Clinical outcomes of radiation-induced carotid stenosis: A systematic review and meta-analysis

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Objectives: Clinical outcomes of radiation-induced carotid stenosis are still unclear. Therefore, a systematic review and meta-analysis is needed to evaluate the short- and long-term outcomes after interventions to treat radiation-induced carotid stenosis.

Methods: PubMed, EMBASE, the Cochrane Library and Web of Science were searched from 1 January 2000 for relevant RCTs and observational studies which reported outcomes after carotid endarterectomy (CEA) and carotid angioplasty and stenting (CAS) for carotid stenosis induced by radiation. Risk of bias were assessed through different scales according to study design. $I^2$ statistic were used to evaluate the heterogeneity, and meta-regression were performed to investigate the source of heterogeneity. Visual inspection of funnel plots was used to judge publication bias.

Results: A total of 26 studies with 1002 patients were included. CEA was performed in 364 patients and CAS in 638 patients. The overall estimated rate of short-term stroke was 0.19% (95% CI: 0.00–0.90%), and the rate of long-term stroke was 2.68% (95% CI: 1.19–4.57%). The rate of cranial nerve injury in CEA group was significantly higher than that in CAS group [risk ratio (RR): 6.03, 95% CI: 1.63–22.22, $P=.007$]. The univariate regression analysis showed that the risk of stroke in CAS group were significantly higher than CEA group in both short- and long-term [incidence rate ratio (IRR): 3.62, 95% CI: 1.21–10.85, $P=.022$; IRR: 2.95, 95% CI: 1.02–8.59, $P=.046$, respectively]. Conclusions: This systematic review provided the worldwide profile of outcome of treatment for radiation-induced carotid stenosis, and also found that CEA can yield better results for these patients than CAS. Nonetheless, as large-scale studies have not yet been conducted, and there is a definite need for further studies in the future.

Keywords: Carotid stenosis—Radiation—Clinical outcomes—Systematic review—Meta-analysis

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Introduction

Cervical radiotherapy (RT) has greatly reduced the mortality of patients with malignant head and neck tumors, which, however, causes some vascular complications including direct vessel damage, accelerated atherosclerosis, intimal-media thickness and peri-adventitial fibrosis.1–3 These complications result in a higher risk of common carotid stenosis for patients with previous RT, which lead to a significant increased risk of ischemic stroke.4 Studies have indicated that 18–38% patients with a history of RT for head and neck neoplasms developed carotid stenosis compared with a prevalence of 2–8% among nonirradiated patients.5,6 Pathologically, the stenosis may be caused by the spontaneous atherosclerotic
plaque, but RT-induced atherosclerosis tends to be less inflammatory and more fibrotic. The stenotic lesions tend to be longer and have different distribution features compared to atherosclerotic carotid stenosis in nonirradiated patients. Some previous studies classified the situation as “hostile neck” or high-risk cases because these patients tend to have skin retraction, previous neck dissection, or even permanent tracheostomy. All described above indicate that radiation-induced stenosis should be considered as a clinically distinct entity. Based on the large population receiving RT, the radiation-induced lesions are not uncommon and present with unique surgical challenges. The true incidence of radiation-induced carotid stenosis may be higher owing to the long interval between irradiation and the appearance of lesions. With the increase of survival for cervical malignancy, patients with prior radiotherapy undergoing a carotid stenosis will form an increasingly important subgroup.

Carotid endarterectomy (CEA) and carotid angioplasty and stenting (CAS) are contemporary two alternatives for radiation induced carotid stenosis. CEA is currently the standard first line surgical therapy for traditional extracranial artery stenosis. But special conditions of carotid artery such as the adhesion of the three layers of the vessel wall and the extensive stenosis, induced by the prior radiation, makes it difficult to eliminate the plaques completely while avoiding damages. Previous studies have shown that patients undergoing CEA had more wound complications such as necrosis, infection and skin breakdown, as well as more temporary cranial nerve injury (CNI). However, some studies reported no obvious differences in complication between RT group and non-radiotherapy group with CEA. CAS is an alternative for high-risk patients because it does not require dissecting through scarred tissue. CAS avoids any cranial nerve injury and reduces wound healing complications.

However, CAS was reported to have a higher risk of stenosis recurrence, especially in the patients with previous radiation therapy, although some studies suggested the restenosis was mostly asymptomatic.

