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Carotid Duplex Sonography for Stented Patients Reaching the End of the Scheduled Three-Dimensional Computed Tomography Angiography Follow-up Period

Ruoyu PENG[1) 2)], Hidemasa NAGAI[1)], Yasuhiko AKIYAMA[1)], Takeshi MIYAZAKI[1)], Mizuki KAMBARA[1)], Tsutomu YOSHIKANE[1)] and Tao SUN[2)]

[1)]*Department of Neurosurgery, Shimane University Faculty of Medicine, Izumo 693-8501, Japan*

[2)]*Department of Neurosurgery, Ningxia Medical University, Yinchuan, China*

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Carotid artery stenting（CAS）patients are routinely assessed for in-stent restenosis（ISR）using three-dimensional computed tomography angiography（3D-CTA）for 2 years after the procedure, because this event typically occurs in some patients within 2 years after CAS. Stented patients reaching the terminal period of the scheduled 3D-CTA are usually observed with carotid duplex ultrasonography（CDU）thereafter. The purpose of this study was to investigate the outcomes for stented patients who are beyond the 2 year follow-up period and to identify risk factors associated with late-onset ISR. Data were retrospectively collected at Shimane University Hospital. We compared the differences between the ISR-positive group and the ISR-negative group to identify factors associated with ISR and compared the relationship between 3D-CTA and CDU with in-stent max intima-media thickness and stenosis rate. We could not discover significant factors to predict ISR. It was a good correlation between 3D-CTA and CDU. We also conclude that 3D-CTA could be replaced with CDU for assessment of ISR in patients who are beyond the 2 year follow-up period after CAS.

Key words: carotid artery stenting, in-stent restenosis, carotid duplex ultrasonography, three-dimensional computed tomography angiography

Corresponding author: Ruoyu Peng
Department of Neurosurgery, Shimane University Faculty of Medicine, 89-1, Enya-cho, Izumo, 693-8501, Japan
Tel: +81-853-20-2245
Fax: +81-853-21-8954
E-mail: nogeka@med.shimane-u.ac.jp

INTRODUCTION

Carotid artery stenting（CAS）represents a therapeutic alternative to carotid endarterectomy. In-stent restenosis（ISR）is a major problem that sometimes occurs during long-term follow-up of patients who have undergone CAS［1］. Such patients are routinely followed via three-dimensional computed tomography angiography（3D-CTA）for 2 years after the therapeutic procedure in our hospital. If in-stent intimal hyperplasia is not observed within this period, intensive follow-up of the stented arteries is terminated. By contrast, if intimal hyperplasia including small plaques is seen in the stented vessels, follow-up will continue after the 2 year period. This subsequent follow-up assessment for late-onset ISR is performed using carotid duplex ultrasonography（CDU）rather than 3D-CTA in order to avoid the side effects（e.g., allergy, nephrotoxicity）of contrast drugs and to reduce medical costs. If ISR is detected, patients can be re-treated via endovascular techniques［so-called target lesion revascularization（TLR）］［2］. However, the optimal method to detect late-onset ISR and the risk factors that might predict late-onset ISR have not been fully established.

The purpose of this study was to investigate the outcomes for stented patients who are beyond the 2 year follow-up period and to identify risk factors associated with late-onset ISR. This study was a pilot study for ongoing patient care.

MATERIALS AND METHODS

Patient selection

This study was approved by the medical ethics board of Shimane University on November 26, 2012

(Study #1171). Among 62 patients (70 carotid arteries) that had been treated by stenting at Shimane University Hospital between January 2009 and October 2010, some were excluded from this study because of the need for re-treatment with a cutting balloon (n=2) or due to internal carotid artery dissection (n=2), a plain angioplasty of the intracranial internal cerebral artery (n=2), severe renal failure (n=1), and loss to follow-up (n=14). The remaining 41 patients (49 arteries) underwent scheduled follow-up with 3D-CTA until 2 years after CAS. The inclusion criteria were performance of a final 3D-CTA after 2 years of CAS and subsequent ongoing follow-up with CDU. The time-lag between the final 3D-CTA and subsequent CDU was within 2 years. CDU data were not available in 27 arteries. Finally, a total of 20 patients (22 arteries) met the study's inclusion criteria on the approval date of the medical ethics board of Shimane University (Fig. 1). Consultations were done from the approval date of April 2013. Patient data were retrospectively collected from outpatient charts.

Evaluation items

ISR was defined as more than 40% stenosis [according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method] as measured on the curved planar reconstruction (CPR) image of 3D-CTA [3]. Images were adjusted with the optimal gray-scale to clearly distinguish in-stent plaque from the stent metal or contrast enhancement (Fig. 2).

