



Carotid Artery Stenting for Patients with Radiation-Induced Carotid Artery Stenosis

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Objective: In radiation-induced carotid artery stenosis (RIS), morphological characteristics, such as bilateral and long lesion distances and in-stent stenosis, have been reported as common after carotid artery stenting (CAS). Here, we present 25 cases at our hospital wherein CAS was performed for RIS and compare the morphological characteristics and the safety of the treatment with cases of atherosclerotic carotid artery stenosis (AS).

Methods: Twenty-five lesions from 21 patients underwent CAS for RIS at our hospital between March 2002 and July 2020. The procedure was performed at a mean of 10.0 ± 5.2 years after radiation therapy with 60–72 Gy, with a median follow-up of 45 months. We retrospectively selected consecutive patients with AS with comparable follow-up times from the beginning of the study as controls. We compared the patients' background, stenosis findings including plaque MRI, perioperative period, and postoperative course.

Results: All patients in both groups completed the procedure, and the median follow-up time for the RIS and AS groups was 45 and 40 months, respectively ($p = 0.1479$). Patients in the RIS group had a lower mean age (69.9 ± 6.9 vs. 75.3 ± 7.04 , $p = 0.0075$), a higher stenosis rate ($79.1 \pm 8.7\%$ vs. $68.6 \pm 11.7\%$, $p = 0.0032$), and longer stenosis greater than one vertebra (long lesions) (10 vs. 1, $p = 0.0046$) compared with the patients in the AS group. Although there was no significant difference in outcomes between the two groups, restenosis tended to be more common in the RIS group. Plaque MRI was characterized by a significantly higher T2WI signal ($p = 0.0381$) in the RIS group, which was attributable to the fact that a necrotic core has been reported commonly in the plaque tissue of RIS.

Conclusion: RIS has a high likelihood of restenosis both morphologically and in terms of plaque characteristics. Thus, close follow-up is crucial.

Keywords ▶ carotid artery stenting, radiation-induced carotid artery stenosis, plaque MRI, treatment outcome

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Introduction

Radiotherapy for head and neck malignancies can cause carotid artery stenosis (AS) several years after treatment.^{1,2} In radiation-induced carotid artery stenosis (RIS), morphological characteristics, including bilateral and long lesions, and in-stent stenosis after carotid artery stenting (CAS) are considered common.^{3,4} This study aimed to investigate the morphological characteristics and treatment outcomes of patients who underwent CAS for RIS. In addition to the findings of previous studies, we focused on MRI plaque images.

Materials and Methods

Study design

Our study included 21 patients who underwent CAS for RIS from March 2002 to July 2020, including 25

consecutive cases. CAS was performed for two cases of esophageal cancer, eight of pharyngeal cancer, nine of laryngeal cancer, and two others (submandibular adenocarcinoma and palatine tonsil tumor) at a mean of 10.0 ± 5.2 years after 60–72 Gy of radiotherapy. The median follow-up period was 45 months.

Patients who were able to be followed-up for an equivalent period of time at the start of the study were included as controls; 25 consecutive patients with atherosclerotic carotid AS who underwent CAS between April 2015 and March 2016 were included as the control group.

This study was approved by the Ethical Review Board of the Graduate School of Medicine at Chiba University.

Evaluation factors

The following factors were compared: patients' backgrounds (age, gender, and medical history), lesion findings (diseased side, the North American Symptomatic Carotid Endarterectomy Trial [NASCET]% stenosis, contralateral occlusion, bilateral stenosis, symptomatic lesion, long lesion, common carotid AS, or plaque MRI sternocleidomastoid ratio using the black blood method), previous perioperative courses (double or multiple stent use, debris, hyperperfusion, carotid sinus reflex, diffusion-weighted image [DWI], or high-intensity lesions), and outcomes (perioperative stroke or death, all-cause mortality, or in-stent stenosis or occlusion). Symptomatic lesions were defined as carotid AS within 6 months of ipsilateral cerebral infarction. Angiographic stenosis of more than one vertebral body in length was defined as a long lesion.

