Stenting Versus Surgery in Patients With Carotid Stenosis After Previous Cervical Radiation Therapy
Systematic Review and Meta-Analysis

Margriet Fokkema, MSc; Anne G. den Hartog, MD; Michiel L. Bots, MD, PhD; Ingeborg van der Tweel, PhD; Frans L. Moll, MD, PhD; Gert Jan de Borst, MD, PhD

Background and Purpose—Patients with both carotid stenosis and previously cervical radiation therapy are considered “high risk” for carotid endarterectomy (CEA). Carotid angioplasty and stenting (CAS) seems a reasonable alternative, but neither the operative risk for CEA nor the effectiveness of CAS has been proven. The purpose of this study was to evaluate perioperative and long-term outcome of both procedures in patients with radiation therapy.

Methods—A systematic search strategy with the synonyms “carotid artery stenosis” and “cervical irradiation” was conducted in MEDLINE and EMBASE databases. To provide and compare estimates of outcomes, pooled and metaregression analyses were performed.

Results—Twenty-seven articles comprising 533 patients undergoing radiation therapy (361 CAS and 172 CEA) fulfilled our inclusion criteria. Pooled analysis showed perioperative risk for “any cerebrovascular adverse event” (CVE) of 3.9% (95% CI, 2.3%–6.7%) in CAS studies against 3.5% (95% CI, 1.5%–8.0%) in CEA studies (P=0.77). Risk for cranial nerve injury (CNI) after CEA was 9.2% (95% CI, 3.7%–21.1%) versus none after CAS. Late outcome showed rates of CVE favoring CEA (P=0.014). The rate of restenosis >50% was significantly higher in patients treated with CAS compared with CEA (P<0.003).

Conclusions—Both CAS and CEA proved to be feasible revascularization techniques with low risk for CVE. Although patients undergoing CEA had more temporary CNI, higher rates of late CVE and restenosis were identified after CAS. (Stroke. 2012;43:793-801.)

Key Words: angioplasty stenting • carotid stenosis • endarterectomy • outcomes • radiation
Materials and Methods

The search strategy and data collection were performed according to the guidelines of MOOSE (Meta-analyses of observational studies in epidemiology).12

Search Strategy

MEDLINE and EMBASE databases were searched on October 17, 2011, using the combination of synonyms for “carotid artery stenosis” and “cervical irradiation” to include all possible eligible studies. No restrictions or filters were applied. Additional studies were identified by searching the reference list of relevant studies. Studies published in books or abstracts of major meetings were searched using the search function on portable document formats. Final search queries are shown in Table 1. A flowchart of the applied search strategy and selection process is summarized in the Figure.

Data Collection and Items

The included articles were divided into 2 groups: (1) CAS group: studies on patients undergoing XRT and CAS; and (2) CEA group: studies on patients undergoing XRT and CEA. Additionally, we systematically extracted the following characteristics: author, publication date, number of patients, number of revascularizations, indication for intervention (symptomatic or asymptomatic stenosis), time interval between XRT and revascularization, length of follow-up, and outcome measures.

Primary outcome measures were: (1) any CVE, defined as a composition of any stroke (fatal, disabling and nondisabling) and/or TIA, either ipsi- and/or contralateral of intervention site for periprocedural (<30 days) and late (>30 days) outcome; (2) CNI specified in transient (no functional consequences and completely resolving <30 days) and permanent (functional consequences and symptoms lasting >30 days); and (3) restenosis and/or occlusion, in which restenosis was defined as duplex ultrasound derived >50% stenosis either symptomatic or asymptomatic.

Table 1. Search Queries

<table>
<thead>
<tr>
<th>MEDLINE</th>
<th>EMBASE</th>
</tr>
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</table>

Study Selection

First, all duplicate articles were removed manually. Second, all citations were independently screened by 2 authors (M.F. and A.G.d.H.) using predefined selection criteria. Inclusion criteria were: (1) presenting data about patients undergoing XRT with carotid stenosis undergoing CEA and/or CAS; and (2) reporting at least 1 relevant outcome measurement. Subsequently, the included articles were read full text and excluded if 1 of the following criteria were applicable: (1) not meeting inclusion criteria; (2) unsuitable study design (case report, review); and (3) articles under review. In case of disagreement regarding selection, a third observer (G.J.d.B.) was consulted to reach consensus.

