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REVIEW ARTICLE

Radiation-induced carotid artery lesions

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Abstract

Purpose To review the current aspects of knowledge related to the risk of cerebrovascular events in patients receiving head and neck radiotherapy.

Methods A literature search was performed in PubMed. Papers meeting selection criteria were reviewed.

Results We provide an update on the problem by identifying key studies that have contributed to our current understanding of the epidemiology, radiologic features, pathogenesis, and treatment of the disease. The incidence of carotid artery stenosis ranged from 18 to 38% in patients who underwent radiotherapy for head and neck cancer versus from 0 to 9.2% among the nonirradiated patients. Neck irradiation increases the intima-media thickness of the carotid artery wall. These changes are the earliest visible alteration in the carotid wall and are also detected with color Doppler ultrasonography. Endovascular treatment with a carotid angioplasty and stenting is the first-line treatment for most symptomatic patients.

Conclusions Radiation-induced atherosclerosis is a different and accelerated form of atherosclerosis, which implies a more aggressive disease with a different biologic behavior. The disease is characterized by a high rate of carotid artery stenosis compared to those observed in nonirradiated control group patients. To prevent the risk of stroke, surveillance and imaging with ultrasonography should enable detection of severe stenosis. Endovascular treatment with a carotid angioplasty and stenting has been proposed as an attractive and minimally invasive alternative for some radiation-induced stenoses.

Keywords Carotid stenosis · Radiotherapy · Head and neck neoplasms · Atherosclerosis · Endarterectomy, carotid

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Strahleninduzierte Läsionen der Karotisarterie

Zusammenfassung

Zielsetzung Untersuchung des aktuellen Wissenstands hinsichtlich des Risikos eines zerebrovaskulären Ereignisses bei Patienten nach Strahlentherapie im Kopf-Hals-Bereich.

Material und Methoden PubMed-Suche nach Artikeln, die die Einschlusskriterien erfüllten.

Ergebnisse Wir aktualisieren das Problem, indem wir Schlüsselstudien identifizieren, die zu unserem gegenwärtigen Verständnis der Epidemiologie, der radiologischen Eigenschaften, der Pathogenese und der Behandlung der Krankheit beigetragen haben. Die Inzidenz der Karotisstenose reichte bei Patienten nach Strahlentherapie aufgrund von Kopf-Hals-Tumoren von 18 bis 38% im Vergleich zu 0 bis 9,2% bei den nichtbestrahlten Patienten. Halsbestrahlung erhöht die Intima-media-Dicke der Karotisarterienwand. Diese Veränderungen stellen die früheste sichtbare Veränderung in der Karotiswand dar und können auch mit Farbdoppler-Ultraschall erkannt werden. Die First-Line-Behandlung beinhaltet für die meisten symptomatischen Patienten eine endovaskuläre Behandlung mit Angioplastie der Karotisarterie und Stentimplantation.

Schlussfolgerung Strahlungsinduzierte Atherosklerose ist eine andere und beschleunigte Form der Atherosklerose, die eine aggressivere Erkrankung mit einem anderen biologischen Verhalten impliziert. Die Krankheit ist gekennzeichnet durch eine hohe Rate an Karotisstenosen im Vergleich zur nichtbestrahlten Kontrollgruppe. Um das Risiko eines Schlaganfalls zu vermeiden, sollten Überwachung und Bildgebung mit Ultraschall die Erkennung einer schweren Stenose ermöglichen. Die endovaskuläre Behandlung mit Angioplastie und Stentimplantation wurde als eine attraktive und minimal-invasive Alternative für einige strahleninduzierte Karotisstenosen vorgeschlagen.

Schlüsselwörter Karotisstenose · Strahlentherapie · Kopf- und Halsneubildungen · Atherosklerose · Karotisendarteriektomie

Introduction

Radiation-induced injury causing atherosclerotic changes in the carotid arteries in both experimental animals and human subjects has been documented for more than 50 years [1, 2]. A significantly increased risk of long-term cardiovascular complications has been observed after radiotherapy (RT) in cancer patients [3–5].

Atherosclerosis associated with RT has been reported to be less inflammatory and more fibrotic than carotid atherosclerotic lesions in nonirradiated patients [6]. The radiation-induced disease can be considered a clinically distinct entity, because it is limited to the irradiated area and is less likely to be associated with atherogenic risk factors [7].

The purpose of this review is to highlight the injuries that radiation therapy produces in the carotid and their neurological consequences, so that prevention and screening programs should be considered for head and neck cancer survivors.

Pathogenesis

Injury to smaller vessels after RT has been well documented. However, the pathogenesis of radiation-induced arterial injury in large vessels has not yet been completely elucidated. The mechanism of irradiation-induced carotid stenosis is a combination of direct vessel damage, accelerated atherosclerosis, intimal proliferation, necrosis of the media and peri-adventitial fibrosis [8, 9].