There are increasing analysis evaluating the efficacy and safety of CEA and CAS in atherosclerotic patients. Brott et al. did a pooled analysis of patients with symptomatic carotid stenosis with and without previous radiation, the findings suggested that although periprocedural outcomes continued to favor CEA, outcomes in the post-procedural period were similar in CAS and CEA group. It is predictable that improvements in the safety of CAS following novel stent devices, embolic protection devices and delivery systems, will provide bright prospect of CAS in the future.

However, for radiation-induced stenosis of carotid artery, the data comparing CEA with CAS is limited. Which one is better for patients with prior radiation remains uncertain. Fokkema et al. performed pooled and meta regression analyses in patients with radiation therapy in 2012. By including 27 articles comprising 533 patients undergoing radiation therapy (361 CAS and 172 CEA), they concluded that both CAS and CEA were proved to have low risk of cerebrovascular adverse events with no preference while CAS was related to more asymptomatic restenosis. However, some of the studies involved in this meta-analysis were case series with less than 10 cases, and no restrictions in the length of follow-up or the interval between radiation-therapy and invention were applied. Additionally, no filters for publication date were used and some of the studies involved were conducted in 1970s to 1990s, which were probably out of date, as the technique of CAS and CEA keeps advancing. There were many recent studies reporting CAS or CEA in radiation-induced stenosis. Therefore, for radiation-induced stenosis of carotid artery, the safety and efficacy of CAS and CEA still need to be clarified and updated.

This systematic review and meta-analysis aimed to obtain the worldwide profile of outcome of treatment for radiation-induced carotid stenosis, and compare the safety and efficacy of CEA and CAS in these patients during periprocedural and postprocedural period based on the latest evidence.

Methods

This study was reported following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The systematic review has been registered in the International Prospective Register of Systematic Reviews ‘PROSPERO’ database: https://www.crd.york.ac.uk/PROSPERO/#recordDetails ID: CRD42019129147.

Eligibility criteria

Study types

Randomized controlled trials (RCTs) were included. In addition, as surgical alternatives were rarely included in randomized studies, and radiation-induced carotid stenosis was a special situation, we also included observational studies including case-controlled studies, cohort studies and case series with at least ten interventions, and it will assist minimize type II error due to lack of statistical power of sole RCTs. The design of each study was recorded to assess inter group heterogeneity and control the bias. We conducted a search for articles published from 1 January 2000 to 18 February 2020 and only those in English were included. We excluded studies published in Chinese journals because of highly suspicions of unstandardized trial design.

Participant characteristics

Patients with carotid stenosis who had a history of radiotherapy for head and neck cancer. The median interval between the completion of radiation therapy and...
development of carotid artery stenosis detected on imaging (or vascular intervention) was no less than 1 years to avoid non-related situations. The target area of the radiotherapy included at least the ipsilateral neck, including part of the carotid system. The internal carotid stenosis was confirmed by angiography, Duplex, 3D angio-CTA or angio-MRI, and stenosis was defined as > 50%, with or without symptom. According to the American Society of Neuroimaging and Society for Vascular Surgery, cutoffs for carotid artery stenosis ranged from 50% to 80% luminal diameter reduction. We therefore adopted a conservative definition of > 50% luminal reduction. The patients treated for restenosis were excluded. In order to acquire adequate data, we included studies with a group of participants reaching all above standards as long as the outcome data was available.

Interventions types

The carotid stenosis induced by radiation was treated with carotid angioplasty and stenting (CAS) and carotid endarterectomy (CEA), and at least one of the two interventions were included in the study. As to the studies including arms with CEA/CAS and other interventions, we included the study but only the arms that used CEA/CAS. The patients who had undergone vascular reconstruction for a second time or more due to restenosis were excluded.

Outcomes measures

At least one of the following outcomes was recorded:

(1) Short-term outcome

(a) Short-term death, stroke, ischemic or hemorrhagic stroke, transient ischemic attack (TIA) rate. The definition of short time was peri-procedural period described in the study or 30 days after the procedure.

(2) Long-term outcomes

(a) Long-term death, stroke, ischemic or hemorrhagic stroke, transient ischemic attack (TIA) rate. The definition of long time was 30 days after the procedure and mean follow-up time ≥ 3 months.

