number of patients and clinical events were small, and the study was retrospective in nature. Although the result of our MDCT analysis was consistent with those of other published studies,(4) the patterns observed

on MDCT require verification by histopathological examination of carotid plaque. In particular, the corresponding histological characteristics of the specific components with radiodensities <0 HU remain to be determined. We did not perform any examination for intraplaque hemorrhage or thrombus. MDCT can differentiate between calcification, fibrous tissue, and lipid cores. However, because hemorrhage could not be distinguished reliably from lipid cores in this study, they were not reported separately.

Conclusions

Our data suggest that the high total volume of the components with radiodensities <0 HU was independently associated with the increased risk of ISR after CAS. MDCT may be useful in the pretreatment quantitative and qualitative assessments of carotid plaque for the prediction of ISR after CAS.

Acknowledgments

We gratefully acknowledge the advice and encouragement of Prof. Jun-ichiro Hamada. We mourn his untimely death.

Conflict of interest

We declare that we have no conflict of interest.

Figure legends

Fig 1. Representative images of multidetector computed tomography (MDCT) and echo-duplex scan of a patient who had in-stent restenosis at 12 months follow-up.

A,B: Sagittal sectional (A) and color mapped (B) images of the plaque on MDCT. The red, yellow, green and blue areas indicate that the Hounsfield value is <0, 0–60, 60–130, and >600, respectively. The grey area indicates intraluminal contrast media that has radiodensity of 130-600. The plaque volume in the red, yellow and blue area accounts for 22.2, 259.9, 568.7 and 268.2 mm^3, respectively.

C,D,E,F: Color Doppler sonography one day after carotid artery stenting (CAS) (C) shows favorable dilatation of carotid artery with the peak systolic velocity of 96 cm/s (E), whereas in-stent restenosis is depicted 12 months after CAS (D) with the peak systolic velocity of 229cm/s (F). Arrow indicates the in-stent restenosis.

Fig 2. Receiver-operating characteristic curve of the volumes of the plaque components with radiodensities < 0 Hounsfield units for the prediction of carotid artery in-stent restenosis. A plaque volume of 7.85 mm^3 provides a sensitivity of 80% and a specificity of 83%, with an area under the curve of 0.85.

Fig 3. Kaplan-Meier analysis result comparing the cumulative freedom from in-stent restenosis between the patients with plaque volumes > 7.85 mm^3 for components with radiodensities <0 HU (solid line) and those whose plaque volumes did not fall within the range (dotted line).

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Table 1. Baseline characteristics

	All patients (n = 52)	Restenosis (n = 5)	No restenosis (n = 47)	P- value
Mean age	70±8	69±11	70±7	0.935
Male	44 (85)	5 (100)	39 (83)	0.208
Degree of stenosis (%)	76±18	75±19	85±8	0.116
Past history				
Symptomatic stenosis	36 (69)	4 (80)	32 (68)	0.843
Hypertension	38 (73)	4 (80)	34 (72)	0.645
Diabetes mellitus	24 (46)	1 (20)	23 (49)	0.165
Dyslipidemia	22 (42)	2 (40)	20 (43)	0.806
Renal insufficiency	5 (10)	3 (60)	2 (4)	0.002
Coronary artery disease	14 (27)	3 (60)	11 (23)	0.057
Peripheral vascular disease	5 (10)	0 (0)	5 (11)	0.686
Contralateral carotid occlusion	3 (6)	0 (0)	3 (6)	0.694
Prior neck radiation	2 (4)	0 (0)	2 (4)	0.767
Smoking	36 (69)	4 (80)	32 (68)	0.696
Stent				
Wallstent	14 (27)	1 (20)	13 (28)	0.996
Precise	38 (73)	4 (80)	34 (72)	0.996
Post-dilatation	41 (79)	5 (100)	36 (77)	0.416
Post-procedure medications				
Aspirin	34 (65)	5 (100)	29 (62)	0.357
Clopidogrel	23 (44)	1 (20)	22 (47)	0.368
Cilostazol	17 (33)	1 (20)	16 (34)	0.547
Peak systolic velocity (cm/s)				
Preoperative	425±176	421±178	425±176	0.933
One day after treatment	92±31	92±32	91±18	0.982
Last examination	95±56	242±28	79±29	0.001
Plaque volume (mm^3)				
Total	671±426	1101±310	625±413	0.043
HU < 0	11±26	30±29	9±25	0.036
HU 0-60	280±206	415±239	265±200	0.177
HU 60-130	340±247	530±221	320±243	0.141
HU ≧600	40±70	126±99	31±61	0.020