Irradiation induces an inflammatory reaction in the vessel wall which triggers a series of events involving the endothelial cells, cytokines, and growth factors that results in changes in the vascular wall [10]. Damage to the endothelial cells seems to be one of the most important mechanisms [11]. The endothelial dysfunction appears earlier than the morphological changes and is attributed to the lack of endothelial nitric oxide synthase expression [12]. This damage results in increased permeability, fibrin deposition in the extravascular space, and platelet adherence to the surface of the endothelium which leads to accelerated atherosclerosis. This is followed by the destruction of the internal elastic lamina and marked thickening of the endothelium. Platelets release platelet-derived growth factor and basic fibroblast growth factor, both of which promote smooth muscle cell proliferation and migration. Smooth muscle cells proliferate in the media and migrate to the intima, where the proliferation continues, followed by deposition of an extracellular matrix, resulting in thickening of the intima [10]. All these modifications result in changes to the structure of the arterial wall, with altered compliance and distensibility of the vessel and luminal narrowing [13]. Moreover, there is an increase in inflammatory cells and mediators of inflammation. Monocytes invade the vessel wall and differentiate into macrophages which are able to scavenge oxidized low-density lipoproteins, permitting them to pass into the subendothelial space and form

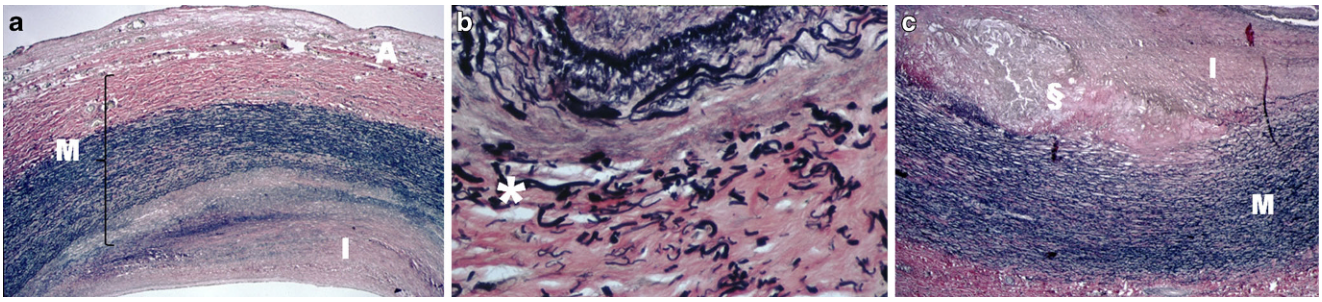

Fig. 1 **a** Thickening of the intima (*I*) with involvement of the internal elastic lamina. The *black line* marks the media layer. **b** Destruction of the elastic lamina (*) in several areas. **c** Radiation-induced atherosclerotic carotid plaque with a lipid core (*§*), hypertrophy of the intima (*I*), and fragmentation of the internal elastic lamellae. **A**: adventitia; **M**: media

foam cells. The foam cells, together with T-lymphocytes and smooth muscle cells, form a "fatty streak." Subsequent matrix production leads to fibrous plaque formation. Other factors involved include transforming growth factor β, interferon γ, tumor necrosis factor α, and the activation of nuclear factor kappa B [14]. Oxidative stress and inflammation may also be involved in the development of radiation-induced carotid stenosis, a late complication of RT [15]. Irradiation of pre-existing atherosclerotic lesions resulted in smaller, macrophage-rich plaques, with intraplaque hemorrhage and increased apoptosis [16].

Irradiation can injure the vasa vasora of the adventitia, reducing their blood flow and facilitating ischemic necrosis [17]. This results in loss of elastic tissue and muscle fibers which are then replaced by fibrosis. Moreover, a remarkable thickening of the endothelium and surrounding peri-adventitial fibrosis producing extrinsic compression is observed [18]. Intima-media thickness is a combined result of both fibrin accumulation in the medial and intimal layers and their gradual replacement with collagen [19].

All these events lead to thickening of the arterial wall, arterial stiffness, stenosis, plaque formation, thrombosis, and disturbance of blood flow or occlusion of the artery [10].

Pathology

It is generally accepted that capillaries and small arteries are the most commonly and severely affected part of the vascular tree, while large arteries are believed to suffer the least [20]. Nevertheless, some reports have suggested that clinically important damage to large arteries is more common than previously thought and is likely to become even more frequent as patients with cancer live longer [21].

Clinically and morphologically, the most frequent pattern of injury to large arteries is progressive stenosis and thrombosis [22]. Progressive stenosis of large arteries is an important delayed complication of RT, usually evolving slowly to produce ischemic effects years or even decades after radiation therapy has been completed [23]. This chronic injury has been recognized as a distinct clinical entity distinguished from spontaneous atherosclerosis in that it appears at a younger age, is typically limited to the irradiated area, and has a tendency for an unusual distribution. In addition, Russell et al. [24] showed a significant increase in the intimal thickness, the proteoglycan content, and the inflammatory cell content in the intima of the irradiated vessels when matched to unirradiated controls, confirming that there are qualitative and quantitative differences in radiation-induced vascular pathology compared to age-related atherosclerosis.

