Long-term Outcomes of Carotid Artery Stenting for Radiation-Associated Stenosis

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Background: In Taiwan, the prevalence of head and neck cancer is relatively high. Because radiation-associated carotid stenosis is a significant risk factor for stroke, carotid artery stenting (CAS), instead of carotid endarterectomy, is indicated in patients with radiation-associated carotid stenosis. We sought to evaluate the effect of neck radiotherapy (XRT) on the long-term outcome of patients undergoing CAS.

Methods: From March 2001 to November 2011, 147 CAS procedures were performed on 129 patients ($n = 43$ for XRT, $n = 86$ for non-XRT). Mean follow-up was 42.7 ± 20.5 months (median: 52 months; range: 1-60 months). Duplex velocity criterion for > 50% restenosis after CAS was defined as peak systolic velocity > 175 cm/s. Endpoints included 5-year freedom from mortality, ipsilateral recurrent stroke, and major adverse cardiovascular events (MACE).

Results: The mean age of XRT patients was significantly lesser than that of non-XRT patients (61 ± 8 vs. 71 ± 8, $p < 0.001$). There was significantly less coronary artery disease and other cardiovascular co-morbidities in XRT patients. No significant differences were noted in the composite 30-day ipsilateral stroke/myocardial infarction/mortality (XRT: 8.6% vs. non-XRT: 6%, $p > 0.05$) and 5-year freedom from mortality, ipsilateral recurrent stroke, and MACE ($p > 0.05$) between the two groups. Intra-stent carotid restenosis > 50% was significantly higher in the XRT group on follow-up.

Conclusion: Long-term outcomes of CAS for radiation-associated stenosis were not altered by a history of neck XRT, except for asymptomatic carotid restenosis.

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Key words: carotid artery stenosis, carotid stenting, radiotherapy

At a Glance Commentary

Scientific background of the subject

For the higher prevalence of head and neck cancer in Taiwan compared with the West, the long term outcomes of carotid artery stenting between radiation induced and atherosclerotic-associated carotid artery stenosis should be investigated.

What this study adds to the field

We provided the data in Asia population. In the radiation induced carotid artery stenosis group, the mean age was significantly lesser, and greater asymptomatic restenosis rate after stenting was noted.

Cerebrovascular disease remains the leading cause of death worldwide. For those who survive, many are disabled. The most effective way to reduce the impact of this public health problem is prevention. Since stroke is a disease with a variety of pathophysiologic mechanisms, efforts have focused on the different mechanisms underlying stroke, with prevention as the primary aim. Among the various stroke mechanisms, extracranial carotid artery (ECCA) occlusive

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disease is one of the more significant causes which can be prevented by medical treatment alone. As shown in our previous study,[1] although the prevalence of ECCA occlusive disease in Taiwanese stroke patients was found to be much lower compared to Caucasians and was not a significant risk factor for stroke in these patients, ECCA occlusive disease is a significant risk factor for stroke in patients with nasopharyngeal cancer (NPC) treated with head and neck radiation.[2]

Carotid stenosis secondary to radiation injury to the carotid arteries is a well-known long-term complication of cervical radiotherapy.[3] Head and neck X-ray therapy (XRT) is a standard and/or adjuvant therapy for head and neck malignancies including NPC, oral and oropharyngeal cancers. Since the prevalence of head and neck cancer in Taiwan is high compared with the West,[4,5] radiation-associated carotid stenosis is not uncommon. In lieu of performing standard carotid endarterectomy (CEA), which may increase the risk of operative complications, carotid artery stenting (CAS) has been suggested in these patients as a minimally invasive alternative.[6] The purpose of this retrospective study was to investigate the effect of neck XRT on the long-term outcome of patients undergoing CAS.

METHODS

The study protocol was approved by the Institutional Review Committee on Human Research of Kaohsiung Chang Gung Memorial Hospital [institutional review board number: 100-0612B] and all the participants had given their informed consents both for the study and publication of their data. The study was a retrospective review of a database of consecutive unselected patients who underwent CAS at Chang Gung Memorial hospital from March 2001 to November 2011.

