Title

Considerations in screening for asymptomatic carotid artery stenosis in irradiated head and neck cancer survivors

Journal

Cancer, 131(1)

ISSN

1097-0142

Authors

Day, Andrew T
Mitchell, Dalia N
Eary, Rebecca L
et al.

Publication Date

2025

DOI

10.1002/cncr.35639

DOI: 10.1002/cncr.35639

EDITORIAL

Considerations in screening for asymptomatic carotid artery stenosis in irradiated head and neck cancer survivors

We applaud Carpenter et al. for conducting their study entitled, "Long-term risk of carotid stenosis and cerebrovascular disease after radiation therapy for head and neck cancer,"[1] which identified a clinically significant risk of asymptomatic carotid artery stenosis (aCAS) in patients who received head and neck radiotherapy. In this editorial, we discuss the study and examine its implications for carotid artery screening in this subpopulation.

STUDY REVIEW AND DISCUSSION

Carpenter et al. evaluated the incidence and predictors of aCAS in irradiated head and neck cancer (HNC) survivors using a single-institution, retrospective cohort study design.[1] The cohort consisted of 628 nonmetastatic HNC survivors treated with definitive or adjuvant radiotherapy between November 2000 and October 2020. Per institutional routine, empiric carotid artery Doppler ultrasound (DUS) screening was performed within 2 years of radiotherapy completion, followed by serial DUS every 3 years. The primary exposure was the absolute volume of carotid artery irradiated to a variety of different dose levels. The primary outcome was the cumulative incidence of aCAS.

The study findings were clinically meaningful. The 5- and 10-year cumulative incidences of aCAS were 17.0% and 29.6%, respectively. Among the 108 patients diagnosed with aCAS, 46% were already on "best medical therapy," 48% were started on medical therapy, between 15% and 22% underwent carotid endarterectomy and/or carotid artery stenting, and 25% progressed to symptomatic CAS. However, the specific nature of the medical interventions is uncertain.

Across all minimum radiation doses except ≥50 Gy, each additional cm^3 of irradiated carotid artery at each dose threshold was associated with a significantly increased adjusted risk of aCAS: "For a given carotid artery of 9-10 mL mean volume, each additional mL of carotid artery receiving ≥10 Gy appears to increase the risk of aCAS by 9%." Sensitivity analyses also yielded critical findings. Two key subsets of patients exhibited similarly high risk of aCAS as the entire cohort: patients without Framingham risk factors and patients without aCAS at the first DUS.

There are some notable limitations to the validity of the study. The median follow-up time was only 4.8 years. The study exhibited a few forms of selection bias, some of which were acknowledged or addressed by the authors in their sensitivity analyses and discussion. The authors appear to suggest that among the 45 patients who experienced cerebrovascular events, all were attributable to CAS, which is improbable.[2,3] Finally, although it would be useful to discover a novel dose–volume threshold above which aCAS is more likely to develop, multicollinearity between the dose–volume metrics limits this analysis. For example, the authors conclude that "doses as low as 10 Gy appear to confer the majority of RT-related CAS risk" and that "there may be no safe carotid artery minimum RT dose." However, the volume of the median carotid artery irradiated did not meaningfully differ across lower radiation doses, whereas it diminished significantly at higher doses (≥10 Gy: 6.84 mL, ≥40 Gy: 6.42 mL; ≥70 Gy: 0.23 mL, respectively). This is expected: elective nodal irradiation typically bathes the entire neck in 50 to 60 Gy. Therefore, the carotid V10 per mL finding may have been significant because the same 93% of the median carotid artery volume radiated with ≥10 Gy was also irradiated with ≥40 Gy.

Notwithstanding these limitations, this study exhibits unique strengths. The authors assembled the largest known observational cohort of HNC survivors screened for aCAS over a 20-year period and conducted important sensitivity analyses. We agree with their conclusion that irradiated HNC survivors may warrant designation as a group at high risk for aCAS, for whom screening is permitted by select societal guidelines. We explore these guideline positions here.

