Long-term imaging follow-up to evaluate restenosis in patients with carotid stenosis after angioplasty and stenting

Jung-Hsuan Chen[a,b], Mei-Han Wu[a,b,c], Chao-Bao Luo[a,b], Jiing-Feng Lirng[a,b], Shu-Ting Chen[a,b], Chia-Hung Wu[a,b,d], Wan-Yuo Guo[a,b], Feng-Chi Chang[a,b,*]

[a]Department of Radiology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [b]School of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC; [c] Department of Medical Imaging—Diagnostic Radiology, Cheng Hsin General Hospital, Taipei, Taiwan, ROC; [d]Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan, ROC

Abstract

Background: Stent patency after carotid angioplasty and stenting (CAS) correlates not only with stroke prevention but also with improvements in cognition and quality of life by positively influencing cerebral perfusion. The long-term outcomes of CAS after more than 5 years have still not been well described. This retrospective study was designed to evaluate the stent patency and significant restenosis (SR) after CAS with more than 5 years of follow-up.

Methods: Between 2006 and 2012, 118 patients with carotid stenosis who underwent 131 CAS procedures with regular annual imaging follow-up for more than 5 years were enrolled. We evaluated their demographic characteristics and the risk factors related to stent restenosis. Patients with SR (restenosis ≥ 50%) were compared with those with no significant restenosis (NSR, patency or restenosis < 50%) to identify the restenosis predictors and restenosis-free survival.

Results: Of the 131 CAS procedures, 16.0% (21/131) had SR. A history of head and neck radiotherapy (HNRT) was a predictor for SR (HR, 6.352; 95% CI, 2.504–16.112; $p < 0.001$) and was associated with shorter restenosis-free survival (log-rank test p value < 0.001, median time of restenosis-free survival was 38 months). Left-sided stenting was an associated factor for SR (HR, 3.007; 95% CI, 1.068–8.467; $p = 0.037$) with a trend of less restenosis-free survival (log-rank test p value 0.067).

Conclusion: Both HNRT and left-sided carotid stenosis were predictors of SR after CAS in more than 5 years of long-term follow-up. Restenosis-free survival was significantly shorter in patients with prior HNRT than in patients without previous irradiation treatment. We suggest close follow-up and aggressive medical treatment for patients with prior HNRT and left-sided carotid stenosis undergoing CAS.

Keywords: Angioplasty and stenting; Carotid stenosis; Outcome; Restenosis

1. INTRODUCTION

Cerebrovascular disease has been an important factor contributing to mortality and disability. Carotid stenosis accounts for up to 25% of ischemic stroke.[1,2] Therapeutic intervention, either carotid endarterectomy (CEA) or carotid angioplasty and stenting (CAS), for significant carotid stenosis contributes enormously to prevention of ischemic stroke, and the efficacies of the two interventions are considered comparable to each other. Successful carotid revascularization not only prevents stroke but also helps improve cognition, dizziness, and quality of life through its efficacy in restoring cerebral perfusion.[3–5] Therefore, long-term stent patency exerts an influence beyond stroke prevention. Although CAS is a valid way to treat carotid stenosis, the majority of reports document the outcomes up to 5 years after CAS.[6–11] The efficacy of long-term outcomes for stroke prevention and stent patency more than 5 years after CAS have seldom been shown in trials, and the risk factors or time schedule for restenosis have not been completely analyzed and remain unclear.[12,13]

Multiple possible risk factors for restenosis after CAS, including age, sex, smoking, diabetes, dyslipidemia, hypertension, radiotherapy, residual stenosis after stenting, and even hemodynamic status, have been discovered.[14] Progressive delayed restenosis of the treated carotid artery can result in "asymptomatic" ipsilateral cerebral hypoperfusion, which may only present with inconspicuous quality of life impairments. Without long-term imaging follow-up, the "asymptomatic" influence of significant late carotid restenosis could be neglected clinically. The aim of this retrospective study was to evaluate the long-term patency of CAS, the risk factors for and the time course of significant restenosis (SR) in clinical and imaging follow-up for more than 5 years.

2. METHODS

2.1. Patient selection

This retrospective study was approved by the institutional review board of our hospital. Informed consent from each patient was obtained before CAS.

*Address correspondence. Dr. Feng-Chi Chang, Department of Radiology, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: fcchang374@gmail.com (F.-C. Chang)

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2021) 84: 87-94.

Received May 24, 2020; accepted July 13, 2020.

doi: 10.1097/JCMA.0000000000000405.

From 2006 to 2012, 568 patients received stenting for cerebrovascular stenosis in our hospital. Of the patients, those who received CAS and had follow-up imaging for more than 5 years were included. We excluded patients with nonatherosclerotic carotid stenosis and patients without regular annual images (Fig. 1). When the treated lesion had restenosis ≥ 50%, it was defined as SR. We defined CAS without restenosis or restenosis less than 50% as no significant restenosis (NSR). Ultimately, 118 patients who underwent 131 procedures (13 patients received bilateral carotid stenting) were enrolled in our study.