(b) Long-term target carotid restenosis, defined as any residual or recurrent severe stenosis ≥ 50% or occlusion of carotid artery detected at any time during follow-up.

(c) Cranial nerve injury specified in transient (sensory or motor deficits developed post-operatively and completely functional recovery ≤ 90 days with conservative management only) and persistent (symptoms lasting ≥ 90 days).

(d) Transient ischemic attack of intervention site during peri-procedural period and through the end of follow-up.

(e) Myocardial infarction (MI).

Search strategy

This review and meta-analysis was performed on the basis of the guidelines of MOOSE (meta-analyses of observational studies in epidemiology) for observational studies and PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines) for RCT and quasi-RCTs. Literature search was performed by two independent reviewers (XW and YF) using the following databases, EMBASE, MEDLINE, Web of Science, and the Cochrane Library. Database-specific-controlled vocabulary and additional free-text terms for the concepts of ‘carotid artery stenosis’, ‘cervical irradiation’, ‘endarterectomy’ and ‘stenting’ were used to include all possible eligible studies. Searches was restricted to studies published in English during 1 January 2000 to 18 February 2020, and conducted in humans. The search terms were provided in detail as online supplementary material (see online Supplement 1. Search strategy). We also scrutinized the reference lists of selected studies and published review articles for other potential studies. Other databases such as the ISRCTN registry, government registries and WHO registries were also searched for ongoing and recently completed studies. When necessary, the authors or conductors of the studies were consulted for further information.

Selection of studies

After searching the databases, two reviewers (XW and YF) independently screened all the results and selected the studies that were eligible for inclusion. Before screening and selection, we first had a pilot trial to make sure the fully understanding and accordence on the criteria for inclusion and exclusion. The formal screening could only be launched until highly agreement (>80%) is achieved. First, reviewers screened the titles, key words as well as abstracts, and then excluded irrelevant studies. Second, we acquired the full articles of all the remaining studies. Subsequently, reviewers read through the studies to assess eligibility for inclusion. In this step, the reasons of all excluded studies were recorded. When more than one articles were based on data from the same trial, we selected the latest study or the one with largest sample size. When disagreement arose, it was settled by consensus or a third reviewer (TW).

Data collection and synthesis

Data extraction and management

Data was extracted independently by two reviewers (XSB and RX) according to a standardized data extraction form. A pilot trial had done to make sure the fully understanding on the form and at least 80% inter-rater agreement before the formal extraction. A third reviewer (TW) was involved when disagreement could not be solved by
discussion. The extracted data included the following information:

1. Study characteristics: year of publication, author(s), journal, sample size, location, single or multicenter trial, number of patients, number of procedures (some patients may have procedure on both sides).
2. Patient characteristics: mean age, gender, follow-up duration, previous cancer, dose of previous radiation therapy and interval between radiation therapy and procedure, degree of preprocedural stenosis, stenosis or occlusion site of extracranial artery.
3. Intervention characteristics including CEA and CAS such as success rate, residual stenosis.
4. Short- and long-term outcomes and the measurements of the outcomes.

We contacted the corresponding authors of each included studies for unclear or missing data.

Risk of bias assessment

Risk of bias was assessed independently by two reviewers (YY and KY) in each included study. Newcastle-Ottawa scale \(^3\) was used aimed at cohort studies as well as case control studies. NOS adequately addresses subject selection, study comparability, and the assessment of outcome or exposure. Each domain was received a score on the risk of bias (low, unclear or high level). The overall risk of bias was defined as low if risk of all bias components was ranked as ‘low’. If one or more of the bias components were scored as unclear or at high risk of bias, the trial was considered as high overall risk of bias. For case series, the method described in Methodological Quality and Synthesis of Case Series and Case Reports \(^3\) was used. We evaluated the bias of each study with regard to four domains: selection, ascertainment; causality and reporting. We used five criteria in the form of questions with binary answers(yes/no), to test if the study met these criteria. The questions included:

1. Did the patients represent the whole case(s) of the investigator (medical center)?
2. Was the exposure adequately ascertained?
3. Was the outcome correctly ascertained?
4. Were other possible diagnoses excluded?
5. Were all important data cited in the report?

Each question was received a score on the study quality. The study with a total of 5 points is considered to have good quality, while study with 4 points is considered moderate. Studies with less than 3 points were defined as low quality.