Histological examination of irradiated carotid arteries reveals atherosclerotic changes like those observed in spontaneous atherosclerosis [25], which occur in an accelerated manner [26]. However, in these cases, necrotizing vasculitis characterized by endothelial thickening and hypertrophy of the intima (Fig. 1a), fragmentation of the internal elastic lamellae (Fig. 1b), focal medial necrosis and edema, and inflammatory infiltration predominantly of the adventitia, media, and intima may be observed. In addition, significant changes were noted in the vasa vasora and peri-adventitial soft tissue, such as swelling and detachment of endothelial cells, subendothelial edema, hyaline, and scattered fibrinoid necrosis of the vessel walls.

Histological examination of endarterectomy samples of radiation-induced carotid plaques shows smaller lipid cores, less inflammation, and more fibrosis than carotid atherosclerotic lesions in unirradiated patients (Fig. 1c). Fokkema et al. [27] suggest that the plaque after RT may be less vulnerable, more stable, and less active than non-radiated atherosclerotic lesions. Conversely, sonographic studies showed a higher incidence of hypoechoic plaques after RT, suggesting an increased risk of stroke [19, 28–31].

Radiation-induced carotid stenosis

The prevalence of asymptomatic carotid artery stenosis (CAS) of 50% or greater ranges between 2 and 8% in the general population [32, 33]. In the USA, an estimated five per 1000 persons aged 50–60 years and approximately

Table 1 Incidence of carotid artery stenosis (CAS) in patients who underwent radiotherapy to the neck compared to controls

Author	No. cases	Grade of CAS	No. controls	Grade of CAS
Brown [40]	44	>50% 8 (18%)	44	>50% 3 (7%)
Moritz [21]	53	>50% 16 (30%)	38	>50% 2 (5.6%)
Carmody [41]	23	70–99% 5 (21.7%)	46	70–99% 2 (4%)
Cheng [42]	96	>30% 35 (37%)	96	>30% 8 (8%)
		>70% 15 (16%)		>70% 0 (0%)
		T. occl. 10 (10.4%)		T. occl. 0 (0%)
Chang [37]	193	>50% 38 (19.8%)	98	>50% 0 (0%)
		>70% 17 (8.9%)		>70% 0 (0%)
		T. occl. 4 (2.1%)		T. occl. 0 (0%)
Lam [43]	80	>50% 24 (30%)	58	>50% 0 (0%)
Dubec [44]	45	>50% 17 (38%)	348	>50% 13 (3.8%)
Cheng [45]	240	>30% 81 (33.8%)	108	>30% 7 (7.4%)
		>70% 28 (11.7%)		>70% 0 (0%)
Gujral [46]	87	>30% 40 (46%)	87	>30% 15 (17.2%)
		>50% 21 (24.1%)		>50% 8 (9.2)
		>70% 3 (3.5%)		>70% 0 (0%)

T. occl. total occlusion

10% of persons older than 80 years have CAS greater than 50% [34]. In a screening study of 1370 patients at risk for atherosclerosis due to the presence of one or more Framingham stroke risk factor (age, smoking history, hypertension, hyperlipidemia, diabetes mellitus, cardio/peripheral vascular disease), asymptomatic extracranial arterial disease was found in only 5.9% of them [35]. More specifically, the prevalence of significant carotid stenosis in a cohort of 1116 members was 7% in women and 9% in men, and a multivariate logistic regression model showed that age, cigarette smoking, systolic blood pressure, and cholesterol were independently related to carotid atherosclerosis. Alcohol consumption was also significant in men, but not in women [36].

CAS >50% incidence has been observed ranging from 18 to 38% in patients who underwent RT for head and neck cancer versus from 0 to 9.2% among the nonirradiated control group patients ([21, 34, 37–43]; Table 1). A systematic review and a meta-analysis carried out by Bashar et al. [44] showed that 105/596 (17.6%) of the patients receiving RT to the neck had significant CAS compared to 6/474 (1.3%) of the controls; furthermore, 89/454 (19.6%) of patients in the RT group had low-grade stenosis, whereas 21/316 (6.6%) had the same diagnosis in the control group, with a RR of 7.54. In addition, Chang et al. [34] have pointed out that in the irradiated group, for any CAS grade, the summation of plaque scores for the bilateral carotid systems and the frequency of occurrence of CAS in more than one artery segment (82.3%) was significantly higher in the irradiated patients than in the control group.

According to Lam et al. [45], the common and internal carotid arteries are most commonly involved (77.5%), followed by the external carotid artery (45%) in the RT group, whereas the control group showed a 21.6% involvement of the common and internal carotid arteries and 2.0% involvement of the external carotid arteries.

The distribution of stenoses is similar to that seen in atherosclerosis [34], with most of the stenoses being observed to involve all or a portion of the carotid bulb plus 2 cm of distal common carotid and proximal internal carotid [46]. These changes can appear as early as 1 to 2 years after RT [38, 41].

Bilateral disease has been reported to be significantly more prevalent in patients treated with RT than in controls, ranging from 11.8 to 69% and from 3 to 33%, respectively [6, 46–49].