2.2. Carotid angioplasty and stenting

The indications for CAS in our study were symptomatic stenosis more than 60% and asymptomatic stenosis more than 80%, modified from the North American Symptomatic Carotid Endarterectomy Trial (NASCET) methods. Our procedure was carried out by femoral artery puncture using the Seldinger technique. Before the procedure, a complete angiogram of the supra-aortic arteries and bilateral common carotid arteries was performed to determine the stent size and length requirements. We routinely used a cerebral embolic protection device [FilterWire EX/EZ (Boston Scientific, Natick, MA, USA)] at the distal cervical ICA. Preferentially, we used a closed-cell stent [Carotid Wallstent (Boston Scientific)] for its better coverage of lesions and an open-cell stent [Acculink (Abbott Vascular, Santa Clara, CA, USA) or Precise (Cordis, Fremont, CA, USA)] was an alternative when deployment of the initial stent failed due to vascular anatomy or lesion morphology. Poststent balloon dilatation was performed to obtain residual stenosis less than 30%. Technical success was defined as successful percutaneous transluminal angioplasty and stenting of the carotid stenosis with residual stenosis less than 30%. Dual antiplatelet therapy was prescribed for all patients at least 3 days before the procedure and for 1 month after stenting with strict blood pressure control. A single anti-platelet medication was to be taken for life after the first month. The periprocedural complications within 30 days were defined as cerebral ischemic or hemorrhagic insults, myocardial infarctions, and death. The primary outcome was set as SR during the follow-up period. Time to restenosis (TR) was defined as the time from the stenting procedure date to the date of images when SR was first noted.

2.3. Clinical evaluation, imaging follow-up, and data collection

Patients had regular clinical follow-up every 3 to 6 months with standard care to maintain lipid profile, blood glucose, and blood pressure within normal ranges. Imaging follow-up of carotid arteries was performed at least once a year, mainly with carotid sonography but also with computed tomography angiography (CTA) or magnetic resonance angiography (MRA) based on the judgment of physicians. Digital subtraction angiography (DSA) was performed in the cases of SR noted in the imaging study. The demographic information of sex, age at stenting, stenting site, prestent stenosis severity, stent type, and follow-up duration and the clinical data of symptoms, signs, comorbidities, and risk factors were collected by chart review of the 131 procedures from the 118 patients until December 31, 2019. For symptoms and signs, we included not only stroke, transient ischemic attack, and amaurosis fugax but also dizziness and syncope, which are not generally considered ischemic symptoms for CAS but were common complaints from our patients. Comorbidities and risk factors included hypertension, diabetes mellitus, dyslipidemia, coronary artery disease (as a history of receiving coronary artery stenting or bypass surgery), and previous head and neck radiotherapy (HNRT).

2.4. Statistical analysis

The categorical data were analyzed by a chi-square or Fisher's exact test. The numerical data were analyzed by an independent two sample *t*-test. Risk factors for restenosis during follow-up were evaluated by Cox regression, and restenosis-free survival was calculated using the Kaplan–Meier method. Two-tailed tests were used to determine statistical significance with a p value < 0.05. All statistical analyses were performed with IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp, Armonk, NY, USA).

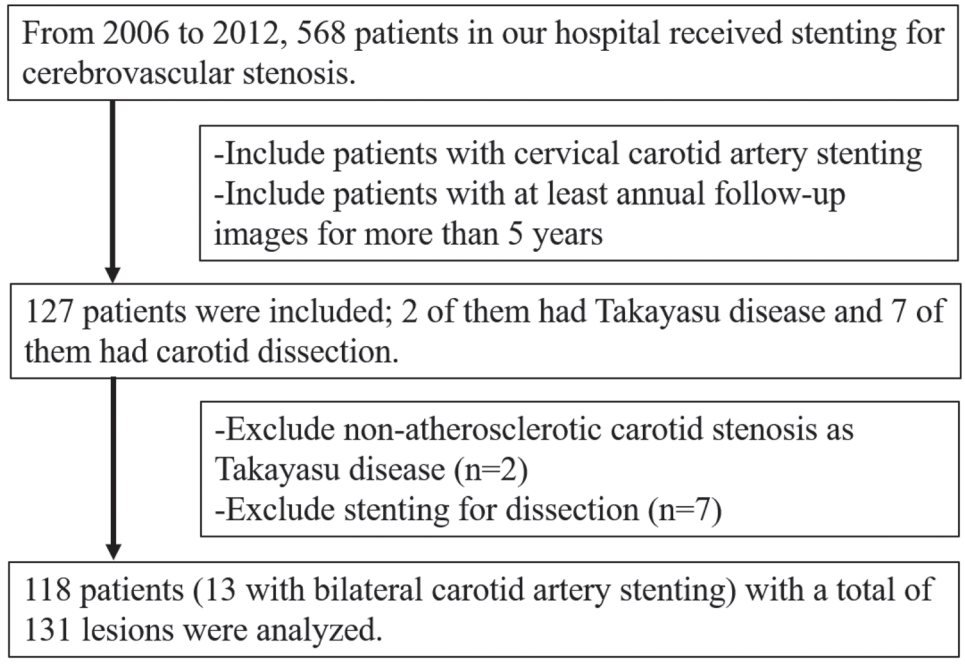

Fig. 1 Funnel map for inclusion and exclusion criteria in our study.

Table 1

Demographic data and periprocedural outcomes of 131 lesions

Variables	*n* = 131
Average age at stenting (y), (SD) (range)	69.9 (9.5) (39–86)
Years of follow-up, (SD) (range)	7.7 (1.97) (5–13)
Gender, *n* (%)	
Male	115 (87.8)
Female	16 (12.2)
Site of stent, *n* (%)	
Left	63 (48.1)
Right	68 (51.9)
Prestenting stenotic rate, (SD) (range)	80.2% (11.2%) (60%–99%)
Stenotic location, *n* (%)	
Common carotid artery	7 (5.3)
Carotid bifurcation	4 (3.1)
Internal carotid artery	120 (91.6)
Significant restenosis (restenosis ≥ 50%), *n* (%)	21 (16.0)
Time to restenosis (TR, mon) (SD) (range)	28.6 (33.3) (5–112)
Periprocedural complications, *n* (%)	8 (6.1)
Subarachinoid hemorrhage	1 (0.8)
Cerebral infarction (minor stroke)	7 (5.3)
Recurrent or new symptoms and signs, *n* (%)	12 (9.2)
Dizziness	10 (7.6)
Headache	1 (0.8)
Amaurosis fugax	1 (0.8)