Figure. Search strategy and selection process.
Secondary outcome measures were procedural-specific outcomes for both techniques. For CAS these included: technical success rate (defined as successful stent deployment with residual stenosis <30% on control angiography or duplex ultrasound), vascular access site complication (hematoma or pseudoaneurysm), and cardiovascular complications (bradycardia or hypotension). For CEA these included: wound infection/delayed healing and bleeding complications needing a reoperation. Different descriptions across studies did not allow us to give more exact definitions for these outcome measures. Measure of outcome for perioperative outcomes was a “proportion” (ie, number of patients experiencing the event divided by total number of patients [n]); and for late outcome, an “incidence rate” (number of patients experiencing the event divided by total number of person-years [n×length of mean or median reported follow-up]).

Data Presentation and Statistical Analysis

Data are presented as results per individual study in a descriptive manner and summarized systematically in tables. Results were evaluated separately for (1) early outcome (day of intervention −30 days); and (2) late outcome (>30 days). Meta-analyses were performed to pool the primary outcome measures. A random effects model was chosen to adjust for heterogeneity between studies; $I^2$ was calculated as a measure for heterogeneity.11 An $I^2$ value <25% was considered as low heterogeneity.12 To assess the difference between both procedures (CAS and CEA group), metaregression was performed with treatment procedure (CAS or CEA) as a factor. Meta-analyses were performed using SAS PROC NLMIXED (Version 9.2). This procedure allows performance of an exact analysis using a binomial distribution for the early outcomes and a Poisson distribution for the late outcomes.13

Results

MEDLINE and EMBASE search strategy yielded a total of 498 hits (Figure). After removal of duplicates and screening citations, 51 articles for full-text evaluation remained. Of those, another 28 articles were excluded based on: not meeting inclusion criteria after critical full text evaluation (20) study design (7), and article under review (11). Four additional studies were retrieved from crossreferencing.17–20 No additional studies were identified from books or abstract of major meetings. As a result, a total of 27 publications were included, comprising 533 patients divided in the CAS group (14 articles17,19–31; 361 patients, symptomatic: median 59% [Quartiles 1–3=51%–75%]) and CEA group (14 articles4,9,18,21,32–41; 172 patients, symptomatic: median 67% [Quartiles 1–3=46%–86%]). One article was included in both groups.21 All studies had an observational study design and were considered valid for inclusion. Characteristics of the individual studies are presented in Table 2 (CAS group) and Table 3 (CEA group).

Radiation Therapy

Indications for XRT in general were head and neck squamous cell malignancies (primary carcinomas or lymph node metastases of unknown origin). Less common indications for cervical radiation were lymphomas (Hodgkin and non-Hodgkin), parotid tumors, and thyroid tumors. In most articles, radiation characteristics were poorly documented. Therefore, exact site (left or right carotid territory) of irradiation was not mentioned for all patients. The therapeutic dose was administered in only 1 article in the CAS group (>60 Gy in 71% of patients).22 In the CEA group, 2 articles reported 62.0 Gy and 43.5 Gy as a mean therapeutic dose.34,35 Range in the mean interval in years between XRT and carotid revascularization was 6.3 to 16.6 years for the CAS group and 1.7 to 17.0 years for the CEA group. More than 50% of patients in the CEA group underwent previous neck surgery in combination with XRT. For the CAS group, this was not clarified.

Early Outcome

Early results are shown in Table 4. In the CAS group (13 studies with 326 patients, 354 procedures), pooled analysis estimated a risk of 3.9% (95% CI, 2.3%–6.7%; $I^2=22.1%$)
for CVE. One fatal stroke was seen in a series of 16 patients. Technical success rate was reported varying from 94% to 100%. Six failures occurred: 3 needed conversion to surgery, 1 stent became lodged in the curve of the introducer sheet (only balloon dilatation was performed), 1 was abandoned owing to failure to pass the guidewire across a tight lesion, and 1 patient had residual stenosis after the procedure.

In the CEA group (14 studies with 172 patients, 190 procedures), pooled analysis showed a risk of 3.5% (95% CI, 1.5%–8.0%; I²/H11005 0%) for CVE. One death occurred due to massive intracerebral hemorrhage. No statistically significant difference was encountered in occurrence of CVE between CAS and CEA (P=0.77).

Meta-analysis of CNI resulted in an estimated risk of 9.2% (95% CI, 3.7%–21.1%) in patients undergoing CEA (12 studies with 157 patients). All injuries were considered to be initial and completely resolved within several weeks, although 1 study reported 9% (1 of 11) permanent CNI. Six studies reporting on this specific end point did not encounter any nerve problems at all. Other procedure-specific complications were incidental, including wound infection and bleeding needing reintervention (Table 4).