Treatment strategy

Double antiplatelet therapy (aspirin 100 mg + clopidogrel 75 mg) was administered for 2 weeks before treatment, including heparinization to activated clotting time (ACT) 250 or higher during treatments. Under local anesthesia, a guiding catheter with a balloon was placed using the transfemoral approach. In difficult-to-access cases, a guiding sheath was placed following the transbrachial approach. Distal protection should be balloon protection. In cases with contralateral occlusion and lack of ischemic tolerance, changes were made to filter protection.

Subsequently, an open-cell stent was implanted; if plaque protrusion was observed, a closed-cell stent was also used for double stenting. Predilatation was performed only in case of severe stenosis where the stent could not be guided, after which post-dilatation was conducted according to the distal diameter. The presence of debris was then

Table 1 Patients' characteristics

	RIS	AS	p value
Age (years \pm SD)	69.9 \pm 6.93	75.3 \pm 7.04	0.0075
Male	21 (100%)	20 (80.0%)	0.0502
Hypertension	13 (61.9%)	17 (68.0%)	0.7604
Diabetes mellitus	8 (38.1%)	9 (36.0%)	n.s.
Hyperlipidemia	12 (57.1%)	15 (60.0%)	n.s.
Ischemic stroke	10 (47.6%)	18 (72.0%)	0.1307
Cardiovascular disease	8 (38.1%)	10 (40.0%)	n.s.
Renal dysfunction	0 (0.0%)	2 (8.0%)	0.4928
Smoking	13 (61.9%)	14 (56.0%)	0.7687

AS: atherosclerotic carotid stenosis; n.s.: not significant; RIS: radiation-induced carotid artery stenosis; SD: standard deviation

confirmed through aspiration using an aspiration catheter or distal filter protection.

Postoperative single photon emission CT (SPECT) at rest was conducted the next day to evaluate the presence of hyperperfusion, and DWI was conducted on the second postoperative day. Hyperperfusion was defined as cerebral blood flow (CBF) $>2\times$ preoperative or $>1.2\times$ contralateral on SPECT.⁵⁾

After discharge, carotid ultrasonography was used to evaluate the presence of stent stenosis or occlusion. Restenosis was defined as a stenosis score of $>50\%$ at the stent location.

Statistical analyses

The t-test was used for continuous variables, whereas the chi-square test was used for categorical variables. A p-value of <0.05 was considered statistically significant. All analyses were conducted using JMP Pro 15.0.0 software (SAS Institute, Cary, NC, USA).

Results

The RIS group comprised 25 lesions in 21 patients. All patients in both groups completed the procedure. The median follow-up time for the RIS and AS groups were 45 and 40 months ($p = 0.1479$), respectively.

Comparison of patients' backgrounds

Age was found to be significantly higher in the AS group ($p = 0.0075$) and all patients in the RIS group were male (**Table 1**). However, other factors were not significantly different.

Lesion findings

The stenosis rate was significantly higher in the RIS group ($p = 0.0032$) and there were more long lesions ($p = 0.0046$)

Table 2 Carotid artery stenotic lesion findings

	RIS	AS	<i>p</i> value
Left side	14 (56%)	10 (40%)	0.3961
Stenosis rate (NASCET% ± SD)	79.1 ± 8.7	68.6 ± 11.7	0.0032
Contralateral occlusion	5 (23.8%)	4 (16.0%)	0.7114
Bilateral stenosis	9 (42.9%)	7 (28.0%)	0.3595
Symptomatic	8 (32%)	11 (44%)	0.5607
Plaque MRI T1WI (SMR ± SD)	1.36 ± 0.50	1.52 ± 0.66	0.3545
Plaque MRI T2WI (SMR ± SD)	2.33 ± 1.47	1.66 ± 0.66	0.0381
Long lesion*	10 (40%)	1 (4%)	0.0046
Common carotid stenosis	5 (20%)	0 (0%)	0.0502