3. RESULTS

3.1. Patient characteristics and periprocedural outcomes

Table 1 shows the characteristics of our patients who underwent the 131 CAS procedures. The average age at stenting was 69.9 ± 9.5 (39–86) years old. The average period of follow-up was 7.7 ± 1.97 (5–13) years. The severity of pretreatment carotid stenosis was 80.2 ± 11.2% (60%–99%). Periprocedural complications were noted in 8 of the 131 procedures (6.1%); these complications included minimal subarachnoid hemorrhage in 1 (1/131, 0.8%) procedure and minor stroke in 7 (7/131, 5.3%) procedures. All these patients had good clinical recovery without neurological deficits at discharge. Neither periprocedural myocardial infarction nor death occurred in our study. Twenty-one of the 131 procedures (16.0%) had SR. The TR first noted in these 21 treated lesions was 28.6 ± 33.3 (5–112) months. We continued follow-up on our patients even after the first SR was noted. Of the 21 patients with SR, 11 patients (52.4%) reported recurrent dizziness or new onset of headache, which were not considered ischemic criteria for CAS, and one patient with restenosis (4.8%) had cerebral ischemic symptom as amaurosis fugax.

3.2. Factors related to restenosis and outcomes

Table 2 summarizes the NSR versus SR groups. For patients with a history of HNRT, statistical significance was noted between SR and NSR (9/21, 42.9% vs 7/110, 6.4%, p value < 0.001).

Univariate and multivariate Cox proportional hazard models were applied to identify variables that could potentially affect the primary outcome of SR. The results of univariate analyses of restenosis factors are shown in Table 3. Closed-cell stent design (HR, 0.312; 95% CI, 0.105–0.927; p value 0.036) and HNRT (HR, 7.636; 95% CI, 3.209–18.169; p value < 0.001) were statistically significant factors for SR.

Multivariate analysis was used for coefficients with a p value less than 0.2, and the results are shown in Table 4. Left-sided carotid stenosis (HR, 3.007; 95% CI, 1.068–8.467; p value 0.037) and HNRT (HR, 6.352; 95% CI, 2.504–16.112; p value <0.001) were significantly associated with an increased risk of SR.

Kaplan–Meier curves for restenosis-free survival of SR with respect to the factors of HNRT and site of carotid stenosis are presented in Fig. 2A, B. In patients with prior HNRT, the median time of restenosis-free survival was 38 months, and the

Table 2

Characteristics and risk factors in cases with no significant restenosis (NSR) or significant restenosis (SR)

Variables	Total lesion (*n* = 131)	NSR (*n* = 110)	SR (*n* = 21)	*p*
Patient Characteristics				
Age of stenting (y), (SD)	69.9 (9.5)	70.0 (9.4)	69.4 (10.2)	0.796
Years of follow-up (SD)	7.7 (1.97)	7.8 (2.0)	7.0 (1.6)	0.062
Gender (male), *n* (%)	115 (87.8)	95 (86.4)	20 (95.2)	0.467
Site of stenting (left), *n* (%)	63 (48.1)	49 (44.5)	14 (66.7)	0.063
Closed-cell stent, *n* (%)	120 (91.6)	103 (93.6)	17 (81.0)	0.076
Prestenting stenotic rate (SD)	80.2% (11.2%)	79.9% (11.2%)	81.8% (11.1%)	0.483
Symptoms and Signs, *n* (%)				
With symptoms	110 (84.0)	94 (85.5)	16 (76.2)	0.289
Major stroke	25 (19.1)	21 (19.1)	4 (19.0)	1.000
Minor stroke (NIHSS ≤5)	5 (3.8)	3 (2.7)	2 (9.5)	0.181
Transient ischemic attack	13 (9.9)	12 (10.9)	1 (4.8)	0.692
Amaurosis fugax	15 (11.5)	12 (10.9)	3 (14.3)	0.708
Dizziness	55 (42.0)	49 (44.5)	6 (28.6)	0.230
Syncope	14 (10.7)	12 (10.9)	2 (9.5)	1.000
Risk Factors, *n* (%)				
Smoking	75 (57.3)	62 (56.4)	13 (61.9)	0.638
Hypertension	114 (87.0)	95 (86.4)	19 (90.5)	1.000
Diabetes mellitus	30 (22.9)	26 (23.6)	4 (19.0)	0.782
Dyslipidemia	48 (36.6)	42 (38.2)	6 (28.6)	0.402
Coronary artery disease[a]	32 (24.4)	30 (27.3)	2 (9.5)	0.101
HNRT[b]	16 (12.2)	7 (6.4)	9 (42.9)	< 0.001

NSR was defined as patent or restenosis < 50% and SR was defined as restenosis ≥ 50%.

[a]Defined as history of coronary artery stenting or coronary artery bypass grafting.

[b]HNRT= head and neck radiotherapy.