Late Outcome

Clinical Outcome

Data for CVE on follow-up extending the postprocedural 30 days were reported in 20 studies (398 patients). Results are summarized in Table 5. In the CAS group (11 studies, 277 patients), a total of 15 events occurred over a total follow-up period of 697.9 person-years, an estimated rate of 4.9 per 100 person-years (95% CI, 3.6–6.6). Two disabling strokes were identified contralateral of the CAS site in a series of 24 patients with a mean follow-up of 39.6 months. Three other strokes were related to restenosis and occurred in a series of 135 patients at a mean interval of 16 months. Another 3 ipsilateral strokes (2 major, 1 minor; not further defined) were identified in a series of 30 patients after a mean follow-up of 58 months, in which 1 patient had carotid stent occlusion after 38 months. No further information was provided on 2 strokes observed in the study by Protack et al (23 patients; mean follow-up, 14.4 months). In total, 5 TIAs were identified: 1 contralateral and 1 ipsilateral of the CAS site, 1 related to restenosis, and 2 due to carotid thrombosis.

In the CEA group (9 studies, 121 patients), 1 event (TIA) over a total of 386.7 person-years of follow-up was reported, on average 2.8 per 100 person-years (95% CI, 2.0–3.9). The difference in the CVE rate between both procedures was significant (P=0.014).

Mortality

Mortality rate for the CAS group and CEA group varied between 0% and 33.0% and 0% and 44.4%, respectively. This rate seemed to be highly influenced by nonvascular causes of death such as pre-existent cancer in both groups.

Restenosis

In the CAS group (13 studies, 319 patients), 72 patients were identified with restenosis and/or occlusion after a total of 725.2 person-years of follow-up, an average rate of 5.4 per 100 person-years (95% CI, 4.3–6.6). Large differences among studies existed. Two small studies (n=5 and n=7) found no restenosis and no reinterventions performed during follow-up (9.3 and 6.0 months). Two slightly larger studies both monitored 16 patients for, respectively, 30 and 28 months and found restenosis rates of 17.6% and 21.0%. The study with the largest patient population (n=135) yielded an overall restenosis (>50%) rate of 12% (n=18) at 30 months. Four of these led to neurological complications. In
the study by Protack et al26 (mean follow-up 14.4 months), 43% of patients undergoing XRT developed restenosis. Also, Dorresteijn et al22 showed a high rate of 42% restenosis in a series of 24 patients measured over a follow-up length of 2 years. Nevertheless, all lesions remained asymptomatic and only in 1 patient was restenting performed.

In the CEA group (9 studies, 121 patients), 13 patients were diagnosed with 50% restenosis and/or occlusion after a period of 386.7 person-years of follow-up, an average rate of 2.8 per 100 person-years (95% CI, 1.9–4.0). The highest reported rate of restenosis was 16.6%; after a mean follow-up of 18 months, duplex scans showed asymptomatic recurrent
stenosis >50% in 3 patients. Another study showed 4 patients (15%) with asymptomatic restenosis after a mean follow-up of 58 months. Because of progressive asymptomatic lesions, 2 of these patients were treated with CAS.21 In the remaining studies, 4 other patients reached this specific end point, 2 in a series of 17 patients (1 symptomatic) and 2 in a series of 24 patients, resulting in 11.8% (n=17) and 8.3% (n=24) restenosis rates, respectively, at 52 and 13 months.36,37 In total 2 patients developed an ipsilateral occlusion.9,37 Comparison of outcomes for restenosis and/or occlusion showed a significant difference favoring CEA (P=0.003).

### Discussion
In this systematic review and meta-analysis, we present an overview of 533 patients treated with CAS or CEA for carotid stenosis after previous cervical XRT (CAS group, n=361; CEA group, n=172). The risk for adverse cerebrovascular events was low after CEA and CAS for both perioperative and late outcome. However, results were statistically different for late outcome favoring CEA. CEA was hampered by a mean risk of 9.2% of—mostly transient—CNI against none after CAS. Furthermore, higher rates of restenosis >50% and occlusion compared with CEA were identified (P=0.003). However, most in-stent restenoses behaved in a benign fashion and remained asymptomatic.

Treatment of carotid stenosis after cervical radiation needs special interest because in the past decennia, survival after cervical malignancy has increased. Simultaneously, the risk for relevant carotid stenosis seems to increase.42 Several carotid intervention studies defined