HU, Hounsfield unit.

Categoric data are shown as number (%) and continuous data as mean ± standard deviation.

Table 2. Results of univariate and multivariate analyses

	Unadjusted hazard ratio (Confidence intervals)	*P*- value	Adjusted hazard ratio (Confidence intervals)	*P*- value
Renal insufficiency	17.734 (2.949-106.641)	0.002	—	
Coronary artery disease	6.241 (0.948-41.104)	0.057	—	
Plaque volume: Total	1.001 (1.000-1.003)	0.043	—	
Plaque volume: HU<0	1.020 (1.001-1.040)	0.036	1.041 (1.006-1.078)	0.021
Plaque volume: HU≧600	1.008 (1.001-1.015)	0.020	—	

HU, Hounsfield unit.

Fig 1.

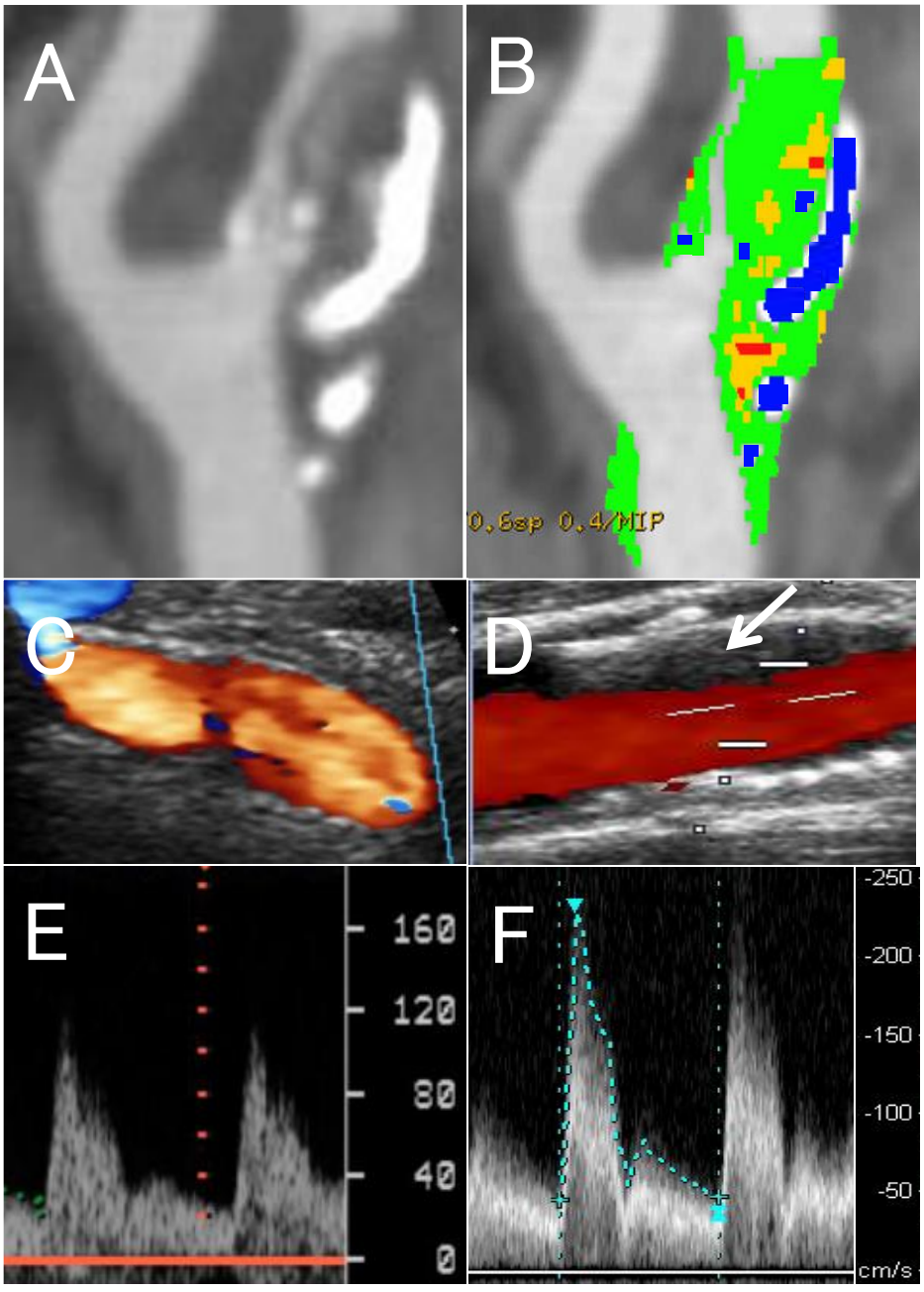
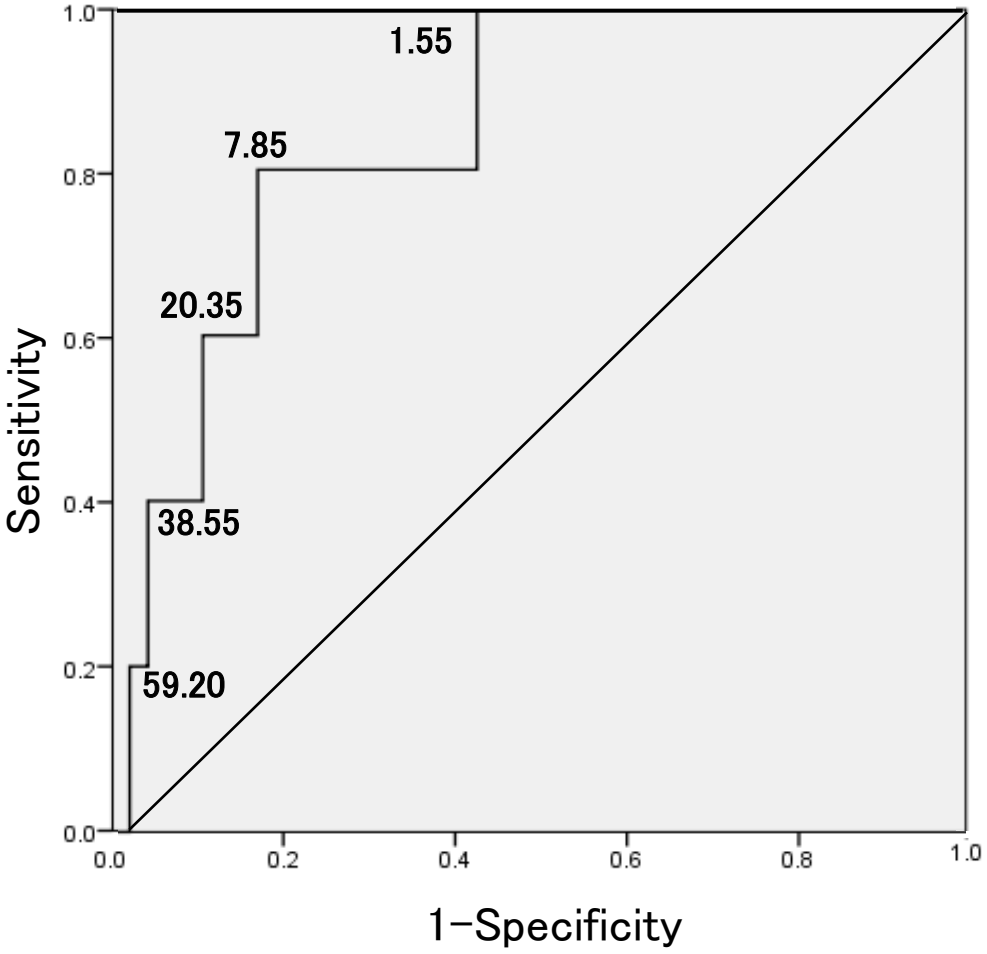


Fig 2.