Table 3

Univariate analysis of factors related to no significant restenosis (NSR) or significant restenosis (SR)

Factors	*p*	Hazard ratio (HR)	95% Confidence interval (CI)
Male	0.315	2.802	0.376–20.892
Left-sided stent	0.076	2.275	0.918–5.641
Closed-cell stent	0.036	0.312	0.105–0.927
With symptoms	0.330	0.606	0.221–1.660
Major stroke	0.893	0.928	0.312–2.759
Minor stroke (NIHSS 1–5)	0.119	3.191	0.742–13.730
Transient ischemic attack	0.390	0.414	0.056–3.088
Amaurosis fugax	0.614	1.370	0.403–4.654
Dizziness	0.207	0.543	0.211–1.402
Syncope	0.908	0.917	0.213–3.944
Smoking	0.540	1.318	0.545–3.188
Hypertension	0.502	1.648	0.383–7.092
DM	0.686	0.798	0.268–2.374
Dyslipidemia	0.447	0.692	0.268–1.786
Coronary artery disease	0.116	0.311	0.072–1.334
HNRT	< 0.001	7.636	3.209–18.169

longest TR first noted was 62 months. In comparison to patients without HNRT, patients with HNRT had shorter restenosis-free survival (log-rank test p value < 0.001). Although not statistically significant, there was a trend of less restenosis-free survival in patients with left-sided CAS (log-rank test p value 0.067).

4. DISCUSSION

The long-term outcomes more than 5 years after CAS were not well described in the literature. The present study analyzed our single-center experience to clarify the stent patency and SR after CAS in long-term follow-up. A history of HNRT is a predictor for SR with a shorter restenosis-free survival. CAS of left-sided carotid stenosis is an additional associated factor for SR. CAS with open-cell stents is likely to be associated with a higher SR rate than closed-cell stents.

Our hospital is a medical center with experienced interventional neuroradiologists and close collaboration between neurologists, neurosurgeons, and neuroradiologists. We have weekly combined meetings to discuss patients with carotid artery stenosis. We are a qualified training center for interventional radiology, and two of our interventional neuroradiologists each have more than 20 years of experience. The periprocedural complication rate was 6.1% (8/131) in this study, but all patients were discharged smoothly without neurological deficits. In the guidelines of American College of Cardiology/American Heart Association and European Society for Vascular Surgery,[11] it is recommended that symptomatic patients receive carotid artery stenting in a medical center with a periprocedural complication (stroke or mortality) rate less than 6%.

Generally, SR is defined as 50% or 70% luminal narrowing. The restenosis rate varies greatly among studies, ranging from 1.6% and even up to 40.7% in the International Carotid Stenting Study, depending on the follow-up interval, study population and definition of restenosis rate. Moreover, the endpoint of the long-term outcome for CAS was usually defined as recurrent ipsilateral stroke.[13–16] However, cognitive impairment and dizziness were reported in patients with significant asymptomatic carotid stenosis.[17,18] Severe carotid stenosis or restenosis can result in intracranial hypoperfusion, which impairs neuronal connectivity and hemodynamic autoregulation. These findings highlight the importance of long-term stent patency after CAS, which exerts additional influence on cerebral function beyond stroke prevention.

Table 4

Multivariate analysis of factors related to no significant restenosis (NSR) or significant restenosis (SR)

Factors	*p*	Hazard Ratio (HR)	95% Confidence Interval (CI)
Left-sided Stent	0.037	3.007	1.068–8.467
Closed-cell Stent	0.093	0.376	0.120–1.177
Minor stroke (NIHSS ≤5)	0.123	3.621	0.706–18.528
Coronary artery disease	0.273	0.426	0.093–1.962
HNRT	<0.001	6.352	2.504–16.112

The primary outcome was defined as SR in our study to identify patients with restenosis early and in a timely manner. The overall SR rate was 16.0% (21/131) in our study. Of the 21 patients with SR, 12 (57.1%) had recurrent or new symptoms and signs. One (1/21, 4.8%) patient with a restenotic lesion presented with cerebral ischemic symptom as amaurosis fugax. No recurrent stroke occurred in our study, but 11 of 21 (52.4%) patients with restenotic lesions presented recurrent dizziness or new onset of headache. These results suggest that SR of CAS is usually asymptomatic from the perspective of stroke prevention. However, SR presenting as dizziness can impair the quality of life of affected patients.[5] Early detection and management of subclinical carotid restenosis is beneficial to improve quality of life for patients who are conventionally regarded as asymptomatic. In our long-term follow-up study, SR occurred after only 16% (21/131) of CAS procedures, and recurrent or new symptoms and signs were experienced by 9.2% (12/131) of patients, indicating the good long-term patency and efficacy of CAS (Fig. 3) and corresponding to reports of large trials.[12,13]

There was no significant difference in demographic characteristics between patients with and without SR after CAS in our study. The patients in our study were predominantly male. This may be explained by the fact that our hospital is a veteran's hospital and a referring center for head and neck cancer. Head and neck cancers are male dominant and affect a considerable portion of patients with SR in our study. However, patient sex had no statistical significance for SR in our research. Prior HNRT was a predictor for SR with shorter restenosis-free survival in long-term follow-up (HR, 6.352; 95% CI, 2.504–16.112; p value < 0.001; log-rank test p value < 0.001). The longest TR first noted was 62 months in patients with prior HNRT. Over half of the patients (9/16, 56.3%) with HNRT had SR within approximately 5 years in our study.