We summarized evaluations of each study in a diagram.

Measures of treatment effect

The Stata statistical software (version 15.0, Stata Corp, College station, Texas, USA) was used to analyze all data. As most of the outcomes were dichotomous data, such as incidence of stroke and restenosis, risk ratios with 95% CIs was used to present the measure of treatment effect. For continuous data such as interval between radiation therapy and carotid procedure, the mean differences with 95% CIs was used.

Dealing with missing data

For missing data, we initially contacted the corresponding authors for information. If no one responded, we dealt with the missing data following the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.\(^3\) According to the cause of data loss, we used specific methods based on the study design to cope with. When we compared the outcomes of CEA and CAS in treating radiation-induced carotid stenosis, the data mostly were 0, and then we add 0.5 to each data. Then sensitivity analysis was performed to evaluate if the assumptions made changes to the results. Finally, the potential impact on the conclusions induced by missing data was discussed.\(^3\)

Assessment of clinical and methodological heterogeneity

Assessment of heterogeneity

Before any outcome was pooled, heterogeneity was measured with \(I^2\) statistic. The results were classified into mild (< 40%), moderate (40–60%) or substantial (> 60%). If there was substantial heterogeneity, subgroup analyses were done to examine the possible sources of heterogeneity.

Additional analysis

We also applied subgroup analysis to explore possible reasons of heterogeneity, which included:

1. Degree of preprocedural carotid stenosis, as confirmed on angiography (50–80% stenosis as moderate stenosis and >80% as severe stenosis).
2. With or without symptom before the surgery.
3. Different locations and settings of the studies.
4. Mean age of the patients.
5. Length and types of RT.

For the studies with high overall risk of bias, sensitivity analysis was performed to evaluate the effect of exclusion.

Assessment of reporting biases

Reporting biases was assessed by scrutinizing the protocols of the included studies. As the number of included studies probably went beyond 10, we assessed the publication bias with funnel plot.
Assessment of pooled effect estimates

If there was substantial heterogeneity of intervention outcomes, the DerSimonian and Laird method for random-effects estimation was adapted. If not, we used Mantel–Haenszel method for fixed-effects estimation. The level of statistical significance was P Values <0.05. Where statistical pooling was unrealistic because of substantial heterogeneity, the results were presented in tables and discussed afterwards.

We evaluated the quality of evidence contributing to pooled effect estimates of the main outcomes with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for observational studies and the principle of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for RCTs. Eventually, we constructed a table summarizing the overall study results.

Data synthesis

Factors, including trial design, mean age, sex, pre-operative stenosis, type of malignancy, treatment time for radiation-therapy, publication time, as well as modeling heterogeneity, may influence the conclusion. Multivariate Poisson regression analysis, therefore, was conducted to adjust potential bias.

Patient and public involvement

As the present study is a systematic review based on published data, patient and the public are not involved in the study design, conduct, data analysis and result dissemination.

Results

Study selection and study characteristics

We identified 2409 references and abstracts from electronic database and references of related articles. Among these studies, 65 full-text articles were retrieved after first-step screen and 26 studies were found eligible for inclusion in the final analysis. The process of study selection is summarized in Fig. 1.

Table 1 shows the main characteristics of the 26 included studies. All studies were published between 2000 and 2020. Studies included case control studies as well as case series studies, with the patient’s number ranging from 10 to 245. Among these studies, 5 involve both CAS and CEA, while 5 and 16 studies involve only CEA or CAS respectively. A total of 1002 patients who underwent CAS or CEA after radiation therapy were included, including 364 patients who undergone carotid endarterectomy and 638 patients who undergone stent placement. Median ages of the patients ranged between 56 and 71 years, mostly above 60 years. The interval between radiation and the intervention ranges between 3 and 19 years. The follow-up ranges between 1 month and 5 years, and 84.6% of the studies have a median follow-up of more than 12 months. Mean preprocedural stenosis ranges between 84% to complete occlusion. The cancer type included lymphoma, breast cancer, head and neck cancers and other kinds of cancers.