Guideline positions on aCAS screening

There is no consensus that subpopulations at high risk for aCAS should be screened. All national and societal organizations recommend against routine screening for aCAS in the general population because of the low prevalence of disease. Recommendations about screening for aCAS in high-risk subpopulations are variable. The United States Preventive Services Task Force "found no benefit in screening [higher-risk] populations."[4] The American Heart Association and the American Stroke Association declined to comment on selective screening in one guideline,[5] and weakly supported it in others (e.g., screening "might be considered" and "some consideration must be given to [screening]"). They and other organizations have applied heterogenous screening eligibility criteria[4–15] such as atherosclerotic disease at other sites, markers of atherosclerotic disease, risk factors for atherosclerosis, other vascular risk factors

(e.g., fibromuscular dysplasia), and history of vasotoxic chemotherapy or head and neck radiation (Table 1). The most commonly cited rationale for selective aCAS screening is based on older modeling data and cost-effectiveness analyses,[8,10] which have suggested that the benefits of aCAS screening outweigh the harms when the prevalence of aCAS in a subpopulation is ≥20%.[16–19]

Screening recommendations for aCAS in irradiated HNC survivors are also either omitted or similarly variable. Many recommendations do not address head and neck radiation as a risk factor (Table 1).[5,7–9] In their 2022 guideline, the Society for Vascular Surgery did not recommend screening this subpopulation "in the absence of other defined risk factors."[10] The authors state "the greatest incidence of carotid stenosis was noted ~15 years after radiation exposure, with ipsilateral rates of stenosis as high as 21.3%" and cite two studies published in 1999 and 2004. They also note "the optimal timing and frequency of [DUS-based] screening are undefined." Conversely, we are aware of nine organizations that at least weakly support screening irradiated HNC survivors (Table 1).[11–15] The European Society of Cardiology recommends DUS 5 years after head and neck radiation and every 5 to 10 years thereafter.[15] The International Cardio-Oncology Society offered the most specific rationale, citing the increased prevalence of CAS in the subpopulation and the opportunity to optimize cardiovascular risk factors in patients, including those without known cardiovascular disease.[12]

Re-considering screening for aCAS in irradiated HNC survivors

An updated evaluation of aCAS screening in irradiated HNC survivors is indicated because of the recent proliferation of relevant

TABLE 1 Definitions of groups at high risk for asymptomatic carotid artery stenosis who may qualify for screening according to select societal guidelines, consensus statements, and practice parameters.

Disease or risk factor category (with examples)	Definitions of groups at high-risk for asymptomatic carotid artery stenosis who may qualify for screening according to select guidelines, consensus statements, and practice parameters										
	Multisocietal					Vascular surgery, cardio-oncology			Other		
	14-S[a]	AHA,ASA[b]	ASN, SVIN	SCAI, SCI SLACI	ECS, EHA, ESTRO, ICOS	SVS	ESVS	ICOS	AHNS	AIUM	USPSTF
Atherosclerotic diseases or markers of atherosclerosis[c]	■	■	■	■		■				■	
Risk factors for atherosclerosis[d]	■	■	■	■		■	■				
Other vascular risk factors[e]										■	
History of head and neck radiation				■	■			■	■	■	
History of vasotoxic chemotherapy				■							

Note: Gray-shaded cells indicate the presence of one, or more than one, risk factors or diseases is needed to qualify as a high-risk group.

Abbreviations: ASN, American Society for Neuroimaging; CAD, coronary artery disease; CS, consensus statement; CSI, Cardiological Society of India; EHA, European Hematology Association; ESC, European Society of Cardiology; ESTRO, European Society for Therapeutic Radiology and Oncology; ESVS, European Society for Vascular Surgery; ICOS, International Cardio-Oncology Society; PAD, peripheral arterial disease; PP, practice parameter; SLACI, Sociedad Latino Americana de Cardiologia Intervencionista; SVIN, Society of Vascular and Interventional Neurology; USPSTF, United States Preventive Services Task Force.

[a]14-S is the 14-society guideline co-authored by the American Stroke Association, American College of Cardiology Foundation, American Heart Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and the Society for Vascular Surgery.

[b]The American Heart Association (AHA) and American Stroke Association (ASA) declined to comment on screening groups at high risk for aCAS in their 2014 guideline but weakly supported the practice in the 14-society guideline. In their 2024 guideline, the AHA and ASA report that "some consideration must be given to [screening] high-risk asymptomatic populations such as those with atherosclerotic risk factors." They also list other risk factors for aCAS, including hypertension, current tobacco use, coronary artery disease, or first-degree family member with a history of stroke.

[c]For example, PAD, CAD, occult cerebral infarction on imaging.