Preoperative patient characteristics

One hundred and forty-seven CAS procedures were performed on 129 patients over a 10-year period. Eighteen patients received CAS on both carotid arteries. Mean follow-up was 42.7 ± 20.5 months (median: 52 months; range: 1-60 months). The patients were stratified according to whether or not they exhibited a history of neck XRT. There were 43 patients with a history of XRT 5 years prior to CAS (XRT group). Eighty-six patients without radiation exposure were selected as the control group (non-XRT group) from the Chang Gung Memorial Hospital's database. Patients' baseline medical data included age, sex, preoperative symptomatic transient ischemic attack (TIA)/stroke, history of hypertension, diabetes mellitus (DM), dyslipidemia, smoking, betel nut consumption, chronic kidney disease, peripheral arterial occlusion disease, metabolic equivalent (MET) values < 4, confirmed coronary artery disease by coronary angiography, and heart failure.

Procedure

Percentage stenosis of the carotid artery was graded using digital subtraction angiography according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria.[7] All CAS procedures were performed by an experienced interventionalist under local anesthesia without sedation, using a transfemoral or transbrachial/transradial approach and embolic protection devices. A perioperative antiplatelet regimen consisting of aspirin (100 mg by mouth daily was started at least 72 h preoperatively and continued indefinitely postoperatively if no bleeding complication occurred), clopidogrel (75 mg by mouth daily with a loading dose of 300 mg one day preoperatively and continued for at least 2 months postoperatively), and intraoperative heparinization was used with the goal of achieving an activated clotting time of 250-350 s.

Endpoints

The perioperative period was defined as within 30 days after CAS. The perioperative complications included hematoma, periprocedural myocardial infarction, pseudoaneurysm, upper gastrointestinal tract bleeding, acute kidney injury, perioperative cerebrovascular events (TIA or any stroke), and death within 30 days after CAS. The primary endpoints were the occurrence within 5 years of all causes of mortality, ipsilateral recurrent stroke, or major adverse cardiovascular events (MACE), defined as cardiovascular death, myocardial infarction, target vessel revascularization, ipsilateral stroke, and all-cause mortality after the perioperative period. The secondary endpoints were patients' follow-up carotid duplex sonographic data (at least 1 year after CAS), where available, assessed for intra-stent restenosis. We defined carotid artery restenosis > 50% as a peak systolic velocity greater than 175 cm/s at the ipsilateral CCA or ICA, as suggested by the retrospectively applied uniform post-stenting criteria.[8]

Statistical analysis

Categorical variables were assessed using Chi-square or Fisher's exact test. Normally distributed continuous variables were compared using two-tailed, unpaired Student's *t*-tests. All values were represented as a mean ± standard deviation, where applicable. Secondary outcomes were evaluated using Kaplan–Meier life-table analyses and compared using log-rank analyses. A $p < 0.05$ was considered statistically significant. The statistical software package used was SPSS version 14.0 for Windows.

RESULTS

Baseline characteristics

The mean age of all XRT patients was significantly lesser compared to those of the non-XRT group (61 ± 8 versus 71 ± 8, $p < 0.001$). There were significantly more patients with CAD, hypertension, hyperlipidemia, DM, and chronic kidney disease in the non-XRT group. Significantly more patients consumed betel nuts in the XRT group. In addition, there was significantly more common carotid artery (CCA) and less internal carotid artery (ICA) involvement in the XRT group [Table 1].

Concerning head and neck cancer type, 30 patients were found to have NPC, 10 patients had oropharyngeal cancer, 2 patients had laryngeal carcinoma, and 1 patient had thyroid cancer. Overall, only seven patients received lymph node dissection or laryngectomy, two had tracheostomy, and one patient received contralateral CEA.

Primary and secondary endpoints

The perioperative complication rates and perioperative cerebrovascular events, including the combined 30-day myocardial infarction, stroke, and mortality rate, did not differ significantly between XRT and non-XRT patients [Table 2]. There was no mortality during the perioperative period, but four patients in the XRT group had ipsilateral TIA/stroke compared to six patients in the non-XRT group. The primary outcomes, including all-cause mortality, any ipsilateral recurrent TIA/stroke, and MACE did not differ significantly between the two groups in the 5 years of follow-up [Figures 1-3].