The 22 vessels were each classified into one of two groups according to the degree of stenosis defined on final 3D-CTA: the ISR-negative group, which had less than 40% stenosis, and the ISR-positive group, which had more than 40% stenosis. The two groups were compared in terms of patient factors, stent factors, laboratory data, medications, and ultrasound values [4]. For example, the relationship between imaging technique of in-stent max intima-media thickness (IMT) and stenosis rate caused by in-stent plaque was studied. Patient-related factors included age, sex, and past/comorbid diseases (e.g., hypertension, diabetes, hyperlipidemia, smoking, coronary artery disease, and cancer). Stent-related factors included number of stents, length of stent, and stent deformation at the most stenotic portion (MSP in-stent). Laboratory data included total cholesterol (TC), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), C-reactive protein (CRP), blood urea nitrogen (BUN), creatine (Crea), estimated glomerular filtration rate (eGFR), and hemoglobin A1c (HbA1c). Medication data included the administration of antiplatelet agents (e.g., aspirin, clopidogrel, and cilostazol), statin potency [defined as no statin=1, pravastatin (10mg)=2, fluvastatin (10mg)=5, pitavastatin (10mg)=10, atorvastatin (10mg)=10, and rosuvastatin (10mg)=20].

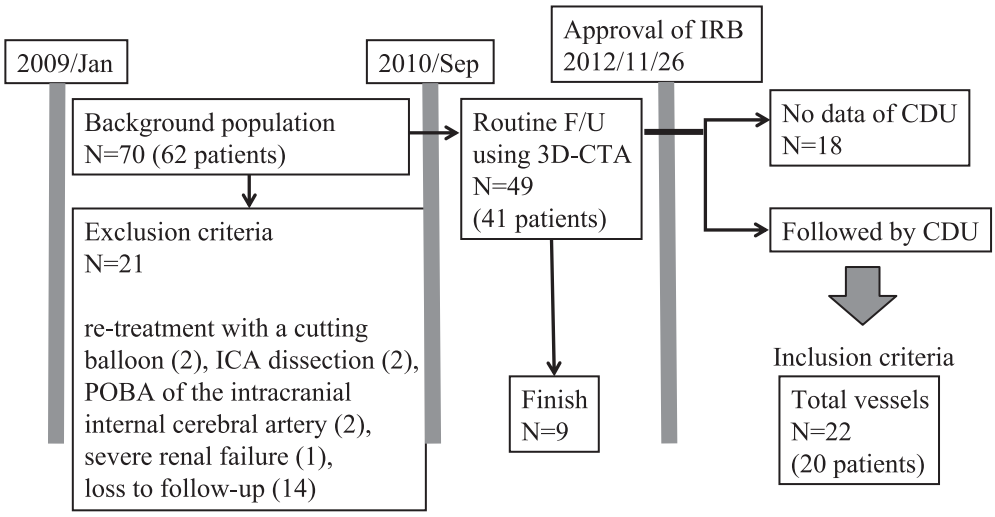

Fig. 1. The process of selecting the target vessels.

We collected data from November 2012 to April 2013. Data from 22 vessels (20 patients) were included in this study.

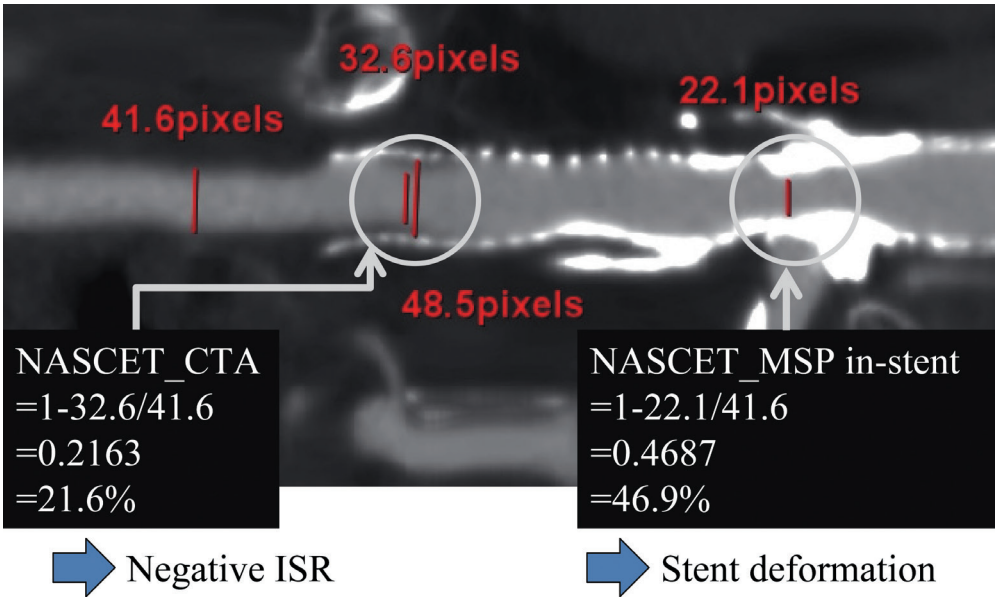

Fig. 2. Illustration.