An annualized rate of progression in general atherosclerosis from mild (<50%) to greater than 50% stenosis of 3.3% has been reported [50]. However, progression of CAS in irradiated arteries is significantly faster than in control arteries. Thus, according to Cheng et al. [26], the adjusted annualized progression rate for CAS less than 50 to 50% or greater was 15.4% in patients who had undergone head and neck RT, compared to 4.8% in control subjects. Dorth et al. [46] have reported actuarial rates of CAS at 2, 3, and 4 years after RT treatment of 4, 11, and 14%, respectively. Furthermore, Greco et al. [6] have shown that 62% of CAS in the RT group and 9% of controls' stenoses evolved to a worse grade 3 years after treatment.

Framingham risk factors and previous neck surgery in irradiated arteries individually are not associated with significant differences in disease progression, which suggests that radiation-induced CAS is not attributable to premature atherosclerosis alone, but is a more aggressive disease with a different biologic behavior [43].

Radiation-induced increase of the intima-media thickness (IMT)

Neck irradiation significantly increases the thickness of the carotid artery wall and the changes appear to be progressive. Changes in the IMT are the earliest visible change in the carotid wall and, in all likelihood, precede other measurable changes such as plaque development [7, 51].

A significant increase of IMT has been observed after a long post-treatment interval (5 to more than 10 years) in irradiated patients compared to nonirradiated cancer patients, ranging from 1.13 to 2.2 mm vs. 0.7 to 0.9 mm, respectively [13, 26, 32, 52].

The increase of the IMT can be detectable as early as at 6 weeks by ultrasound; even after this short time, mean IMT of the carotid artery increases significantly [31]. Muzaffar et al. [51] have reported an annual rate of increase in thickness 21 times higher than in age-matched and sex-matched control subjects from epidemiological studies (mean IMT of the CCA increases with age at a rate of 0.008 mm/year). They observed a significant increase in the carotid IMT 12 months after irradiation, which increased in a linear fashion in patients who had completed a 24-month follow-up. These changes were limited to the portions of the vessels exposed to radiation. Nevertheless, other authors failed to show an increase in carotid IMT in the first 2 years after RT, but long-term prospective studies (7 years after RT) demonstrated that mean increase of IMT in the irradiated carotid arteries was more than five times higher than the IMT increase in the nonirradiated arteries (0.11 and 0.02 mm, respectively) [53]. Radiation in the acute phase not only increases the IMT but also causes new plaque formation and changes in plaque size and increased echogenicity in old plaques present prior to RT, suggesting an inflammatory process rather than a purely atherosclerotic mechanism [31].

Previous published reports have many limitations, including small numbers, weaknesses inherent to retrospective series, lack of pre-RT ultrasonography, and confounding variables. By analyzing patients with head and neck cancer who did not receive RT as controls, it is possible to overcome many of these weaknesses of study design. Multiple logistic models can help to find independently related factors. However, in four prospective studies in which patients with head and neck cancer not treated with RT were used as controls, carotid artery stenosis and IMT progressed much more rapidly in irradiated carotid arteries compared with control arteries [6, 34, 37, 53]. Furthermore, in two systematic reviews including 34 and 8 studies, respectively, there was a consistent difference in CAS and IMT between irradiated and unirradiated carotid arteries [7, 44].

Factors influencing radiation-induced atherosclerosis

The effect of RT dose on the carotid artery in development of radiation-induced atherosclerosis is not clear. Radiation doses associated with the development of atherosclerosis range from 35 to 45 Gy (patients undergoing RT for lymphomas), to 50 to 80 Gy (patients undergoing RT for head and neck carcinomas). Significant subclinical vascular damage has been observed at total body irradiation doses of 10–12 Gy in long-term survivors of high-risk neuroblastomas [54]. Some authors have reported that CAS or mean carotid IMT increased as the radiation dose increased, suggesting a dose effect with regard to vessel wall changes and damage [7, 34, 55, 56]. Based on 272 arteries treated with IMRT, Dorth et al. [46] calculated that mean RT dose for the carotid bulb plus 2 cm and to the entire carotid were 57 and 50 Gy, respectively. Three-year carotid artery stenosis rates by artery were higher if the mean RT dose to the carotid bulb plus 2 cm fell above the median value ($\leq$ vs. >57 Gy, 5% vs. 10%) or within the highest quartile ($\leq$ vs. >67 Gy, 4% vs. 19%). In these patients, the hazard ratio for carotid artery stenosis was 1.4 for every 10-Gy increase in mean RT dose to the carotid bulb plus 2 cm [46]. Judicious use of IMRT may facilitate RT dose reduction to the carotid arteries for early-stage laryngeal cancer or when planning RT boost volumes to gross disease. Others did not find correlation of treatment variables with the risk of CAS or carotid IMT [1, 37, 46, 57]. On the other hand, fractionation schemes or stereotactic radiosurgery have not been correlated with carotid radiation-induced lesions.