As the secondary endpoints, 19 patients in the XRT group and 54 patients in non-XRT group had follow-up carotid duplex sonographic data for the assessment of intra-stent restenosis. There were significantly more patients with carotid restenosis > 50% in the XRT group [Table 2]. During the follow-up of 2 years after first CAS, one NPC patient underwent re-stenting of the right CCA due to restenosis of 64%. The re-stented right CCA occluded 2 years later.

DISCUSSION

Our study population consisted of 43 Taiwanese patients with a history of XRT 5 years before CAS in comparison to 86

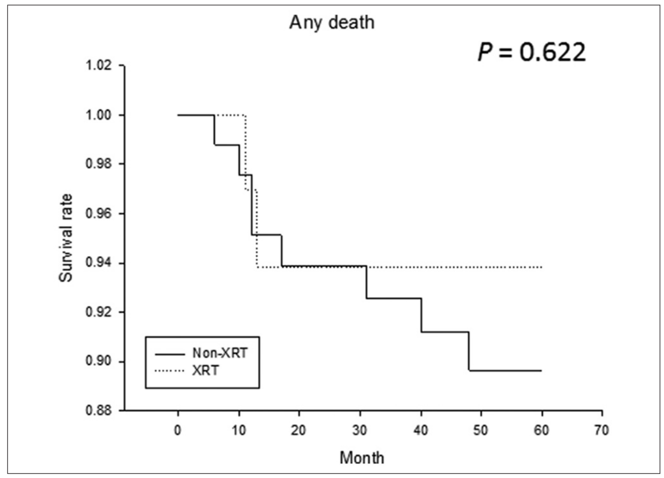

Figure 1: All-cause mortality (XRT, X-ray therapy; non-XRT, non–X-ray therapy)

Table 1: Baseline characteristics of the total population following stratification into XRT and non-XRT patients

	XRT (*n*=43)	Non-XRT (*n*=86)	*p* value
Age (years)	61±8.0	71±8	<0.0001
Gender, male	37 (86.0)	72 (83.7)	0.731
Symptomatic stroke or TIA	31 (72.1)	50 (58.1)	0.122
Coronary artery disease	9 (21.9)	57 (66.3)	<0.0001
Heart failure (NYHA functional class≥2)	2 (4.7)	11 (12.8)	0.148
Hypertension	28 (65.1)	76 (88.4)	0.002
Diabetes mellitus	9 (20.9)	36 (41.9)	0.019
Smoking	22 (51.2)	39 (45.3)	0.533
Dyslipidemia	21 (48.8)	61 (70.9)	0.014
Peripheral arterial occlusive disease	0 (0)	3 (3.5)	0.550
MET<4	0 (0)	2 (2.3)	0.552
Betel nut use	11 (25.6)	1 (1.2)	<0.0001
Chronic renal disease	3 (7.0)	22 (25.6)	0.012
	XRT (*n*=47)	Non-XRT (*n*=100)	*p* value
Characteristics of target vessels			
Percent carotid artery stenosis	77±11	77±11	0.798
Internal carotid artery stenosis	23 (48.9)	77 (77.0)	0.001
Common carotid artery stenosis	12 (25.5)	10 (10.0)	0.014
Both internal and common artery stenosis	12 (25.5)	13 (13.0)	0.059

One hundred and forty-seven procedures were performed on 129 patients, Data expressed as mean±standard deviation or number (%), The level of statistical significance was set at $p<0.05$
Abbreviations: XRT: X-ray therapy; non-XRT: Non-X-ray therapy; TIA: Transient ischemic attack; NYHA: New York Heart Association; MET: Metabolic equivalent

Table 2: Perioperative complications and endpoints

	XRT (*n*=47)	Non-XRT (*n*=100)	*p* value
Perioperative complications (<30 days)			
Hematoma	0 (0)	2 (2.0)	1.000
Periprocedural myocardial infarction	0 (0)	0 (0)	-
Pseudoaneurysm	0 (0)	1 (1.0)	1.000
Upper gastrointestinal bleeding	0 (0)	1 (1.0)	1.000
Acute renal injury	0 (0)	2 (2.0)	1.000
Ipsilateral TIA/stroke	4 (8.6)	6 (6.0)	0.287
Mortality	0 (0)	0 (0)	-
Ipsilateral TIA/stroke/mortality	4 (8.6)	6 (6.0)	0.287
	XRT (*n*=19)	Non-XRT (*n*=54)	
Intra-stent restenosis>50% at 36 months	3 (15.8)	1 (1.9)	0.022
	XRT (*n*=43)	Non-XRT (*n*=86)	*p* value
5-year survival outcome			
Long-term all-cause mortality	2 (4.7)	8 (9.3)	0.622
Long-term any ipsilateral recurrent TIA/stroke	5 (11.6)	7 (8.1)	0.222
Long-term MACE	7 (16.2)	16 (18.6)	0.643