The stenosis rate was calculated by using the curved planar reconstruction image of three-dimensional computed tomography angiography (CTA) on the basis of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method. These value were expressed as the stenosis rate of the NASCET based on CTA (NASCET_CTA). The in-stent restenosis (ISR) was defined as NASCET_CTA > 40% stenosis degree. Stent deformation was assessed by the NASCET method at the most stenotic portion in-stent. These value were expressed as the stenosis rate at the Most Stenotic Portion (MSP) in-stent according to the NASCET (NASCET_MSP in-stent).

3D-CTA and ultrasound factors

Next, we compared the relationship between final 3D-CTA and subsequent CDU. 3D-CTA factors included in-stent max IMT on the axial view (IMT_axCTA), IMT on the sagittal view (IMT_sagCTA), stenosis rate using the area method (Area_CTA), stenosis ratio using the European Carotid Surgery Trial (ECST) method (ECST_CTA), stenosis ratio using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method (NASCET_CTA), and the duration between CAS and 3D-CTA. The deformity of stent was represented as the stenosis ratio by the NASCET method at the most stenotic portion in-stent (NASCET_MSP in-stent). CDU factors included in-stent max IMT on the axial view (IMT_axUS), IMT on the sagittal view (IMT_sagUS), in-stent peak-systolic velocity (PSV), stenosis rate using the area method (Area_US), stenosis rate of ECST method (ECST_US), and the duration between CAS and CDU.

Imaging equipment and CAS

One of two ultrasound apparatuses were used on a random basis: a Toshiba Aplio500® (TOSHIBA Medical System Corp., Tokyo, Japan) with a 7.5 MHz Linear Array Transducer (PLT-704SBT) or a Philips iE33® (Philips Electronics Japan, Tokyo, Japan) with a 11-3 MHz broadband Linear Array Transducer (L11-3). Three-dimensional computed tomography angiography was performed using a CT scanner with 320-row detector Aquilion One® (TOSHIBA Medical System Corp, Tokyo, Japan). Carotid artery stenting was performed according to the Parodi's modified method. A seat belt and air bag technique was used for cerebral protection during carotid stenting. The self-expanding open-cell PRECISE® stent (Cordis Corp, Johnson & Johnson Company, Miami Lakes, FL, USA) was used in all patients.

Statistical analysis

All analysis was performed using commercially available statistical software (JMP®9 version 9.0.0, SAS Institute, Inc., Cary, NC, USA). Continuous values are presented as mean ± standard deviation (SD). Continuous values were compared statistically using the nonparametric Wilcoxon signed-rank (Mann-Whitney) test. Categorical data were analyzed with a two-sided Fisher's exact test and

are presented as counts and expected values. Correlations are described as correlation formations and determination coefficients and were analyzed by one-way analysis of variance (ANOVA). A probability value less than 0.05 was considered to indicate a statistically significant difference.

RESULTS

Descriptive analysis

The laterality of 22 stented arteries was left/right =14/8. The study population consisted of 20 patients (age; mean±SD=72.5±9.5 years, 95% confidence interval=68.3−76.8 and gender; female/male =2/18) with bilateral carotid artery stents placed in two patients. Laboratory testing yielded the following results: TC=158.8±34.5 mg/dl, LDL=82.5±26.1 mg/dl, HDL=60.1±27.9 mg/dl, CRP=1.11±2.83 mg/dl, BUN=18.4±6.6 mg/dl, Crea=1.08±0.75 mg/dl, eGFR=61.7±20.3 ml/min/1.73 m2, and HbA1c=6.1±0.94%. The duration between CAS and 3D-CTA was 553±301 days. The duration between CAS and CDU was 904±193 days. In this study, ISR occurred in two stented vessels among 70 cases of CAS over a 2 year period. Therefore, the occurrence rate of ISR was 2.85% per 2 years.

Difference between ISR-positive group and ISR-negative group

The following factors were compared between the ISR-positive group and ISR-negative group to identify factors related to ISR (1) patient-related factors, (2) stent-related factors, (3) laboratory data, (4) medications, and (5) CDU findings (Table 1). Among these

Table 1. Statistical description of ISR-related factors.