[d]For example, hypertension, hyperlipidemia, tobacco smoking.

[e]For example, Takayasu arteritis.

studies.[1,20,21] Next, we discuss select arguments for and against aCAS screening in this subpopulation.

Arguments against aCAS screening in irradiated HNC survivors

The case against screening for aCAS in irradiated HNC survivors is strong because the harms of screening may outweigh the benefits. These arguments hinge on the lack of knowledge about radiation-associated CAS, the uncertain benefit of screening, and the known harms of screening and treatment.

Our lack of knowledge about the epidemiology and biology of aCAS in irradiated HNC survivors constrains projections about the benefits or harms of screening. Relative to primary atherosclerotic CAS, radiation-associated CAS exhibits unique pathophysiology, patterns of vessel injury, stenosis locations (at and beyond the vessel bulb), stenotic segment lengths, and patterns of plaque echolucency on DUS.[22–25] These features may impact treatment decisions and treatment efficacy, yet have not been comprehensively characterized. Further, in this subpopulation, the proportion of strokes attributable to carotid artery disease, the proportion of patients with aCAS who progress to symptomatic CAS, the validity of DUS for screening, and the efficacy of aCAS treatment are poorly understood. The appropriate time to initiate screening is also unknown. One meta-analysis reports a 3-year cumulative incidence of 21% with a broad 95% confidence interval (9–36%), curbing certitude in this point estimate.[20]

The benefit of screening is unclear. First, there is no direct evidence that screening reduces morbidity or mortality. A randomized controlled trial comparing aCAS screening versus no screening in irradiated HNC survivors or any other population has not been performed.

Second, CAS might not account for many strokes in irradiated HNC survivors, limiting the potential benefit of screening. The current annual incidence of ipsilateral ischemic stroke in patients with aCAS is only 0.9%,[26] although this low rate does reflect improvements in aCAS treatment. Working backward, if 8% of irradiated HNC survivors experience an ischemic stroke after treatment[27] and if we presume that 7% to 18% are attributable to carotid disease, as is true in the general stroke population,[2] then perhaps only 0.6% to 1.4% of irradiated HNC survivors experience carotid-related ischemic strokes.

Third, the primary screening test for aCAS might not adequately detect disease in this subpopulation. In general adults, DUS validity is presumed to be compromised at the superior cervical carotid (at and below the skull base).[28] This area is radiated in patients with oropharyngeal and nasopharyngeal cancers and is therefore at higher risk for stenosis. Consequently, DUS validity might be lower in these groups.

Screening will also confer some harm through unnecessary testing and treatment. Many screened patients will receive false-positive results. Although the precise validity of DUS is uncertain and varies according to stenosis severity,[29,30] we apply the United States Preventive Services Task Force estimate for >60% CAS (sensitivity: 94%; specificity: 92%).[4] Assuming an aCAS prevalence rate of 20%, the positive predictive value of DUS is only 75%. Therefore, 25% of positively screened patients will receive false positive tests and thus undergo unnecessary additional testing and potentially, unnecessary noninvasive or invasive treatment.

Finally, screening will also confer harm through aCAS treatment. Carotid endarterectomy (CEA) and carotid artery stenting are procedures which improve carotid artery blood flow but result in an ~3% risk of perioperative stroke or death.[5,6,9,10] Also, the safety and efficacy of CEA and carotid artery stenting in irradiated HNC survivors is poorly understood.[31]

Arguments for screening

The case for aCAS screening in irradiated HNC survivors is also strong because the benefits of screening may outweigh the harms. Proponents may argue that a sufficiently high-risk group can be identified, evidence-based screening tests and treatments are available, the potential benefits of screening are far-reaching, and the harms may be limited.

The cumulative incidence of aCAS in irradiated HNC survivors likely eclipses the theoretical 20% high-risk designation threshold for aCAS screening. In addition to the present study's findings, recent meta-analyses of irradiated HNC survivors report aCAS prevalence rates of 25% to 26%.[20,21] Regardless of their radiation history, many HNC survivors may be eligible for aCAS screening because of their high prevalence rates of vascular disease or vascular risk factors.[1,32]