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Abbreviations: XRT: X-ray therapy; non-XRT: Non-X-ray therapy; TIA: Transient ischemic attack; MACE: Major adverse cardiovascular events

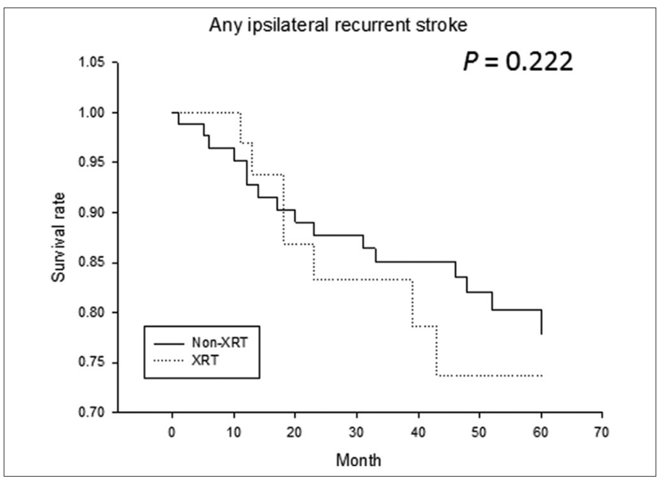

Figure 2: Any ipsilateral recurrent stroke (XRT, X-ray therapy; non-XRT, non–X-ray therapy)

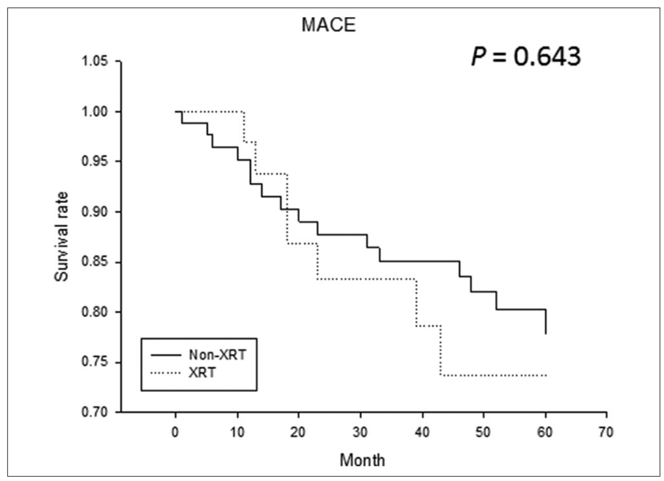

Figure 3: Major adverse cardiovascular events (XRT, X-ray therapy; non-XRT, non–X-ray therapy; MACE, major adverse cardiovascular events)

Taiwanese patients who received CAS without XRT exposure. Information regarding such a large number of XRT patients is a unique characteristic of our study when compared to similar studies performed in the West.[9,10] The mean age of our XRT patients was significantly lesser compared to the non-XRT patients. In addition, there were significantly fewer patients with CAD, hypertension, hyperlipidemia, DM, and chronic kidney disease in our XRT group, and this finding differed from similar studies reported in the Western literature.[9,10]

The perioperative complications and primary outcomes, all causes of mortality, ipsilateral recurrent stroke, and MACE, did not significantly differ between the XRT and non-XRT patients, as noted previously.[9,10] However, a significantly higher restenosis rate was observed in our XRT patients, which correlated with previous studies.[9]