The continuous data were presented as mean ± standard deviation (SD). The categorical data were described as the real value and expected value in parenthesis.

Groups	mean±SD	ISR negative groups (N=20)	ISR positive groups (N=2)	p-value (Wilcoxon)	p-value (Fisher)
Patient factors	age	72.0±9.8	78.5/2.1	0.30	
	sex	M/F=18/2	Male only		1.00
	lateratity	L/R=13/7	L/R=1/1		1.00
Past hisotry	hypertension	16 (16.36)	2(1.64)		1.00
	diabetes type 2	8(8.18)	1(0.82)		1.00
	hyperlipidemia	17(17.27)	2(1.73)		1.00
	smoking	10(10)	1(1)		1.00
	coronary artery disease	6(5.45)	0(0.55)		1.00
	cancer	9(10)	2(1)		0.48
Stent factors	number of stent	1.6±0.6	1.0±0	0.22	
	length of stent	52.5±15.9	35.0±7.1	0.07	
	deformation (MSP in-stent)	24.4±22.5	43.5±9.2	0.19	
Laboratory data	TC	162.6±33.9	121.0±4.2	0.19	
	LDL	83.5±27.2	72.5±3.5	0.61	
	HDL	62.6±28.0	35.0±1.4	0.07	
	CRP	1.21±2.96	0.05±0.04	0.25	
	BUN	18.2±6.4	20.6±11.2	1.00	
	Crea	1.10±0.78	0.93±0.30	1.00	
	eGFR	61.6±20.7	63.2±22.4	0.86	
	Hb-A1c	6.1±1.0	6.2±0.4	0.69	
Medications	aspirin	40.0±50.3	50.0±70.7	0.84	
	clopidogrel	52.5±35.3	62.5±17.7	0.94	
	cilostazol	26.3±63.6	0±0	0.55	
	statin potency	7.5±4.9	10.0±0	0.36	
Duration	CAS_3D-CTA	499.5±254.0	1096.5±200.1	0.03 *	
	CAS_CDU	895.3±184.2	993.0±347.9	0.61	

factors, only duration between CAS and 3D-CTA was significantly different when comparing the ISR-positive group and the ISR-negative group (Table 1). The duration between CAS and 3D-CTA was significantly longer in the ISR-positive group than in the ISR-negative group because they underwent 3D-CTA for a longer period of time. As the result of extensive checkup of medical charts in ISR-positive group, 3D-CTA had been examined more frequently in ISR-positive groups, and the date of 3D-CTA in ISR-positive group was likely later than that in ISR-negative group.

3D-CTA and ultrasound factors

We compared the relationship between final 3D-CTA and subsequent CDU. 3D-CTA factors included IMT_axCTA, IMT_sagCTA, Area_CTA, ECST_CTA, NASCET_CTA, and the duration between CAS and 3D-CTA. The deformity of stent was NASCET_MSP in-stent. CDU factors included IMT_axUS, IMT_sagUS, PSV, Area_US, ECST_US, and the duration between CAS and CDU. There was a good correlation between 3D-CTA and CDU in regards to in-stent max IMT and stenosis rate(Fig. 3).