Short-term outcomes

In the overall meta-analysis (Table 2), the rate of short-term stroke after intervention was 0.19% (95% CI:
0.01% (95% CI: 0.00%–0.02%) and the rate after CAS was 1.12% (95% CI: 0.19%–2.55%). The rate of transient ischemic attack was 0.16% (95% CI: 0.00%–0.85%) with low heterogeneity ($I^2 = 19.95\%$) (Supplementary Fig. 4), among which the rate after CEA was 0.39% (95% CI: 0.20%–0.57%) and the rate after CAS was 0.07% (95% CI: 0.00%–0.19%). The estimated rate of short-term death in both groups after intervention were less than 0.01% (95% CI: CEA group: 0.00%–0.12%; CAS

### Table 2. Summary of meta-analysis of short- and long-term outcomes of CEA and CAS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Total (%) (95% CI)</th>
<th>CEA (%) (95% CI)</th>
<th>CAS (%) (95% CI)</th>
<th>$I^2_T$ (%)</th>
<th>$I^2_{CEA}$ (%)</th>
<th>$I^2_{CAS}$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-term outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>0.16 (0.08–0.25)</td>
<td>0.39 (0.20–0.70)</td>
<td>0.07 (0.00–0.15)</td>
<td>19.95</td>
<td>0.00</td>
<td>38.29</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.19 (0.09–0.39)</td>
<td>0.00 (0.00–0.11)</td>
<td>1.12 (0.19–2.55)</td>
<td>8.67</td>
<td>0.00</td>
<td>15.96</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0.00–0.12)</td>
<td>0.00 (0.00–0.11)</td>
<td>0.00 (0.00–0.11)</td>
<td>0.00</td>
<td>0.00</td>
<td>17.34</td>
</tr>
<tr>
<td><strong>Long-term outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>0.45 (0.17–1.00)</td>
<td>0.02 (0.00–0.11)</td>
<td>0.9 (0.05–2.45)</td>
<td>19.95</td>
<td>0.00</td>
<td>35.87</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.68 (1.19–4.57)</td>
<td>0.18 (0.03–0.37)</td>
<td>3.76 (1.95–5.97)</td>
<td>8.67</td>
<td>0.00</td>
<td>26.10</td>
</tr>
<tr>
<td>Death</td>
<td>11.60 (6.79–17.24)</td>
<td>18.66 (14.13–23.55)</td>
<td>11.11 (5.46–18.07)</td>
<td>0.00</td>
<td>62.32</td>
<td>74.09</td>
</tr>
<tr>
<td>Occlusion</td>
<td>0.71 (0.21–2.23)</td>
<td>0.72 (0.49–1.00)</td>
<td>0.83 (0.52–1.20)</td>
<td>8.67</td>
<td>0.00</td>
<td>5.75</td>
</tr>
<tr>
<td>MI</td>
<td>0.15 (0.01–0.31)</td>
<td>0.00 (0.00–0.11)</td>
<td>1.81 (0.12–4.73)</td>
<td>0.00</td>
<td>3.83</td>
<td>39.79</td>
</tr>
<tr>
<td>CNI</td>
<td>2.06 (0.47–4.37)</td>
<td>2.99 (0.91–5.81)</td>
<td>0.37 (0.05–2.07)</td>
<td>19.95</td>
<td>57.66</td>
<td>0.00</td>
</tr>
</tbody>
</table>

$CI$ confidence interval, $TIA$ transient ischemic attack, $I^2$ the variation attributable to heterogeneity, $I^2_T$ heterogeneity in overall meta-analysis, $I^2_{CEA}$ heterogeneity in the CEA group, $I^2_{CAS}$ heterogeneity in the CAS group.
group: 0–0.48%), each with low heterogeneity (Supplementary Fig. 5).

Long-term outcomes

As is shown in Table 2, the pooled estimated rate of long-term stroke was 2.68% (95% CI: 1.19–4.57%) (Fig. 2), among which the rate after CEA was 0.18% (95% CI: 0–3.73%) and the rate after CAS was 3.76% (95% CI: 1.95–5.97%). The estimated restenosis rates after CEA and CAS were 6.34% (95% CI: 1.37–13.43%) and 13.86% (95% CI: 10.89–17.07%). The standard of restenosis varied from studies. The estimated rate of cranial nerve injury after CEA was 2.99% (95% CI: 0.91–5.81%) (Supplementary Fig. 6) and showed decreasing tendency over time (Fig. 3). The overall rate of death after intervention was 11.6% (95% CI: 6.79–17.24%) (Supplementary Fig. 7).