However, there is a broad consensus that the latency period between radiation therapy and the occurrence of the carotid artery damage symptoms is generally long, one to two decades [34, 37, 41]. Thus, Cheng et al. [42] reported that the mean interval from irradiation for patients with CAS >70% was 150.3 months, compared with 67.7 months for those with CAS <70%. In addition, those having their neck irradiated more than 5 years previously were 8–15 times more likely to develop CAS relative to those with a post-RT time interval of less than 60 months [42, 58]. Different multivariate logistic regression analyses revealed that post-RT interval was the most significant independent predictor of severe CAS associated with RT [37, 39].

There is also general agreement that duration after RT is significantly associated with mean carotid IMT and increased linearly after adjustments for other risk factors [48]. Although some authors have observed an early IMT increase in irradiated patients (mean increase: 0.1 mm at 6 months and 0.25 mm at 12 months) [59], others only showed significant differences in IMT during a post-RT interval of more than 10 years [13].

The contribution of chemotherapy to developing abnormal scans has been evaluated. However, no significant differences were found in the IMT and CAS between those who had both RT and chemotherapy and those who only received RT [43, 57, 60].

There is controversy regarding the role of neck dissections in the development of CAS. Brown et al. [37] found a rate of 32% of CAS in patients who had undergone neck dissection compared with those who had not (4%). Nevertheless, other studies revealed that neck surgery was not a significant independent predictor of severe CAS associated with RT, even if a radical neck dissection was performed [21, 39].

The fact that age is a significant risk factor (patients aged > 60 years had a 9.5-times higher risk of developing CAS) suggests that a mechanism of accelerated atherosclerosis may augment the initial radiation injury [39]. Accordingly, Cheng et al. [42] have reported that patients most likely to have CAS of 70% or greater were older; those aged 60 years or more had a threefold increase in risk of developing a 70% CAS compared to those under age 60. Conversely, recent reports revealed that atherosclerotic response in the carotid artery is more severe in younger patients compared to the reference group [61]. On the other hand, when evaluated by multiple linear regression, advancing age was found to be significantly associated with higher IMT in post-RT patients [48, 57]. With each 10-year increase in age, IMT at follow-up was 0.05 mm thicker [53].

Male subjects had higher plaque scores and higher IMT compared with female subjects, and the plaque score increased as the time interval increased. It is possible that some hormonal influence might explain the results [34, 57].

Apart from the aforementioned factors, other cardiovascular risk factors have a limited effect. Some authors did not find significant associations between developing post-RT CAS and Framingham stroke risk factors [38, 40, 45]. Although individual cardiovascular risk factors have not been significantly associated with the presence of >50% CAS, the presence of multiple cardiovascular risk factors was significantly associated with higher prevalence of >50% CAS [57], exerting a summation effect with a similar relative risk of 2 to 3 per additional Framingham stroke risk factor [62]. Finally, some studies have revealed that smoking [39], platelet counts [48], hyperlipidemia [34], hypertension [50], and low-density lipoprotein cholesterol levels [63] were isolated significant independent predictors of severe CAS associated with RT.

Assessment of carotid atherosclerosis

Neck auscultation

Clinical examination of the patient should include neck auscultation for carotid bruits. A recent meta-analysis asserts that a carotid bruit increases the risk of TIA by four times and doubles the risk of stroke [64].

Evaluation of CAS

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) define CAS as mild (0–29%), moderate (30–69%), severe (70–99%) and totally occlusive. Stenosis of ≥50% is considered significant.

Color Doppler Ultrasound (CDUS) is the first choice for CAS screening [19]. The B mode provides information on plaque features and allows measurement of the thickness of the artery wall. The duplex mode (Doppler combined with B mode) is used to measure velocities in the carotid artery. The percent stenosis of the CCA and ICA are recorded by pulsed-wave spectral Doppler US using standard criteria based on peak systolic velocity and end diastolic velocity as well as ICA/CCA ratios. Increased velocities in the vessel indicate narrowing. The sonographic appearance of post-radiation plaque was reported to be more noncalcified with more hypoechogenic areas, and therefore more unstable [19, 31, 65].

Digital subtraction angiography has largely been replaced by non-invasive techniques [66]. CT angiography has the advantages of high spatial resolution, fast imaging, and ease of calcified plaque identification. MR angiography is considered to be a safe and convenient tool for detecting vessel stenosis. Several studies revealed that MR angiography has similar accuracy to CT angiography for evaluating CAS [66]. Radiation-induced carotid lesions are significantly longer than carotid lesions caused by atherosclerosis. The maximal stenosis of radiation-induced carotid lesions tended to be at the end of the stenotic area and within a wider range than the nonradiation-induced lesions, including in the proximal CCA [67].