Head and neck cancer has higher incidence in Eastern countries, with an increasing trend in Taiwan in recent years. Radiotherapy plays a main role in the treatment of head and neck cancer.[19] The pathogenesis of radiation-induced carotid artery disease is hypothesized to be endothelial dysfunction, vasa vasorum injury, and accelerated atherosclerosis.[20] Radiotherapy is known to be a major risk factor for carotid stenosis and is also associated with restenosis after CAS. A study by Dorresteijn et al[21] showed that radiotherapy increased the incidence of restenosis after CAS from 17% at 3 months to 42% at 2 years. We believe that radiotherapy has a persistent effect on the carotid artery, which explains the high SR in our HNRT patients. We suggest that patients with HNRT should receive close follow-up care during the first 5 years after CAS and regular follow-up thereafter. Of our 21 CAS with SR cases, 9 (42.9%) involved patients with prior HNRT. Eight lesions of the above 9 SRs of HNRT patients were successfully treated with repeated CAS. One lesion failed repeated CAS because the patient was not cooperative during the procedure. Fig. 4 demonstrates the management of a patient with prior HNRT who had bilateral CAS

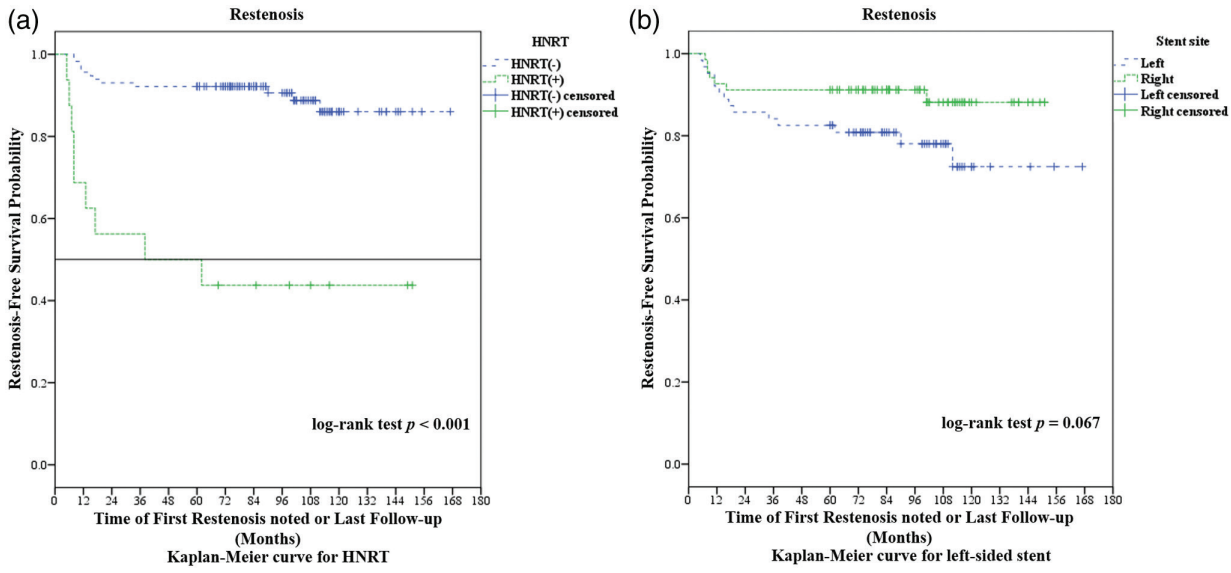

Fig. 2 Kaplan–Meier curves of restenosis-free survival for SR in patients with prior HNRT (A) and of different stent sites (B). Shorter restenosis-free survival was observed in patients with prior HNRT. A trend of less restenosis-free survival of left-sided stents was discovered.

and refractory restenosis. A drug-eluting balloon is an emerging device for refractory restenosis in CAS, and some studies have reported good results.[22,23] However, more time is needed to confirm the long-term effects.

Restenosis was more likely to occur in left-sided carotid stents in our study (HR, 3.007; 95% CI, 1.068–8.467; *p* value 0.037). There was also a trend of less restenosis-free survival in patients with left-sided CAS (log-rank test *p* value 0.067). In a study by Rodriguez-Hernandez et al,[24] left-sided intima-media thickness and left-sided carotid artery mean velocity flow rate had higher values than the right side in patients with untreated hypertension; in addition, the population-based stroke registry in the authors' hospital revealed a higher incidence of left-sided nonlacunar stroke. A community-based study in Taiwan by Chou et al[25] also discovered that the left carotid artery had a higher risk of plaque formation than the right carotid artery in healthy participants. The exact cause of this left-sided preference of SR was not clarified. We hypothesize that it could be related to higher flow rates