The outcomes of comparison between CEA and CAS

We also performed a meta-analysis comparing the outcomes of CEA and CAS in 5 studies (Table 3). Results showed that all rates of short-term outcomes had no significant differences (Supplementary Fig. 13). The rate of CNI was higher in CEA group compared with the rate in CAS group (RR: 6.03, 95% CI: 1.63–22.22, \( P = .007 \)) (Fig. 4). The estimated rate of CNI after CEA was 2.99% and no cases of cranial nerve injury was reported after stent placement. Apart from that, all rates of long-term outcomes including stroke, restenosis, or death, showed no significant differences (Supplementary Fig. 14).

Meta regression analysis

The univariate meta-regression analysis was conducted between the outcomes and type of intervention (Table 4).
The result revealed that both rates of short-term stroke and long-term stroke had significance with the type of intervention (IRR: 3.62, 95% CI: 1.21–10.85, P = 0.022; IRR: 2.95, 95% CI: 1.02–8.59, P = 0.046), indicating that the risk of stroke in CAS group is higher than the rate in CEA group, whether in short or long term.

Risk of bias

Quality assessment was performed using the Newcastle Ottawa scale and its adjusted version for case series. As is shown in Supplement 3 (Assessment of study quality), NOS scores from 7 to 9 (9 being the highest possible score), with a mean of 8.2, median of 8. For cases series (Supplement 2), 61.9% studies had good, 33.3% had moderate and 4.8% had low quality. Agreement between two reviewers in assessing the methodological quality was evaluated. Publication bias was examined by funnel plots, and results showed no obvious reporting bias for the pooled studies (Supplementary Fig. 12).

Discussion

In this systematic review grounded on a total of 1002 patients from 26 studies, we evaluated both short- and long-term outcomes after intervention in treating patients with carotid artery stenosis caused by radiotherapy. Furthermore, this study was the most comprehensive meta-analysis to compare the outcomes of CEA and CAS for patients with carotid artery stenosis caused by radiotherapy.
carotid artery stenosis caused by radiotherapy. Firstly, in our study we presented not only the approximated rates of short-term and long-term TIA, stroke, death after CEA and CAS for carotid stenosis caused by radiotherapy, but also the rates of restenosis, occlusion, MI and CNI (Table 2; Fig. 2; Supplementary Figs. 4–8). Secondly, through the outcomes of comparison between CEA and CAS, it was demonstrated that the rate of CNI in CEA group was higher than CAS group (Table 3; Fig. 4; Supplementary Figs. 13–15). And thirdly, the meta-regression analysis proved that both the short-term and long-term stroke rates of the CAS group overtopped the rates of CEA group (Table 4).

The rates of short-term outcomes after intervention of carotid stenosis caused by radiotherapy were gradually decreased in recent years, however, the rates of long-term outcomes were relatively high. A meta-analysis by Fokkema et al. included 533 post-radiotherapy patients from 27 studies, and the rates of perioperative cerebrovascular adverse events were 3.5% in CAS group and 3.9% in CEA group. Compared to the study by Fokkema et al., our study included the researches published after the year of 2000 and showed decreased rates of short time cerebrovascular adverse events. The reason for it probably lies in the strengthened perioperative management such as careful preoperative preparation, meticulous surgical techniques and intensive monitoring. By contrast, the high rates of long-term adverse events may be related to treatment method itself. The surgical treatments of carotid artery stenosis have always been CEA and CAS for a long time, and no commonly agreed guide focusing on this group of patients has been published. More RCTs and cohort studies are needed to provide evidences in improving the long-term efficacy of surgical treatments for this disease in the future.

In our study, the short-term and long-term stroke rates were low, but the long-term death rate was relatively high. This result also was found in other study, and the reason for high rate of long-term death was presumably the recurrence of head and neck tumors, and may have less relation with the disease of vasculopathy.

As to restenosis, different studies had different results. Protac et al. demonstrated that the rate of carotid restenosis caused by stenting in post-radiotherapy patients was nearly threefold higher than those without radiotherapy. In our study, the rate of restenosis was notably high regardless of CEA or CAS group. Compared with carotid plaque caused by atherosclerosis, the carotid plaque caused by radiotherapy has the unique characteristics as follows: first, the radiation could damage the endothelial cells, which could lead to endothelial dysfunction and the progression of carotid plaque formation; second, radiation also causes the injury of vasa vasorum in carotid artery adventitia, and leads to adventitia necrosis. All these reasons could result in vessel wall thickness and thus increasing the risk of restenosis.