Regarding baseline preoperative characteristics and comorbidities between the XRT and non-XRT patients, one prior study showed no difference in age, gender, hypertension, DM, dyslipidemia, smoking, chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, and heart failure,[9] and another showed differences only with respect to hypertension and gender.[10] This is in contradistinction to our findings where the XRT patients were significantly younger in age compared to the non-XRT patients. The epidemiology of NPC, oral and oropharyngeal cancer is quite different in Taiwan compared with the West,[4,5] and the median age of diagnosis is significantly lower than in the West. The etiology for the higher incidence of NPC in Taiwan includes Epstein–Barr virus infection interaction, environmental factors (irritant fumes, certain preserved foods rich in nitroso compounds and volatile nitrosamines), and a genetic component.[4,11] Moreover, the incidence of oral and oropharyngeal cancer rises in Taiwan annually due to increased consumption of betel quid, primarily in young adult males.[12] We believe this is the underlying reason for the significantly younger age of the XRT patients in our study compared with the other studies in the West.[9,10,13]

In patients who have undergone neck XRT for malignancy, chronic radiation vasculopathy affects both intra- and extracranial arteries, with increasing rates of stenosis over time.[14] The relative risk of TIA or ischemic stroke is at least doubled,[15] and the interval between the completion of XRT and the stroke event is more than 10 years.[2] Our data showed that the CCA lesions were more frequently affected by XRT in our patients, in accordance with other studies.[9,16] Previous studies have shown that radiation-induced carotid stenosis is more diffuse in distribution and has a different sonographic plaque characterization (less shadowing calcification but higher incidence of hypoechoic plaque) compared with carotid stenosis without radiation exposure,[16] possibly due to instability of the plaque in the XRT patients.[17,18] Radiation dose was found to have no significant influence on the progression of atherosclerosis when a total dose of more than 40 Gy or even higher than 55 Gy was used.[19,20]

Significantly higher restenosis rates in XRT patients were observed in our study; however, the restenosis rate was not so high.[9] We know that aging is a major risk factor for atherosclerosis and carotid artery disease. The younger age of our XRT patients may mask the risk of restenosis. Although we found no significant difference in the secondary outcomes between XRT and non-XRT patients in 5 years of follow-up, further data from studies with longer follow-up are needed.

The patients with radiation-associated carotid stenosis were labeled as “high risk” for standard CEA; however, a current review showed that patients treated with CEA had lower rates of late cerebrovascular adverse events and restenosis compared with those treated with CAS.[21] Therefore, the choice for revascularization therapy should be considered on an individual basis.

Our study had several limitations. First, since only a small percentage of patients undergoing CAS had a history of neck XRT, there was a significant discrepancy in the sample sizes between our two groups of patients (XRT vs. non-XRT). Second, our patients were followed at different outpatient departments by different neurologists and/or cardiologists. The rate of routine follow-up carotid duplex examination in this entire cohort was only approximately 80% in the first year and 70% by the third year. Another important limitation of our study was the inability to distinguish radiation-induced ICA stenosis from other etiologies such as atherosclerotic occlusive disease. The decreased incidence of coronary artery disease in our XRT patients, however, supported our assumption that all occlusions were radiation induced. Furthermore, because of the retrospective nature of our study design (analysis of the carotid artery stenosis patients with CAS at our hospitals), our study can neither provide data on the prevalence of radiation-induced carotid artery disease nor on the prevalence of stroke in NPC, oral and oropharyngeal cancer patients. Nevertheless, other potential causes of stroke, which could play a role in XRT patients, such as hypercoagulable state, have not been checked.[22] However, a hypercoagulable state was not anticipated since most patients were not in an active malignancy state. Finally, it is difficult to evaluate the effect of the difference in age between XRT and non-XRT patients, which may mask a higher restenosis rate in XRT patients. Physicians should be aware of the long-term complications of XRT in patients and evaluate the extracranial carotid arteries, especially 5 years after the completion of radiotherapy, with or without stroke.[14] In all XRT patients after CAS, routine follow-up carotid duplex examination at 1 month, 6 months, and annually is indicated and is felt to be cost effective.[23]

CONCLUSION

We demonstrated that XRT patients receiving CAS in Taiwan were significantly younger and had more underlying cardiovascular comorbidities, compared to the non-XRT group. Long-term outcomes of CAS for radiation-associated stenosis were not altered by a history of neck XRT, except for asymptomatic carotid restenosis.

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