### Table 5. Late Outcome (>30 Days)

<table>
<thead>
<tr>
<th>CAS Group</th>
<th>Mean Follow-Up (Range), Mo</th>
<th>TIA, No.</th>
<th>Stroke, No.</th>
<th>Death, No.</th>
<th>Restenosis, No./Occlusion, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tallarita et al21</td>
<td>58 (1–132)</td>
<td>0</td>
<td>3</td>
<td>11</td>
<td>6/2</td>
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<tr>
<td>Dorresteijn et al22</td>
<td>39.6 (3.6–132)</td>
<td>2</td>
<td>2†</td>
<td>7</td>
<td>7/0</td>
</tr>
<tr>
<td>Sadek et al23</td>
<td>9 (0.5–45)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1/0</td>
</tr>
<tr>
<td>Favre et al24</td>
<td>30 (3–95)</td>
<td>3</td>
<td>3</td>
<td>30</td>
<td>18/9</td>
</tr>
<tr>
<td>Younis et al25</td>
<td>24 (6–99)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>7/0</td>
</tr>
<tr>
<td>Protack et al26</td>
<td>14.4 (NA)</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>9/2</td>
</tr>
<tr>
<td>Ecker et al27</td>
<td>9.3 (1–24)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Harrod-Kim et al28</td>
<td>28 (5–78)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4/2</td>
</tr>
<tr>
<td>Hassen-Khodja et al29</td>
<td>18 (NA)</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>McKevitt et al30</td>
<td>1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ting et al30</td>
<td>30 (5–55)</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3/0</td>
</tr>
<tr>
<td>Alric et al31</td>
<td>10 (3–18)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1/0</td>
</tr>
<tr>
<td>Houdart et al31</td>
<td>8 (3–24)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Al Mubarak et al31</td>
<td>8 (NA)</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0*</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>CEA Group</th>
<th>Mean Follow-Up (Range), Mo</th>
<th>TIA, No.</th>
<th>Stroke, No.</th>
<th>Death, No.</th>
<th>Restenosis, No./Occlusion, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tallarita et al21</td>
<td>58 (1–132)</td>
<td>0</td>
<td>0</td>
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<td>4/0</td>
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<tr>
<td>Frego et al4</td>
<td>40 (0–156)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0†</td>
</tr>
<tr>
<td>Boules et al32</td>
<td>1</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Mozes et al33</td>
<td>1</td>
<td>NR</td>
<td>NR</td>
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<td>NR</td>
</tr>
<tr>
<td>Lesche et al34</td>
<td>40 (3–99)</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td>3/0</td>
</tr>
<tr>
<td>Cazaban et al35</td>
<td>1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Friedell et al9</td>
<td>37 (12–60)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0/1</td>
</tr>
<tr>
<td>Hassen-Kodja et al36</td>
<td>52 (12–108)</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td>2/0</td>
</tr>
<tr>
<td>Kashyap et al37</td>
<td>13 (1–156)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2/1</td>
</tr>
<tr>
<td>Rockman et al38</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Andros et al18</td>
<td>24.9 (NA)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Atkinson et al39</td>
<td>49 (NA)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Francort et al40</td>
<td>26 (6–48)</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Silverberg et al41</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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</tr>
</tbody>
</table>

CAS indicates carotid angioplasty and stenting; TIA, transient ischemic attack; NA, no data available; CEA, carotid endarterectomy; NR, not reported.

*Measured at 6 mo of follow-up.
†Defined as duplex ultrasound derived >30% stenosis.
‡Disabling stroke.
patients undergoing XRT as a high-risk group for CEA.\(^2\,4^3\,4^4\) This classification remains controversial because the definition was based on theoretical arguments and still no risk stratification for patients undergoing XRT exists today.\(^4^5\) Additionally, the concept of “high risk” is doubtful and multiply interpretable; patients can be either high-risk for stroke or high-risk for surgery, or both.\(^4^6\) Notwithstanding, radiation was accepted as 1 of the anatomic high-risk criteria among contralateral occlusion, previous ipsilateral endarterectomy, and high carotid bifurcation; thus, patients undergoing XRT were included in studies investigating the effectiveness and safety of CAS in deemed high-risk groups.\(^1\,5\) Although appraisal of subset analyses in these studies is not precise due to the small patient populations, the XRT group often showed better but nonsignificant perioperative results compared with the other high-risk subgroups. One study on CAS found the combined all stroke/death risk in the overall high-risk group \((n=103)\) was 9.7% versus 7.0% in a non high-risk control group \((n=373; P>0.05)\).\(^3^0\) However, all stroke/death risk in the XRT subgroup \((n=17)\) was 0%. Others found that the periprocedural risk of CAS in patients undergoing XRT appeared to be comparable to CAS in non-XRT patients.\(^2^3\,4^7\) By performing this review we aim to expand this evidence by identifying that CAS and CEA can be performed safely for revascularization of patients undergoing XRT with carotid stenosis with no early deaths and low risk for CVE. On the other hand, even like in recent prospective randomized studies in symptomatic patients at normal risk,\(^4^8\,4^9\) late clinical events happened more frequently after endovascular repair as compared with CEA \((P=0.014)\). Furthermore, rates for restenosis were higher after CAS as compared with both CEA and non-XRT references for the treatment of carotid artery stenosis. In 4 studies,\(^2^2\,2^4\,–\,2^6\) CAS was initially feasible in patients undergoing XRT, but during follow-up, restenosis rates were significantly higher than in other deemed high-risk subgroups. The underlying mechanism leading to in-stent restenosis after CAS is explained by myointimal hyperplasia with smooth muscle cell proliferation. Stent deployment in a pre-existent fibrotic (postradiation) process may be associated with a faster and higher incidence of restenosis.\(^2^5\) Contrary to CAS, rates for restenosis after CEA seem to be comparable to those with surgery in the absence of radiotherapy.\(^9\,2^9\,3^7\) Only Lesche et al\(^1^4\) suggest that in patients who experienced cervical radiation, restenosis is markedly higher than in those patients without XRT. However, no data were provided on the exact location of restenosis why these restenoses might have occurred somewhere else in the radiated plane or in-stent/within the region of previous endarterectomy.