According to previous studies, the CEA was superior to CAS in terms of long-term efficacy for patients with severe carotid stenosis caused by radiotherapy, but CAS may cause CNI while CAS hardly causes CNI. The rate of CNI in patients with carotid severe stenosis caused by radiotherapy ranged from 2% to 27% in different studies. Fokkema et al. reported the rate of CNI as 9.2%. Boitano et al. included 18832 patients and divided them into two groups, one of which was carotid stenosis caused by radiotherapy containing 281 patients, and the other one was non-radiotherapy carotid stenosis containing 18551 patients. After the meta-analysis, the rate of CNI in radiotherapy group was 3.2%, while in non-radiotherapy group the rate was 4.2%. In our study the incidence of CNI after CEA was 2.99%, and gradually decreased with time elapsing. The underlying mechanism may be as follows: the accumulated radiation damages the soft tissue and nerves in the head and neck, leading to the formation of large amount of cicatrical tissue, which adds to the operation difficulty of CEA and increases the risk of CNI. But the injury is usually temporary, and could slowly recover after the use of neurotrophic drugs. In our study, the rate of CNI would gradually decrease over time, and it was likely to be associated with the accumulated operation experience and improved surgical skills of surgeons.

It was found in our study that the rates of short-term and long-term stroke in CAS group were higher than CEA group, similar findings were also reported in previous studies. Kasivisvanhatan et al. reported that the stroke or death rate of surgical procedure in symptomatic postradiotherapy carotid stenosis patients was 2.7%, and 1.1% in asymptomatic patients, while in CAS group the rate was 5.1% and 2.1%, respectively. Batchelder et al. overviewed primary and secondary analyses from 20 RCTs comparing CAS with CEA, and concluded that CAS had higher rates of 30-day death or stroke than CEA, ipsilateral stroke was same for CEA and CAS after 30 days. Although results may differ among the studies, the conclusions tended to be indicative of CEA’s advantage compared to CAS.

Previous studies reported that CAS was the better management for carotid artery stenosis caused by radiation, however, in our study the primary outcomes in CEA group are superior to CAS group. Whether CEA will become the golden standard for this disease in the future remains unclear. Furthermore, providing individualized treatment for such patients is also crucial for clinicians. More RCTs and larger cohort studies are needed to offer more evidence.

Limitation

There were some limitations in this meta-analysis. First, although all related literatures published ranged from 2000 to 2020 were searched, we still had insufficient
sample size to obtain high accuracy pooled result. Second, the included studies were largely observational studies, so the level of merged evidences was relatively low. Given the above two reasons, substantial heterogeneity was a challenge for this study. Further well-designed RCTs or cohort studies with sufficient sample size are needed to avoid the above limitations, and high-quality studies are also needed to update the results.

**Conclusion**

In general, this study obtained the worldwide profile of outcomes of treatment for radiation-induced carotid stenosis, and also compared the safety and efficacy of CAS and CEA in these patients in both short- and long-term aspects. The evidence from this study suggested that CEA may be more suitable in treating patients with prior history of radiotherapy. However, as no large-scale studies had been conducted, there were limitations in the result interpretation, and further research studies are needed in the future.

**Ethics and dissemination**

Ethics approval is not needed as systematic review is based on published studies. Study findings will be presented at international conferences and published on a peer-reviewed journal.

**Declaration of Competing Interest**

The authors report no conflicts of interest in this work.

**Funding**

This work was supported by the National Key Research and Development Project (2016YFC1301703). The funder has no role in study design, data analysis and writing the manuscript.

**Contributions**

XZ, YY, KY contributed equally to this article. Conception and design: XZ, TW, YM, LJ. Analysis and interpretation: XZ, YY, YM, LJ, BY. Data collection: XZ, YY, KY, XSB, FY, WX, RX. Statistical analysis: KY, XZ, TW. Writing the article: YY, XZ, KY, YM, LJ. Critical revision of the article: ZX, YY, KY, XSB, TW, LJ, YM. Obtained funding: LJ. Overall responsibility: YM, LJ.

**Supplementary materials**

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2020.104929.

**References**

RADIATION-INDUCED CAROTID STENOSIS