Evidence-based screening tests and treatments for aCAS are widely available. There are three screening tests for aCAS: DUS, the first-line screening test for CAS, computed tomography angiography, and magnetic resonance angiography.[33] Three evidence-based treatment paradigms improve net outcomes for general patients with clinically diagnosed aCAS. Best medical therapy (BMT) is the first-line standard of care. BMT involves a combination of lifestyle modifications (smoking cessation, healthy diet, physical activity, and strict glycemic control in diabetics) and pharmacologic therapy (antiplatelets, antihypertensives, and high-intensity statins).[9,10,34] Given their perioperative risks, CEA and carotid artery stenting are reserved for patients with severe aCAS and >3% risk of an adverse event on BMT.[5,35,36] The safety and efficacy of BMT, CEA, and carotid artery stenting have improved over time, requiring new trials to evaluate their comparative effectiveness in patients with severe aCAS (≥70%).[37]

Early detection and treatment of aCAS will confer benefit, directly and indirectly. There is some evidence that BMT directly reduces the risk of CAS progression and stroke in general adults[5,34,38,39] and is noninferior to CEA and carotid artery stenting, even among patients with ≥70% aCAS.[39] As noted previously, CEA and carotid artery stenting benefit select patients with severe aCAS.

Older modeling studies afford insight into the potential limited benefit of screening high-risk subpopulations for aCAS. For example, Whitty et al. modeled screening and CEA-based treatment in a subpopulation with a 20% prevalence rate of aCAS (>60%) using old trial data.[40,41] They estimated 6 to 11 net strokes were prevented over 5 years per 1000 people screened.[40] By applying updated trial data[39] and replacing CEA with BMT in this model, we might presume that more than 6 to 11 net strokes are prevented over 5 years per 1000 people screened.

Early detection may also indirectly confer benefit by facilitating optimization of other cardiovascular risk factors or diseases. Cardiovascular disease is one of the top three leading causes of death in HNC survivors,[42] and in a cohort of 38,857 US veterans with HNC, "47% had at least one uncontrolled vascular risk factor."[32] Among patients with newly diagnosed CAS and other cardiovascular disorders, initiation or reinforcement of BMT will broadly reduce cardiovascular risk, not just cerebrovascular risk.[43] For example, carotid artery disease is independently associated with coronary artery disease[44] and increased risk of myocardial infarction in patients without a history of cardiovascular disease,[45] although it is unclear whether this finding is also true in irradiated HNC survivors. Therefore, early detection of aCAS and initiation of BMT in irradiated HNC survivors might also reduce the risk of adverse cardiac events in these patients.

Finally, the harms of treatment with BMT are low. More common or severe potential harms include gastric toxicity or hemorrhage from antiplatelet therapy[46] and muscle injury or hepatic dysfunction from statins.[47]

CONCLUSIONS

There is insufficient evidence to justify routinely screening irradiated HNC survivors for aCAS: the benefits of screening may outweigh the harms, or vice versa. Amid this uncertainty, national organizations and societies have variably staked out unique positions on screening for aCAS in high-risk populations, including irradiated HNC survivors. Detractors cite the first set of arguments, whereas proponents might cite the latter set, as well as evidence for screening other irradiated cardiovascular structures (e.g., the heart). Given these heterogeneous national and societal positions, clinicians have "cover" to either screen or decline to screen irradiated HNC survivors for aCAS. Shared decision-making with patients is strongly encouraged when addressing this issue.

This profound uncertainty and potential for benefit provides a strong basis for the development of a national screening trial, though more evidence is needed to optimize the study design. Basic questions about the epidemiology of aCAS and the potential benefits and harms of screening need to be answered. We encourage screening programs to account for data about CAS risk obtained through routine cancer surveillance imaging. Given the potential sweeping cardiovascular and oncologic benefits of BMT (e.g., smoking cessation) for HNC survivors with CAS, we also encourage inclusion of broad cardiovascular outcomes and survival as secondary trial endpoints.

In conclusion, we thoroughly congratulate the authors for contouring more than 1200 carotid arteries and substructures and making this significant contribution to the literature. These data, in combination with other studies, are persuasive that irradiated HNC survivors are at high-risk for aCAS. In addition to "unlocking" a discussion about the secondary prevention of aCAS, these data also facilitate exploration of oncologic treatment and survivorship care approaches that identify, mitigate, and manage cardiovascular risk in irradiated HNC survivors.