*Long lesion: more than one vertebral body in length. AS: atherosclerotic carotid stenosis; NASCET: the North American Symptomatic Carotid Endarterectomy Trial; RIS: radiation-induced carotid artery stenosis; SD: standard deviation; SMR: sternocleidomastoid muscle ratio; T1WI: T1 weighted image; T2WI: T2 weighted image

(**Table 2**). Furthermore, although common carotid AS was observed only in the RIS group, symptomatic stenosis was more common in the AS group. The plaque MRI sternocleidomastoid ratio also revealed a significantly higher T2 signal in the RIS group than in the AS group ($p = 0.0381$).

Procedural characteristics and postoperative course

Notably, no significant difference was observed between the two groups based on the procedure (**Table 3**). Distal protection in RIS and AS groups was 19 balloon (Guard-Wire [Medtronic, Minneapolis, MN, USA] and 6 filter protection (4 FilterWire EZ [Boston Scientific, Tokyo, Japan], 2 Spider [Medtronic]) and 22 balloon (GuardWire) and 3 filter protection (Spider), respectively. Moreover, the first open cell stents in RIS and AS groups were 22 Precise (Cordis, Santa Clara, CA, USA) and 3 Protégé (Medtronic), and 24 Precise and 1 Protégé, respectively. The second closed stent for double stenting was Carotid WallStent (Boston Scientific) in all cases. In addition, no significant difference was observed between the two groups based on the postoperative course (**Table 3**). Although three patients each had hyperperfusion on SPECT, they were asymptomatic.

Outcome

No statistically significant difference was observed in term of outcomes of the two groups (**Table 4**). Furthermore, although no postoperative stroke or death occurred due to neurological causes in any of the groups, all-cause mortality was higher in the RIS group, reflecting the time that has passed since the CAS was performed. Additionally,

Table 3 Procedural characteristics on stenting and postoperative image findings

	RIS	AS	<i>p</i> value
Double stent	2 (8%)	4 (16%)	0.6671
Tandem stent	5 (20%)	0 (0%)	0.0502
Debris	10 (40%)	9 (36%)	0.7755
Carotid sinus reflex	2 (8%)	4 (16%)	0.6671
Hyperperfusion	3 (12%)	4 (12%)	n.s.
Multiple diffusion restrictions	2 (8%)	4 (16%)	0.4912
Spot high intensity on DWI	10 (40%)	11 (44%)	

AS: atherosclerotic carotid stenosis; DWI: diffusion weighted image; n.s.: not significant; RIS: radiation-induced carotid artery stenosis

Table 4 Clinical outcomes

	RIS	AS	<i>p</i> value
All strokes	0 (0%)	0 (0%)	1
Death (neurological cause)	0 (0%)	0 (0%)	1
Restenosis	2 (8%)	0 (0%)	0.4898
Occlusion	1 (4%)	0 (0%)	1
All death	4 (19%)	2 (8%)	0.4174

AS: atherosclerotic carotid stenosis; RIS: radiation-induced carotid artery stenosis

postoperative restenosis and stent occlusion were observed only in the RIS group, but there was no significant difference between them.

Discussion

Radiation-induced carotid stenosis was associated with a lower mean age, higher stenosis rates, and longer lesions than atherosclerotic stenosis. However, plaque MRI was characterized by a significantly higher signal on T2 weighted image (T2WI). Furthermore, although not statistically significant, the patients were more men, had more cases of common carotid artery lesions, and experienced fewer cerebral infarctions previously. Moreover, even though we observed a trend toward a more postoperative in-stent stenosis or occlusion, no difference in the outcome existed.

Plaque MRI of radiation-induced carotid stenosis

A representative characteristic plaque MRI is presented in **Fig. 1**. This image indicates that although the sternocleidomastoid ratio was equal to or slightly higher on T1-weighted images, it was higher on T2-weighted images. Therefore, a significant difference was evident compared to the AS group (**Table 2**).