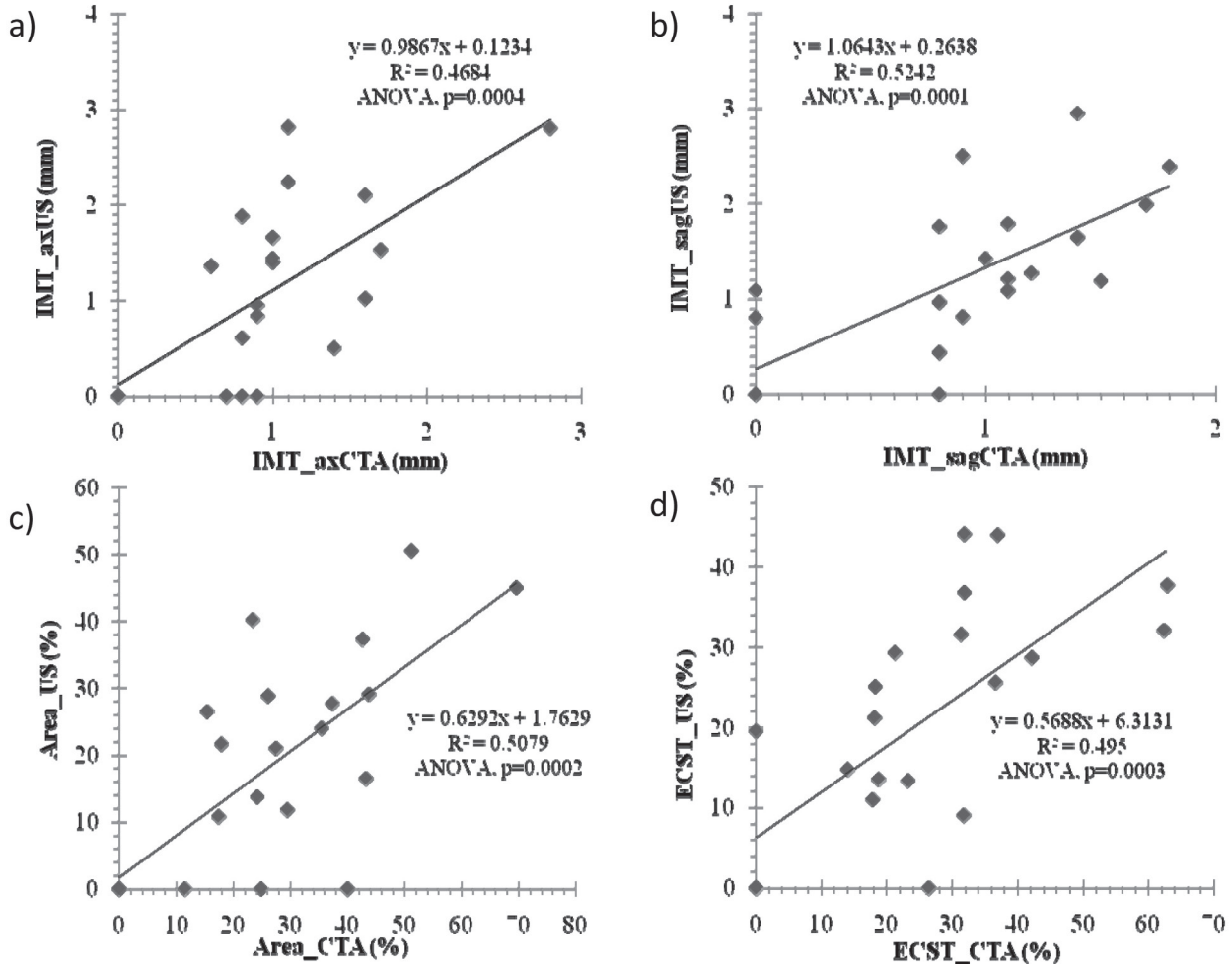

Fig. 3. About intima-media thickness (IMT) and stenosis rate, the correlation between three-dimensional computed tomography angiography (3D-CTA) and carotid duplex ultrasonography (CDU).

a) For IMT_axial, there is a significant correlation between CTA and CDU ($y=0.9867x+0.1234$, $R^2=0.4684$, one-way analysis of variance (ANOVA), $F=17.62$, $p=0.0004$*).

b) For IMT_sagittal, there is a significant correlation between CTA and CDU ($y=1.0643x+0.2638$, $R^2=0.5242$, ANOVA, $F=22.03$, $p=0.0001$*).

c) For stenosis grade calculated by the area method, there is a significant correlation between CTA and CDU ($y=0.6292x+1.7629$, $R^2=0.5079$, ANOVA, $F=20.64$, $p=0.0002$*).

d) For stenosis grade calculated by the European Carotid Surgery Trial (ECST) method, there is a significant correlation between CTA and CDU ($y=0.5688x+6.3131$, $R^2=0.495$, ANOVA, $F=19.60$, $p=0.0003$*).

The correlation between CTA and CDU is the strongest for the IMT_sagittal view, according to one-way ANOVA.