Measurement of the IMT

CDUS enables the early detection of wall changes in the carotid artery. IMT consists of a double-line pattern on both walls of the CCA in a longitudinal image: the lumen–intima and media–adventitia interfaces (Fig. 2). IMT can be measured at the carotid bifurcation or ICA in a region free of plaques, preferably on the far wall of the CCA [68]. Increased IMT is an early imaging biomarker of atherosclerosis

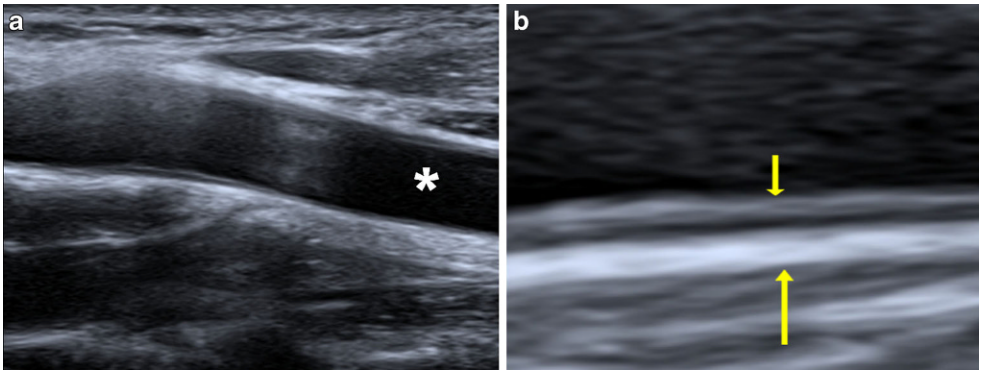

Fig. 2 **a** B mode ultrasound of a longitudinal plane of the common carotid artery (*). The measurement of intima-media thickness is carried out using a semi-automated edge-detection software. **b** Close-up of the far wall of the common carotid artery. *Short arrow* illustrates the intimal layer and *long arrow* illustrates the adventitial layer

rosis and predicts subsequent risk of death from myocardial infarction and stroke [7, 13, 19, 31, 43, 51, 65].

Arterial stiffness

Elastic modulus (Ep) and B stiffness index are two parameters that have been used to calculate arterial stiffness and are related to changes in both arterial pressure and diameter. RT-induced damage increases arterial stiffness and results in higher values of both parameters. According to Gujral et al. [69], Ep is a reliable measure of increased arterial stiffness in irradiated carotid arteries.

Speckle tracking is another ultrasound technique that offers the possibility to evaluate the vascular tissue motion and deformation during the cardiac cycle. According to Bjällmark [70], this method may be superior to the conventional measures of arterial stiffness.

The high incidence of radiation-induced CAS indicates the importance of regular screening with carotid duplex examinations and early antiplatelet prophylaxis in patients with significant stenosis (>50%) [34]. A focused screening of this high-risk population may be cost effective and medically beneficial in terms of risk factor modification and stroke prevention [13, 42, 43, 49, 65].

Neurological complications due to carotid damage

The most frequent clinical manifestations of radiation-induced carotid lesions include transient ischemic attacks, amaurosis fugax, paresis, sensory disturbances, aphasia, and dysarthria. Cognitive decline, caused by the injury to the temporal lobe, is also a significant but largely unrecognized sequela following irradiation for head and neck tumors, particularly cancer of the nasopharynx and paranasal sinuses [10, 71].

A significant number of irradiated patients (13–15%) have symptoms of cerebrovascular insufficiency compared to the controls [38–40]. According to Cheng et al. [39], two thirds of the patients with CAS of 70% or more had a stroke or transient ischemic attack after they underwent RT, with a relative risk of 38.5. On the other hand, 37.5% of patients with more than 50% diameter reduction of the carotid artery had a previous history of either transient ischemic attacks or stroke [40]. In comparison, a stroke incidence of 1 to 1.6% person-years found in an elderly community-based cohort has been reported [72].

Elevated stroke rates of 3.8 to 12% in cohorts of patients treated for head and neck tumors have been reported, with generally a minimum follow-up of 5 years after cervical irradiation [7, 53, 58, 61, 73–75]. Stroke risks in these head and neck cancer cohorts clearly exceeded risks in comparable healthy populations by two to nine times [7, 58, 61, 73, 74]. Furthermore, comparing the incidence rate of stroke in irradiated patients with an age-matched population, Wilbers et al. [53] revealed a six-fold increased risk (8.9 versus 1.5 per 1000 person-years). The age at which treatment with RT was received seems to influence the risk of stroke [61]. Thus, Dorresteijn et al. [74] noticed a relative risk of 9.8 in the group of patients younger than 50 years old during RT, compared with 4.5 in the group of patients older than 50 years during RT. The incidence rate of stroke in a cohort with a median age of 54 years was comparable with the incidence rate of persons in their eighth decade [53]. Similar results were observed in a cohort of 1094 irradiated nasopharyngeal cancer patients at the younger ages of 35–54 years compared to the general population [76].

Unexpectedly, patients who undergo surgery plus RT do not show an increased cerebrovascular risk or have even less, probably because they received lesser doses of RT [61, 73]. Furthermore, in a survey of 1413 elderly patients with early-stage glottic laryngeal cancer from the SEER database, Hong et al. [77] found a similar high burden of cerebrovascular events after surgical management or RT (48.7% vs. 56.5%, respectively), possibly because the small fields of RT for early glottis cancer do not cause a significant rate of carotid atherosclerosis.

A factor that significantly increases the relative risk of stroke is the IMT of the carotid artery. An increment of

0.55 mm in wall thickness is associated with an approximately 40% increased risk of stroke [78]. In a systematic review and meta-analysis on the data of 37,197 subjects, for an absolute carotid IMT difference of 0.1 mm, Lorenz et al. [79] reported that the stroke risk increased by 13 to 18%.