One of the main concerns toward CEA in patients with a history of cervical radiation is the potentially higher rate of CNI. Outside standard conditions, theoretically cranial nerve deficits may be more frequent in hostile necks\(^3\); and perivascular soft tissue fibrotic changes probably explain the greater risk.\(^5^0\) A literature review calculated a 9% risk (range, 2%–27%) of temporary palsy after CEA in patients without a hostile neck.\(^5^1\) Two other extensive studies reported a rate of 5.0% with only 0.5% lasting more than a few months in patients at normal risk.\(^5^2\,5^3\) Furthermore, a rate of 7.7% in a high-risk group with local risk factors was observed without a significant difference with the reference low-risk group \((6.6%)\).\(^3^3\) These outcomes were very comparable with our pooled estimate of 9.2% of initial deficits, which were transient in most cases. Therefore, the risk for permanent CNI should probably not being considered as a contraindication for CEA in irradiated patients. However, we should state that we were not informed about the exact preoperative tissue condition of the treated cervical region, and details on combined XRT and cervical surgery could not reliably be analyzed, possibly influencing this consideration. In a recent study,\(^2^1\) this issue was well documented, in which patients with prior radical neck dissections had more wound complications \((14%\text{ versus }5\%)\) and CNI \((28%\text{ versus }9\%)\) compared with those without neck dissections. Thus, if the cervical anatomy is highly affected not only by XRT, but especially through previous surgery making redo surgery hazardous, CAS might be considered as a suitable alternative. The relative impact of patients’ characteristics on the risk of complications for CAS or CEA have led to different approaches to perform meta-analysis.\(^5^4\) Due to limited patient data for XRT-induced carotid stenosis, we were not able to select the best technique on the basis of particular patient characteristics. The role of medical treatment in limiting disease progression and prevention of stroke in previously radiated patients stays unclear at this point.

**Study Limitations**

The main problem of lack of randomized studies is the inevitable confounding by indication. Patient selection must have resulted in differences in outcome, which favored CEA, probably because less appropriate surgical candidates (eg, due to previous neck surgery) were excluded for this procedure and treated by CAS. Moreover, as a consequence of small individual sample sizes and lack of reporting specific details, we were not able to distinguish between results of symptomatic or asymptomatic status as the initial indication for revascularization. Also inherent to meta-analysis of observational studies is the chance of publication bias. Although we included all available study data in the literature of the past decades, we could have missed outcomes of a few patients, especially of articles in which patients undergoing XRT were not well stratified from other high-risk groups. Furthermore, assessment of generally accepted duplex criteria for grading stenosis after CEA has been shown to be not reliable after CAS, because placement of a stent in the carotid artery can cause an increase in duplex velocities in the absence of residual or true in-stent stenosis.\(^5^5\) This could have led to distorted outcomes in the CAS group. Finally, decreasing trends in stroke and mortality are usually observed as techniques and technology are improving. Therefore, older studies could possibly lead to worsened results for total outcome, especially within the CAS-treated cohort, yet there is a therapeutic dilemma that calls for a randomized comparison. Based on the low risks
Conclusions
According to the available literature, both CAS and CEA proved to be feasible revascularization techniques with low risk for cerebrovascular adverse events in patients with previous XRT. Patients undergoing CEA had more temporary CNI, whereas patients treated with CAS were shown to have a greater risk on late CVE and restenosis >50%. These results do not indicate a preferred revascularization treatment and therefore, in patients with previous cervical radiation, the choice for revascularization therapy should be considered on an individual basis.

Disclosures
None.

References


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