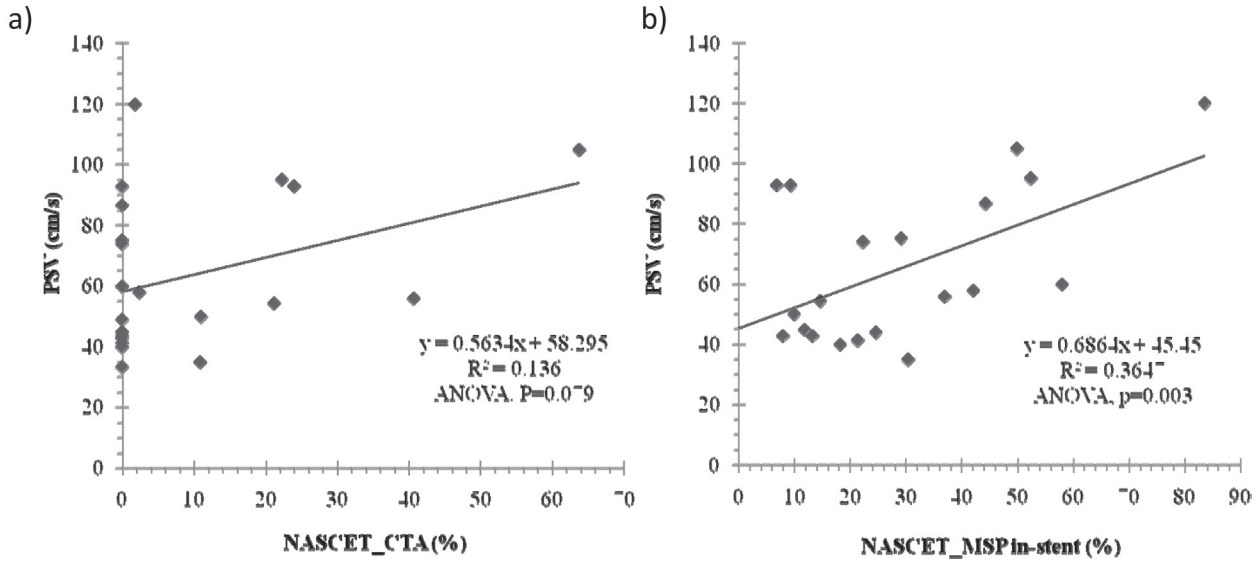

Fig. 4. Relationship between NASCET_CTA, NASCET_MSP in-stent, and peak-systolic velocity（PSV）.

a）There is no significant correlation between the NASCET_CTA and PSV（y=0.5634x+58.295, R^2=0.136, ANOVA, F=3.148, p=0.079）.

b）NASCET_MSP in-stent correlates with PSV（y=0.6864x+45.45, R^2=0.3647, ANOVA, F=11.481, p=0.003*）.

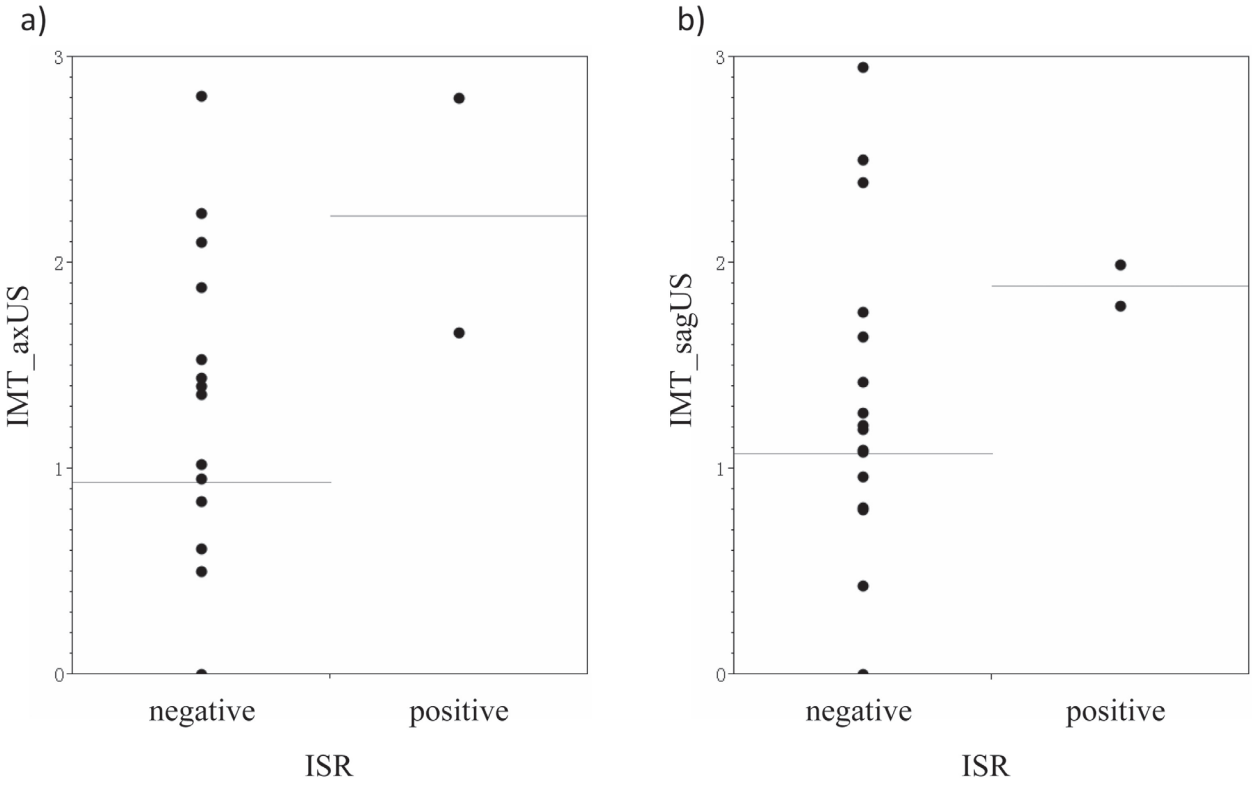

Fig. 5. The relationship between IMT on CDU and ISR defined by 3D-CTA.