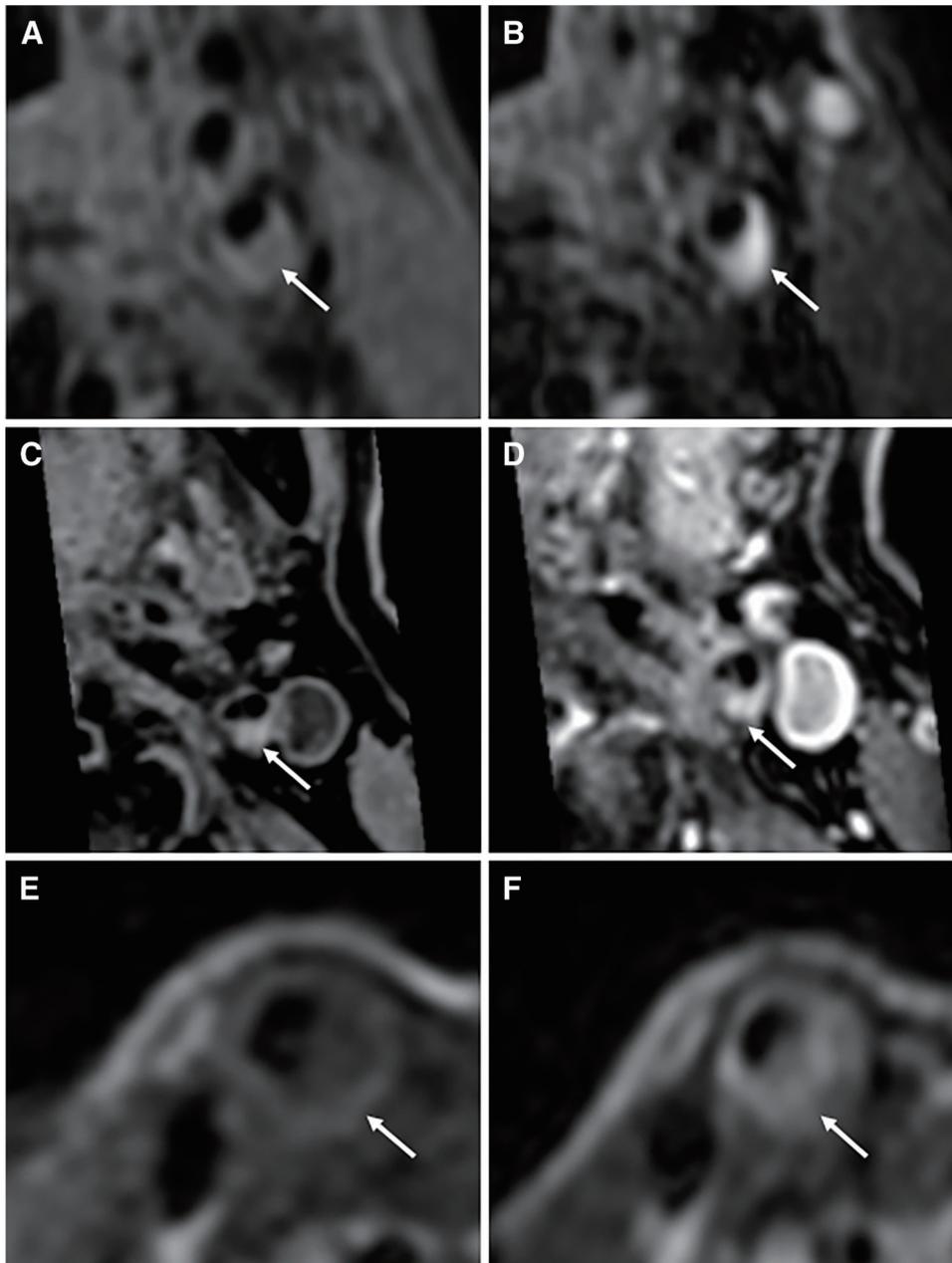


Fig. 1 T1-weighted (A, C, and E) and T2-weighted (B, D, and F) images of plaque MRI using the black blood method. Arrows (A–F) indicate plaques. (A and B) A 63-year-old man after radiotherapy for pharyngeal cancer. CAS was conducted for left carotid AS. His sternocleidomastoid ratios were 1.16 (A) and 5.75 (B). (C–F) A 73-year-old man after radiotherapy for laryngeal cancer. First, CAS was conducted for left carotid AS (C and D). Then, CAS was conducted three years later for right common carotid AS (E and F). His sternocleidomastoid ratios were 1.39 (C), 1.81 (D), 0.85 (E), and 1.43 (F). AS: artery stenosis; CAS: carotid artery stenting

Table 5 Plaque MRI findings

	RIS	AS	<i>p</i> value
Plaque MRI T1WI (SMR ± SD)	1.36 ± 0.50	1.52 ± 0.66	0.3545
Plaque MRI T2WI (SMR ± SD)	2.33 ± 1.47	1.66 ± 0.66	0.0381

AS: atherosclerotic carotid stenosis; RIS: radiation-induced carotid artery stenosis; SD: standard deviation; SMR: sternocleidomastoid muscle ratio; T1WI: T1 weighted image; T2WI: T2 weighted image

Plaque MRI with a high T1 weighted image (T1WI) signal can reflect fibrosis, lipid or necrosis, or hemorrhage, whereas a high T2WI signal reflects only lipid or necrosis.⁶⁾ In addition, the high T2WI signal in plaque MRI of RIS reflects necrosis, as necrotic foci are observed in plaque tissue samples from RIS.⁷⁾ In contrast, reportedly, the pathology of RIS is characterized by fibrosis and a lack of inflammatory changes at the lesion site.⁸⁾

Furthermore, hypothetically, atherothrombotic plaques may accumulate after radiation-induced stenosis in highly stenosed lesions requiring CAS,^{9,10} which may have led to the difference in plaque MRI findings. Although this outcome is interesting, further investigation is necessary, as our study was based on a single evaluation of plaque signal values.

Outcomes of CAS for radiation-induced carotid stenosis