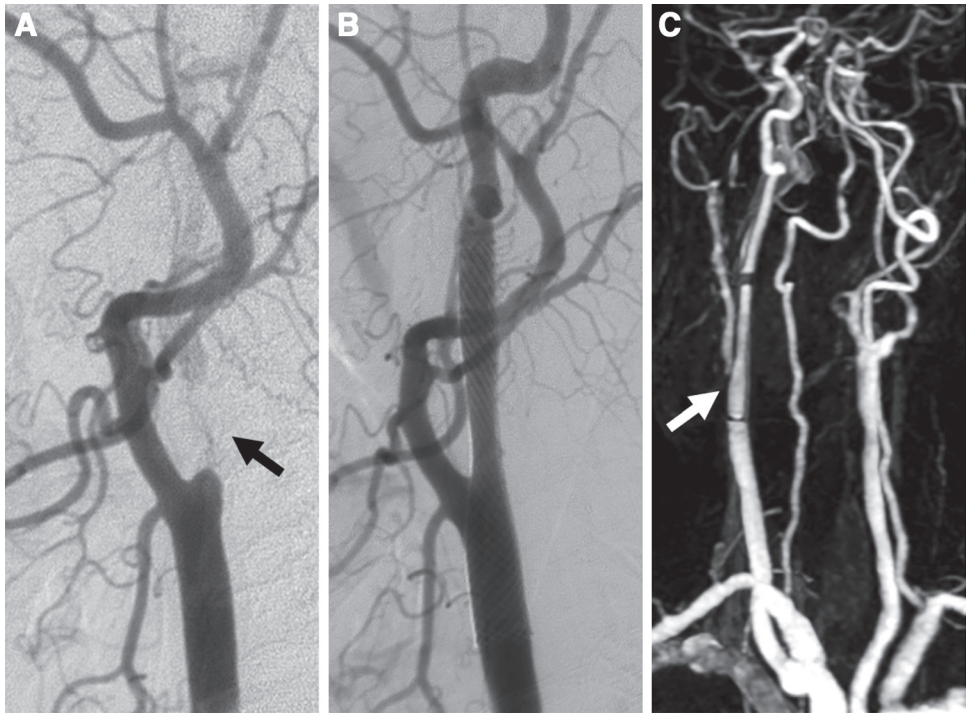

Fig. 3 A 64-year-old man with major stroke and right cervical carotid artery 99% stenosis (A) received CAS with no residual stenosis (B). Follow-up magnetic resonance angiography (MRA) (C) after 11 years revealed excellent patency.

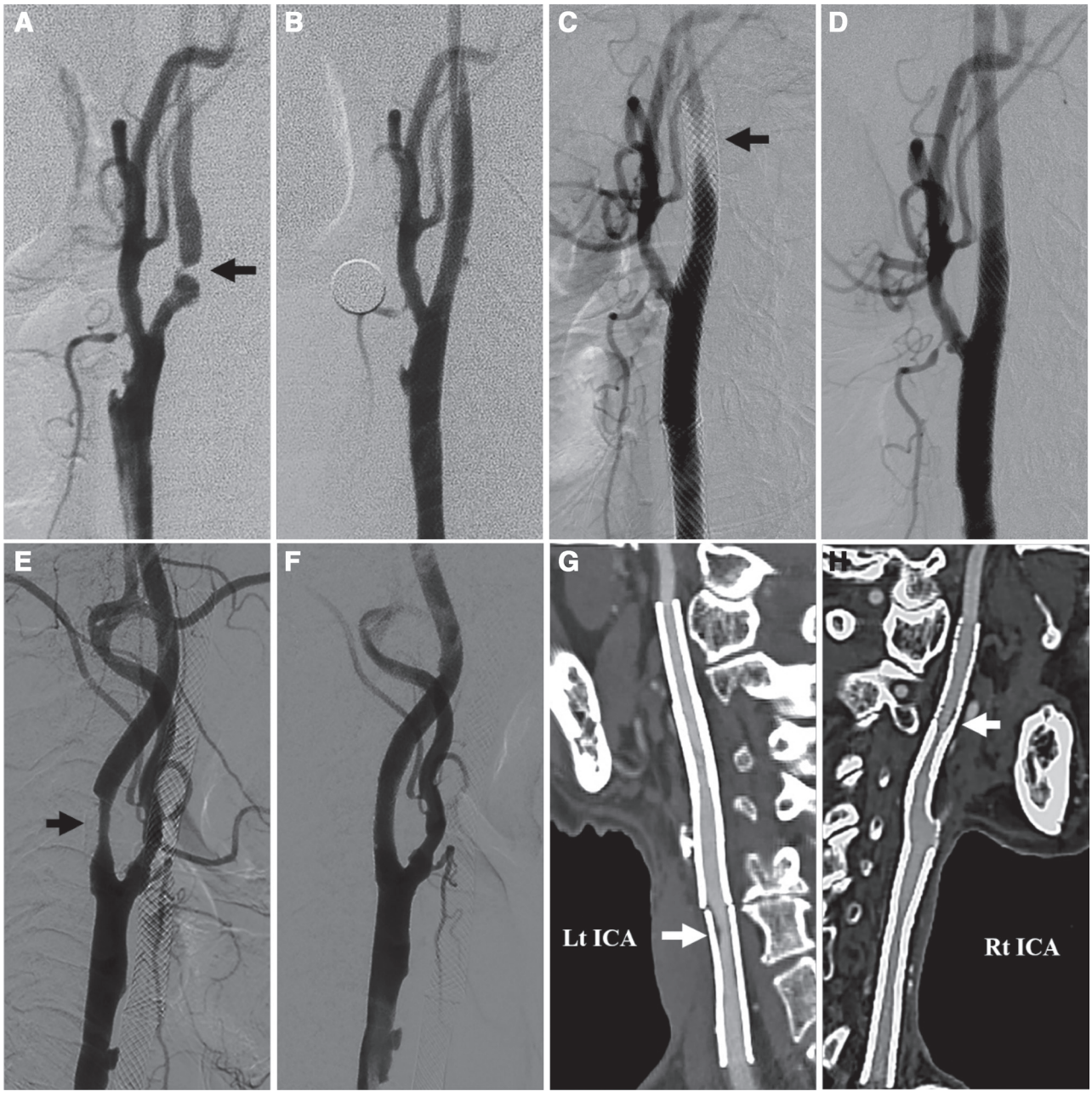

Fig. 4 A 74-year-old male who had prior HNRT. He had carotid angioplasty and stenting (CAS) in 2008 for left internal carotid artery 98% stenosis and common carotid artery ulcerative plaque (A) without residual stenosis (B). Repeated stenting after 15 months for 95% restenosis (C) was performed with good results (D). He had CAS in 2014 for right internal carotid artery 70% stenosis (E) with postprocedural patency (F). Repeated right-sided stenting was performed in 2018 for another 80% stenotic lesion and 50% restenosis. Both sides revealed mild restenosis less than 50% in the last follow-up computed tomography angiography (CTA) in 2019 (4G–H).