a）There is no significant difference between the ISR and IMT on the axial view of CDU（R^2=0.122, ANOVA, F=3.926, p=0.061）.

b）There is no significant difference between the ISR and IMT on the sagittal view of CDU（R^2=0.030 ANOVA, F=1.651, p=0.213）. The line bars of negative/positive group are meant for the mean value of each group.

By contrast, the correlation between NASCET_CTA and PSV was not good (Fig. 4), however, the correlation between PSV and NASCET_MSP in-stent was better than the correlation between PSV and NASCET_CTA.

Since in-stent max IMT of 3D-CTA correlated with that of CDU, we compared the ISR-positive group and negative group with regard to in-stent IMT of CDU findings (Fig. 5). However, there was no statistical difference when comparing these values.

DISCUSSION

ISR-related factors

According to the Carotid Revascularization Endarterectomy versus Stenting Tiral (CREST) study, ISR occurs in 6.0% of patients over a 2 year period [5], which is consistent with data from the present study. Further, ISR was related to the following factors: female gender, hypertension, diabetes, hyperlipidemia, low HDL, high LDL, inflammation, stent deformity, and antiplatelet medications [1, 4, 5]. However, there were no significant differences between the ISR-positive group and the ISR-negative group, likely because the number of ISR cases was too small in this study. Regardless, there was a non-significant trend towards stent deformation, low HDL, and absence of cilostazol treatment in the ISR-positive group when compared with the ISR-negative group.

Categorical factor data, including those related to gender, laterality and past medical history were not significant different when comparing between the ISR-positive group and the negative-group (p=1.00 in Fisher's exact test), but the incidence of a past history of cancer was higher in the positive-group (2 of 2cases) when compared with the negative-group (9 of 20cases) (p=0.48 in Fisher's exact test). In fact, all ISR-positive cases had a past history of early cancer which were end of therapy (gastric cancer, n=1; esophageal cancer, n=1). The cancer-history in ISR-negative group was 9 cases (gastric cancer, n=4; colon cancer, n=2; laryngeal cancer, n=2; prostate cancer, n=1), including three patients with a history of advanced cancer. We analyzed the status of cancer (i.e., still treated or end of therapy), but the cancer-activity was not significantly related to ISR according to Fisher's exact test (p=1.00). Interestingly, the contingency table between ISR and past history of cancer indicated that the real number of cancer-history (n=2) was 2 times the expected value of cancer-history (n=1) in ISR-positive groups with cancer-history. Indeed, this result indicates a weak relationship between cancer-history and ISR, however, we thought that it should not be overlooked as expected data. Therefore, a past history of cancer might be a risk factor for late-onset ISR, possibly due to neointimal hyperplasia derived from an immunoreaction against cancer. However, further study is needed to explore this question.

Ultrasound follow-up

There was a relatively high correlation between 3D-CTA and CDU (Fig. 3), which suggests that CDU can replace 3D-CTA for long-term follow-up of stented patients. It is not yet clear which CDU variable (e.g., IMT, stenosis grade, or PSV) is optimal for follow-up. Some researchers have described ISR as best defined by the PSV value [6]. However, as shown in Figure 4, the PSV was better correlation with NASCET_MSP in-stent than that with NASCET_CTA. Why was the PSV well correlated with the NASCET_MSP in-stent related to stent deformation? We thought that flow velocity was affected by stent deformation in the range of PSV values less than 130 cm/s. We guess that PSV might be inadequate to predict late-onset ISR and it was difficult to recognize development of intimal hyperplasia in the range of PSV values less than 130 cm/sec.

As shown in Figure 5, a CDU-derived in-stent IMT less than 1.0 mm corresponded to ISR-negative status, and in-stent IMT more than 2.0 mm correlated with ISR-positive status. Therefore, we focused attention on in-stent IMT and advocate the use of ultrasound-based detection of ISR as defined by the IMT value and stenosis grade. Specifically, ultrasound-based detection of ISR was defined as either a stenosis ratio >30% when using the ECST method or in-stent IMT >2.0 mm, as measured by color-coded image or B mode. The in-stent max IMT on the final 3D-CTA was significantly higher in the ultrasound ISR-positive group than in the ultrasound