A previous study compared 84 lesions in 65 patients with radiation-induced internal carotid AS and 150 lesions in 129 patients with atherosclerotic stenosis and found no significant difference in mortality, perioperative stroke, or ipsilateral stroke (risk of 1.2%/year in both groups).³ Other studies have reported that in RIS, the stenosis frequently extended to the common carotid artery and can be managed by the use of multiple stents,^{3,11} which was similar to the present study. Conversely, in-stent restenosis or occlusion is a common feature of carotid AS.^{4,12} Although no statistically significant difference was observed in this study, it should be noted that both restenosis and occlusion were observed only in the RIS group.

RIS

The proportion of patients who were previously irradiated and later developed significant carotid stenosis ranged from 18% through 7.5 years of follow-up, as reported by Brown et al.,¹ to 40% through 10 years of follow-up, as reported by Steele et al.¹³ Ischemic stroke has also been reported to occur on an average of 11 years after radiotherapy for head and neck malignancies.¹⁴ In our study, treatment was administered at an average follow-up of 10 years after radiotherapy, which we consider to be a comparable course.

As stated above, RIS is characterized by long lesions, large plaque volume, and vulnerable plaques. Thus, careful follow-up for restenosis is important.

Limitations

This study was a single-center retrospective study. However, postoperative DSA follow-up is essential in radiation-induced carotid stenosis. Hence, multi-center studies are required in the future. Furthermore, we only performed carotid ultrasonography. Therefore, additional objective evaluations are necessary. We aim to obtain further long-term follow-up results in future studies.

Conclusion

Although CAS can be safely performed for RIS, close follow-up is necessary because of the high risk of restenosis in terms of morphology and plaque properties.

Disclosure Statement

The authors declare no conflicts of interest.

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