or hemodynamic changes in the left carotid artery than in the right carotid artery. Generally, the left common carotid artery originates from the aortic arch, and the right common carotid artery derives from the innominate artery. Energy transfer from the heart is considered direct and thus greater in the left-sided carotid artery. In both studies,[24,25] the difference in intima changes or plaque formation between bilateral carotid arteries was concluded to be related to hemodynamic effects resulting from anatomy and geometry of the carotid arteries. Moreover, in a study conducted by van Vuuren et al,[26] the flow velocities and volume flow rates in common and internal carotid arteries had left-sided arterial dominance in right-handed people and vice versa. It was proposed that the language-dominant hemisphere accommodated greater perfusion demands. The majority of people around the world are right handed. As the left carotid artery is vulnerable to higher flow stress and higher subsequent plaque formation than the right carotid artery, we believe that left-sided CAS has a higher risk of restenosis than the right-sided procedure. We thus suggest close clinical and imaging follow-up in patients with CAS for left carotid stenosis.

Open-cell stent type was a predictor for SR in the univariate analysis (HR, 0.312; 95% CI, 0.105–0.927; p value 0.036) but had no statistical significance in the multivariate analysis in our study. Closed-cell stents are the most often used type in our

daily practice because of their better plaque coverage. In cases of tortuous artery anatomy, closed cell–type stents may not be deployed smoothly due to their rigidity, and open cell–type stents can be an excellent alternative.[27] Closed-cell stents and open-cell stents are comparable to each other in periprocedural events and stroke recurrence, but the restenosis rate in different stent types is controversial.[28–31] In a study by Alparslan et al,[30] more development of intimal hyperplasia was considered the main reason for restenosis in the open-cell stent because of the lower scaffolding potential related to the stent's larger free cell area. In Müller's study, a significant difference in restenosis between open-cell stents and closed-cell stents was only observed in cases where restenosis was ≥ 50% but not in restenosis ≥ 70%, and neointimal hyperplasia resulting from greater irritation of the vessel wall by closed-cell stents was suggested as the cause for restenosis.[29] However, follow-up time, image modality for monitoring and definition of restenosis varied in studies, and further studies are needed to differentiate the restenosis rate between closed-cell stents and open-cell stents. For patients with a high risk of restenosis, such as those with prior HNRT, we prefer using closed-cell stents rather than open-cell stents to perform CAS.

There are some limitations of our study. This is a single-center, nonrandomized, and retrospective study with small case numbers. Our medical center is primarily for veterans and is likely to have uneven sex and age distribution of patients, which makes analysis difficult. The retrospective study design also made the follow-up image modality nonuniform. Fortunately, we usually arranged additional image modalities when the result of the first modality was not conclusive. We suggest a prospective study with a standard and uniform method of imaging follow-up to evaluate the long-term outcomes of CAS, especially in patients with head and neck cancer.

In conclusion, history of HNRT and left-sided carotid stenosis exert a significant influence on restenosis after CAS in long-term follow-up of more than 5 years. Restenosis-free survival is shorter in patients with HNRT than in patients without previous irradiation treatment. We suggest close imaging follow-up and aggressive medical treatment for patients undergoing CAS who have prior HNRT and left-sided carotid stenosis.

ACKNOWLEDGMENTS

This research was cosponsored by Taipei Veterans General Hospital (grant number: V109C-062), the Ministry of Science and Technology of Taiwan (grant number: MOST 108-2314-B-075-006), and Veterans General Hospitals and University System of Taiwan Joint Research Program (VGHUST109-V1-5-2).