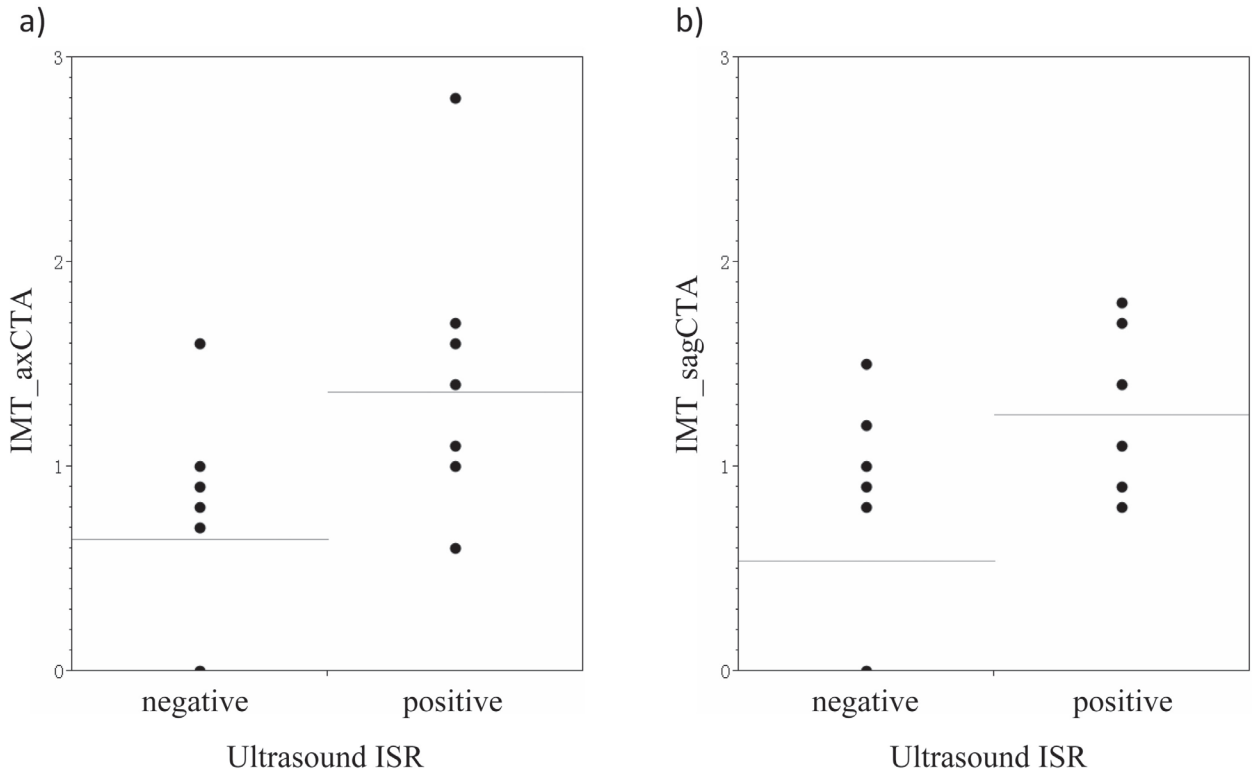

Fig. 6. The relationship between IMT on 3D-CTA and ISR defined by ultrasound.

a) It is a significantly difference between ultrasound ISR-positive group and ultrasound ISR-negative group from the IMT_axial view on 3D-CTA (R^2=0.274, ANOVA, F=8.917, p=0.0073*).

b) It is a significantly difference between ultrasound ISR-positive group and ultrasound ISR-negative group from the IMT_sagittal view on 3D-CTA (R^2=0.342, ANOVA, F=11.91, p=0.0025*). The line bars are meant for the mean value of each group.

ISR-negative group (Fig. 6). Further, there was a time-lag between the final 3D-CTA and subsequent CDU. Therefore, the positive ISR in 3D-CTA was included in the positive ISR in CDU. We suspect that the use of in-stent max IMT on the final 3D-CTA combined with subsequent ultrasound-based detection of ISR is a good strategy for follow-up of patients undergoing CAS.

Limitation

Our results did not reached to the statistical level, because the number of ISR positive group was only two cases in this pilot study. We need the additional study to improve our results. It will be achieved by increasing the number of participants in the future. We are planning to further examination on the post-stented patients.

CONCLUSIONS

This study investigated possible risk factors for late-onset ISR and evaluated the use of CDU for ongoing follow-up after the 2 year 3D-CTA for patients who underwent CAS. A past history of cancer might be a risk factor for ISR. Further, CDU was an acceptable up method for follow-up of CAS patients beyond the 2 year follow-up time point. Specifically, the in-stent max IMT of CDU could predict late-onset ISR.

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