1.55
7.85
20.35
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Sensitivity
1-Specificity
0.0
0.2
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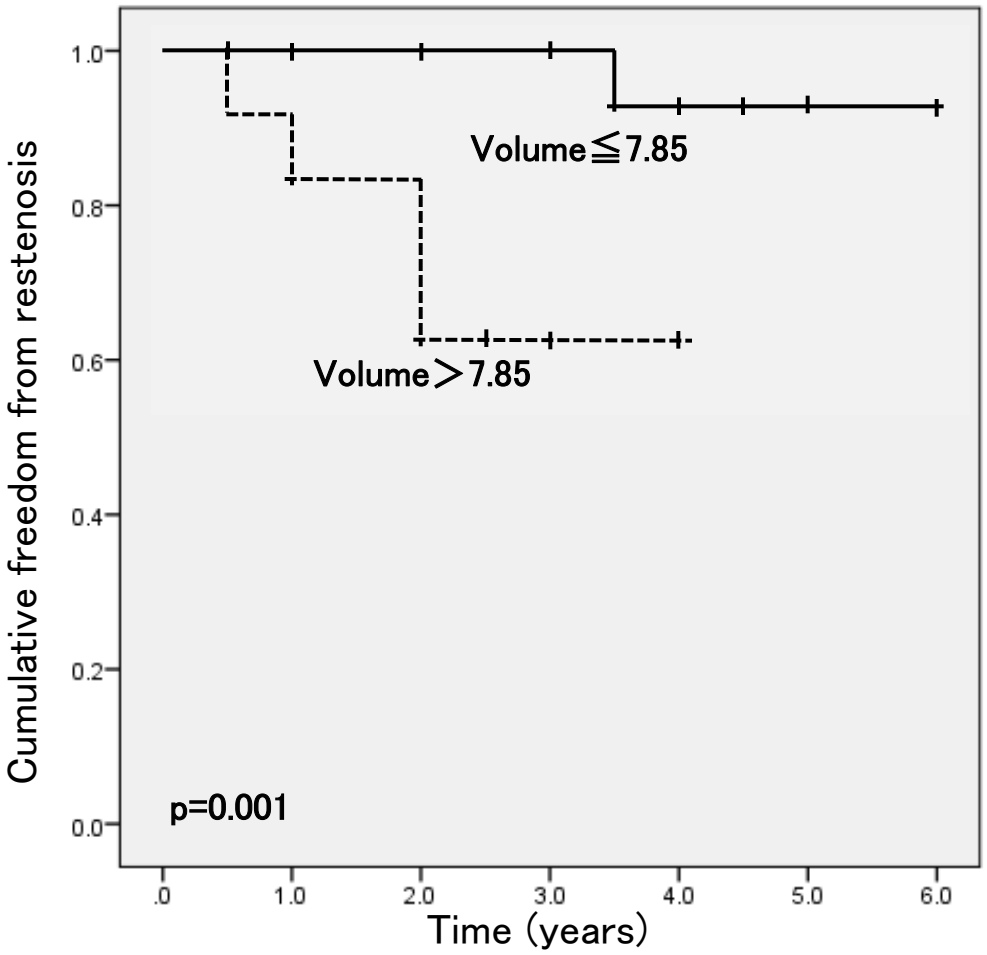
1.0

Fig 3.



Volume≦7.85	40	40	40	40	39	39	39
Volume＞7.85	12	10	8	8	8		