An increased IMT and prevalence of plaque in the ICA was noted in patients with nasopharyngeal cancer who had developed temporal lobe necrosis after RT compared with patients without temporal lobe necrosis, suggesting there is a correlation between CAS and temporal lobe necrosis [80]. The degree of CAS correlates with the incidence of ischemic stroke and transient ischemic attacks. Out of 41 patients with internal CAS > 70% and previous neck irradiation, 16 had had an ischemic stroke or a transient ischemic attack [81]. In observational studies, patients with CAS > 50% have been found to develop ipsilateral stroke at the rate of 1–3% per year. The risk was 3.2% per year for patients with CAS of 60–99% [10]. Nevertheless, the oncologist must keep in mind that the major risk for mortality of patients with new or recurrent head and neck cancer, CAS, and a history of neck irradiation is not having a stroke but to die of malignancy [81].

Management of carotid artery stenosis

Treatment is primarily directed toward the reduction of stroke risk. In 2011, the Society for Vascular Surgery published an updated guideline for treatment of carotid artery disease based on the severity of CAS. The committee recommends carotid endarterectomy (CEA) as the first-line treatment for most symptomatic patients with stenosis of 60 to 99%. The perioperative risk of stroke and death in asymptomatic patients with stenosis of 60–99% must be <3% to assure benefit for the patient. Asymptomatic patients at a high risk for intervention or with <3 years life expectancy should be considered for medical management as the first-line therapy [82].

Medical therapy

Treatment of hypertension, hypercholesterolemia, and efforts at smoking cessation are recommended to reduce stroke and overall cardiovascular events [7, 13, 65, 82]. Control of diabetes is important. Dobs et al. [83] showed that diabetes was associated with progression of IMT of the carotid artery.

An antiplatelet and lipid-lowering therapy with statins is indicated in patients with severe plaque formation and relevant carotid stenosis [65], and may be effective in preventing the progression of radiation-induced CAS [70, 84, 85]. Angiotensin-converting enzyme inhibitors have been found to reduce IMT in the carotid arteries and the risk of stroke in patients with CAS. However, the effect of these modifications on radiation-induced carotid artery atherosclerosis has not been specifically investigated [7].

Surgical therapy

The gold standard for treatment of carotid stenosis is endarterectomy [82]. However, a history of therapeutic irradiation to the neck complicates the management of carotid artery occlusive disease and is the reason why carotid angioplasty and stenting (CAST) has been proposed as the minimally invasive alternative for patients considered to be at "high risk." Previous neck radiation therapy is considered an anatomic risk factor, resulting in a "hostile" neck with involvement of the CCA, scarring of the skin, and soft tissue fibrosis [65, 70, 86, 87].

Carotid endarterectomy is an open procedure that basically consists of a vertical arteriotomy of the CCA and the ICA. The plaque is trimmed in the proximal end point in the distal CCA and continued up into the ICA until finding a normal intima (Fig. 3). Finally, the arteriotomy is repaired with a patch angioplasty. A variety of patch materials are available for use. Autologous material is especially recommended because of the presumed increased risk of infection in patients who have had external neck radiation therapy [86, 88, 89]. Cranial nerve injury has been reported to be one of the commonest complications of CEA, with an estimated incidence from 4.0 to 16.0% [90]. Tallarita et al. [91] have shown that open surgery in patients with prior radical neck dissections is more prone to wound complications (14% vs. 5%) and higher cranial nerve injury (28% vs. 9%) compared to those patients without prior neck dissections.

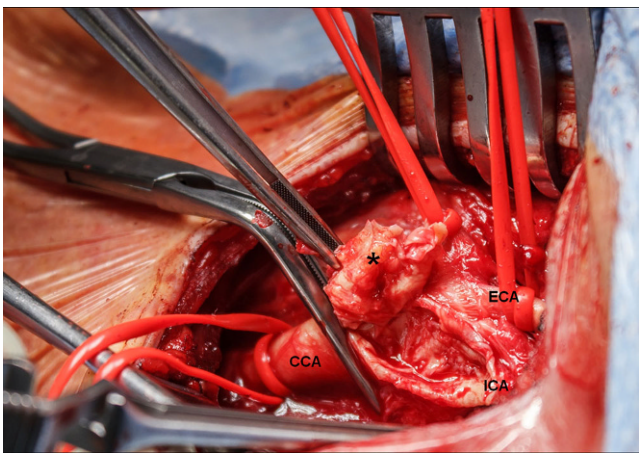

Fig. 3 Carotid endarterectomy. Common carotid artery, external carotid artery, and internal carotid artery have been isolated and clamped. Longitudinal arteriotomy has been made and the plaque (*) is pulling away from the artery