REFERENCES

1. Hsieh FI, Chiou HY. Stroke: morbidity, risk factors, and care in Taiwan. *J Stroke* 2014;**16**:59–64.
2. Flaherty ML, Kissela B, Khoury JC, Alwell K, Moomaw CJ, Woo D, et al. Carotid artery stenosis as a cause of stroke. *Neuroepidemiology* 2013;**40**:36–41.
3. Chen YH, Lin MS, Lee JK, Chao CL, Tang SC, Chao CC, et al. Carotid stenting improves cognitive function in asymptomatic cerebral ischemia. *Int J Cardiol* 2012;**157**:104–7.
4. Cheng HL, Lin CJ, Soong BW, Wang PN, Chang FC, Wu YT, et al. Impairments in cognitive function and brain connectivity in severe asymptomatic carotid stenosis. *Stroke* 2012;**43**:2567–73.
5. Hsu LC, Chang FC, Teng MM, Chern CM, Wong WJ. Impact of carotid stenting in dizzy patients with carotid stenosis. *J Chin Med Assoc* 2014;**77**:403–8.
6. Ringleb PA, Kunze A, Allenberg JR, Hennerici MG, Jansen O, Maurer PC, et al; Steering Committee of the SPACE Study. The stent-supported percutaneous angioplasty of the carotid artery vs. endarterectomy trial. *Cerebrovasc Dis* 2004;**18**:66–8.
7. Gurm HS, Yadav JS, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, et al; SAPPHIRE Investigators. Long-term results of carotid stenting versus endarterectomy in high-risk patients. *N Engl J Med* 2008;**358**:1572–9.
8. Bonati LH, Ederle J, McCabe DJ, Dobson J, Featherstone RL, Gaines PA, et al; CAVATAS Investigators. Long-term risk of carotid restenosis in patients randomly assigned to endovascular treatment or endarterectomy in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): long-term follow-up of a randomised trial. *Lancet Neurol* 2009;**8**:908–17.
9. Bonati LH, Dobson J, Featherstone RL, Ederle J, van der Worp HB, de Borst GJ, et al; International Carotid Stenting Study investigators. Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the International Carotid Stenting Study (ICSS) randomised trial. *Lancet* 2015;**385**:529–38.
10. Rosenfield K, Matsumura JS, Chaturvedi S, Riles T, Ansel GM, Metzger DC, et al; ACT I Investigators. Randomized trial of stent versus surgery for asymptomatic carotid stenosis. *N Engl J Med* 2016;**374**:1011–20.
11. Morris DR, Ayabe K, Inoue T, Sakai N, Bulbulia R, Halliday A, et al. Evidence-based carotid interventions for stroke prevention: state-of-the-art review. *J Atheroscler Thromb* 2017;**24**:373–87.
12. Mas JL, Arquizan C, Calvet D, Viguier A, Albucher JF, Piquet P, et al; EVA-3S Investigators. Long-term follow-up study of endarterectomy versus angioplasty in patients with symptomatic severe carotid stenosis trial. *Stroke* 2014;**45**:2750–6.
13. Brott TG, Howard G, Roubin GS, Meschia JF, Mackey A, Brooks W, et al; CREST Investigators. Long-term results of stenting versus endarterectomy for carotid-artery stenosis. *N Engl J Med* 2016;**374**:1021–31.
14. Dai Z, Xu G. Restenosis after carotid artery stenting. *Vascular* 2017;**25**:576–86.
15. Bonati LH, Gregson J, Dobson J, McCabe DJH, Nederkoorn PJ, van der Worp HB, et al; International Carotid Stenting Study investigators. Restenosis and risk of stroke after stenting or endarterectomy for symptomatic carotid stenosis in the International Carotid Stenting Study (ICSS): secondary analysis of a randomised trial. *Lancet Neurol* 2018;**17**:587–96.
16. Xin WQ, Li MQ, Li K, Li QF, Zhao Y, Wang WH, et al. Systematic and comprehensive comparison of incidence of restenosis between carotid endarterectomy and carotid artery stenting in patients with atherosclerotic carotid stenosis. *World Neurosurg* 2019;**125**:74–86.
17. Lin CJ, Tu PC, Chern CM, Hsiao FJ, Chang FC, Cheng HL, et al. Connectivity features for identifying cognitive impairment in presymptomatic carotid stenosis. *PLoS One* 2014;**9**:e85441.
18. Lal BK, Dux MC, Sikdar S, Goldstein C, Khan AA, Yokemick J, et al. Asymptomatic carotid stenosis is associated with cognitive impairment. *J Vasc Surg* 2017;**66**:1083–92.
19. Hwang TZ, Hsiao JR, Tsai CR, Chang JS. Incidence trends of human papillomavirus-related head and neck cancer in Taiwan, 1995-2009. *Int J Cancer* 2015;**137**:395–408.
20. Xu J, Cao Y. Radiation-induced carotid artery stenosis: a comprehensive review of the literature. *Interv Neurol* 2014;**2**:183–92.
21. Dorresteijn LD, Vogels OJ, de Leeuw FE, Vos JA, Christiaans MH, Ackerstaff RG, et al. Outcome of carotid artery stenting for radiation-induced stenosis. *Int J Radiat Oncol Biol Phys* 2010;**77**:1386–90.
22. Pohlmann C, Höltje J, Zeile M, Bonk F, Urban PP, Brüning R. Recurrent stenosis following carotid artery stenting treated with a drug-eluting balloon: a single-center retrospective analysis. *Neuroradiology* 2018;**60**:81–7.
23. Bhatia K, Akhtar IN, Akinci Y, Liaqat J, Siddiq F, Gomez CR, et al. Drug-eluting balloon angioplasty for in-stent restenosis following carotid artery stent placement. *J Neuroimaging* 2020;**30**:267–75.
24. Rodríguez Hernández SA, Kroon AA, van Boxtel MP, Mess WH, Lodder J, Jolles J, et al. Is there a side predilection for cerebrovascular disease? *Hypertension* 2003;**42**:56–60.
25. Chou CL, Wu YJ, Hung CL, Liu CC, Wang SD, Wu TW, et al. Segment-specific prevalence of carotid artery plaque and stenosis in middle-aged adults and elders in Taiwan: a community-based study. *J Formos Med Assoc* 2019;**118**(1 Pt 1):64–71.
26. Jansen van Vuuren A, Saling MM, Ameen O, Naidoo N, Solms M. Hand preference is selectively related to common and internal carotid arterial asymmetry. *Laterality* 2017;**22**:377–98.
27. Setacci C, Mele M, de Donato G, Mazzitelli G, Benevento D, Palasciano G, et al. Device selection for carotid stenting: reviewing the evidence. *Expert Rev Cardiovasc Ther* 2017;**15**:787–96.

28. Lee HJ, Chang FC, Luo CB, Guo WY. Influence of stenting with open-cell stents vs close-cell stents on the outcomes of patients with bilateral carotid stenosis. *J Chin Med Assoc* 2019;**82**:66–71.
29. Müller MD, Gregson J, McCabe DJH, Nederkoorn PJ, van der Worp HB, de Borst GJ, et al. Stent design, restenosis and recurrent stroke after carotid artery stenting in the International Carotid Stenting Study. *Stroke* 2019;**50**:3013–20.
30. Alparslan B, Nas OF, Eritmen UT, Duran S, Ozkaya G, Hakyemez B. The effect of stent cell geometry on carotid stenting outcomes. *Cardiovasc Intervent Radiol* 2016;**39**:507–13.
31. Texakalidis P, Giannopoulos S, Kokkinidis DG, Lanzino G. Effect of open- vs closed-cell stent design on periprocedural outcomes and restenosis after carotid artery stenting: a systematic review and comprehensive meta-analysis. *J Endovasc Ther* 2018;**25**:523–33.