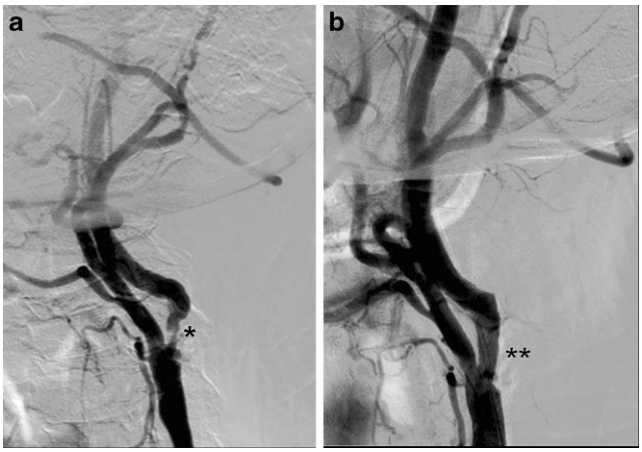

Fig. 4 Carotid angioplasty and stenting. **a** Preoperative intraarterial digital subtraction arteriography of carotid vessels showing a severe stenosis in the proximal internal carotid artery (*). **b** Post-stent (**) deployment arteriography demonstrating normal flow to internal carotid artery

Nevertheless, some studies have shown that open surgery is safe in selected patients who have had external neck radiation therapy. Leseche et al. [92] reported a series including 30 cases of CAS treated by open surgery, and no perioperative CNI, delayed wound healing problems, or infections were documented. Furthermore, Kashyap et al. [90] and Thalhammer et al. [65] have observed that patency rates, transient cranial nerve palsy, or wound infections were comparable to those of patients without previous radiotherapy.

Endovascular treatment with a carotid angioplasty and stenting (CAST) has been proposed as an attractive and minimally invasive alternative for radiation-induced CAS [84, 93]. The current approach for carotid artery stenting is transfemoral and is performed under local anesthesia. Percutaneous transfemoral access is established with a guide catheter, and selective carotid and cerebral angiography is performed to confirm the degree of stenosis. The lesion is traversed using an embolic protection device, pre-dilatated with an angioplasty balloon, and stented with a nitinol self-expandable stent. Completion cervical and cerebral angiography is obtained after retrieval of the embolic protection device (Fig. 4).

In the long-term results of the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) [94] including up to 10 years of follow-up, no significant differences in terms of periprocedural stroke, myocardial infarction, or ipsilateral stroke and subsequent death were found between 1262 patients who underwent CAST and 1240 who underwent open endarterectomy. Nevertheless, during the periprocedural period, there was a 37% higher risk of stroke in the stenting group than in the CEA group. Proximal embolic protection and mesh-covered stents may lower the rates of periprocedural stroke. Restenosis was infrequent and occurred in 12.2% of the patients treated with CAST and in 9.7% of those treated with CEA [94]. These findings underscored that CAST results are non-inferior to CEA results for patients with symptomatic severe CAS [95].

Comparative studies of CAST and endarterectomy for radio-induced CAS are rare. Absence of CNI or wound complications in patients with a history of RT are the main advantages of CAST [87, 91], but a history of head and neck RT seems to be associated with a higher rate of restenosis after CAST [96]. Huang et al. [97] reported a significantly higher intra-stent stenosis >50% in the RT group (15.8%) than in the nonirradiated group (1.9%). The restenosis rate with CAST is significantly higher for patients with previously cervical radiation therapy [88, 98]. Fokkema et al. [87] in a systematic review reported a rate of restenosis of 28% with CAST compared with 20% of endarterectomy in irradiated patients after 5 years. Tallarita et al. [91] showed inferior rates of restenosis (18%) after 3 years. These differences may depend on the cutoff point for restenosis and the duration of follow-up. It is well known that long-segment angioplasty and placement of longer or additional stents predisposes to intimal hyperplasia and promotes a higher recurrence rate [71].

Carotid endarterectomy or CAST have proved to be feasible revascularization techniques and have shown comparable results. CAST has an obvious advantage in treating radiation-induced CAS in patients with “hostile” neck anatomy, especially if there is a history of neck dissection. Although patients undergoing open endarterectomy have more temporary CNI, higher rates of restenosis are identified after CAST. Therefore, in patients with previous cervical radiation, the choice for revascularization therapy should be considered on an individual basis.

Conclusion

Radiation-induced atherosclerosis is a different and accelerated form of atherosclerosis, which implies a more aggressive disease with a different biologic behavior. The disease is characterized by a high rate of carotid artery stenosis compared to that observed in nonirradiated control group patients. Most patients with post-radiation CAS remain asymptomatic, but a significant number of them have symptoms of cerebrovascular insufficiency consistent with transient ischemic attacks, amaurosis fugax, or others. To prevent the risk of stroke, surveillance and imaging with ultrasonography should enable detection of severe stenosis and the selection of patients requiring medical treatment, carotid endarterectomy, angioplasty, or stenting.

Conflict of interest V. Fernández-Alvarez, F. López, C. Suárez, P. Strojan, A. Eisbruch, C.E. Silver, W.M. Mendenhall, J.A. Langendijk, A. Rinaldo, A.W.M. Lee, J.J. Beitler, R. Smee, J. Alvarez, and A. Ferlito declare that they have no competing interests.

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