KEYWORDS

carotid artery stenosis, head and neck cancer, prevention, radiation, screening, survivors, survivorship care

ACKNOWLEDGMENTS

E.Y. reports research funding from CSL Behring, Boehringer Ingelheim and Eli and Lily Company, Bristol Myers Squibb, Amgen; consulting fees from Xencor, Edwards Lifesciences; and speaker honoraria: Zoll Medical, NCCN. A.D. reports research funding from the National Cancer Institute and Cancer Prevention Research Institute of Texas, as well as consulting fees from Regeneron.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

FUNDING INFORMATION

CSL Behring, Boehringer Ingelheim and Eli and Lilly Company, Bristol Myers Squibb, Amgen

Andrew T. Day MD, MPH[1]
Dalia N. Mitchell BS, BA[1]
Rebecca L. Eary DO, MPH[2]
Erica Jones MD, MPH[3]
Marco C. Pinho MD[4]
Vlad G. Zaha MD, PhD, MBA[5]
Eric H. Yang MD[6]
David J. Sher MD, MPH[7]

[1]*Department of Otolaryngology-Head and Neck Surgery, UT Southwestern Medical Center, Dallas, Texas, USA*
[2]*Department of Family and Community Medicine, UT Southwestern Medical Center, Dallas, Texas, USA*
[3]*Department of Neurology, UT Southwestern Medical Center, Dallas, Texas, USA*
[4]*Department of Radiology, UT Southwestern Medical Center, Dallas, Texas, USA*
[5]*Department of Cardiology, UT Southwestern Medical Center, Dallas, Texas, USA*
[6]*UCLA Cardio-Oncology Program, Division of Cardiology, Department of Medicine, University of California – Los Angeles, Los Angeles, California, USA*
[7]*Department of Radiation Oncology, UT Southwestern Medical Center, Dallas, Texas, USA*

Correspondence
Andrew T. Day, Department of Otolaryngology – Head and Neck Surgery, UT Southwestern Medical Center, 2001 Inwood Road, Dallas, TX, USA.
Email: Andrew.day@utsouthwestern.edu
Andrew T. Day and Dalia N. Mitchell should be considered joint first authors.

DATA AVAILABILITY STATEMENT

Data sharing not applicable – no new data generated, or the article describes entirely theoretical research.

ORCID

Andrew T. Day https://orcid.org/0000-0001-7187-4125
David J. Sher https://orcid.org/0000-0003-3943-7480

REFERENCES

1. Carpenter DJ, Patel P, Niedzwiecki D, et al. Long-term risk of carotid stenosis and cerebrovascular disease after radiation therapy for head and neck cancer. *Cancer*. 2023. doi:10.1002/cncr.35089
2. Barrett KM, Brott TG. Stroke caused by extracranial disease. *Circ Res*. 2017;120(3):496-501. doi:10.1161/circresaha.117.310138
3. Inzitari D, Eliasziw M, Gates P, et al. The causes and risk of stroke in patients with asymptomatic internal-carotid-artery stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med*. 2000;342(23):1693-1700.
4. Krist AH, Davidson KW, Mangione CM, et al. Screening for asymptomatic carotid artery stenosis: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2021;325(5):476-481. doi:10.1001/jama.2020.26988
5. Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the primary prevention of stroke. *Stroke*. 2014;45(12):3754-3832. doi:10.1161/str.0000000000000046
6. Brott TG, Halperin JL, Abbara S, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease. *Stroke*. 2011;42(8):e464-e540. doi:10.1161/cir.0b013e31820d8c98
7. Bushnell C, Kernan WN, Sharrief AZ, et al. 2024 Guideline for the primary prevention of stroke: a guideline from the American Heart Association/American Stroke Association. *Stroke*. 2024. doi:10.1161/STR.0000000000000475
8. Qureshi AI, Alexandrov AV, Tegeler CH, Hobson RW, 2nd, Dennis Baker J, Hopkins LN. Guidelines for screening of extracranial carotid artery disease: a statement for healthcare professionals from the multidisciplinary practice guidelines committee of the American Society of Neuroimaging; cosponsored by the Society of Vascular and Interventional Neurology. *J Neuroimaging*. 2007;17(1):19-47. doi:10.1111/j.1552-6569.2006.00085.x
9. Naylor AR, Ricco JB, de Borst GJ, et al. Editor's choice - management of atherosclerotic carotid and vertebral artery disease: 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg*. 2018;55(1):3-81. doi:10.1016/j.ejvs.2017.06.021
10. AbuRahma AF, Avgerinos ED, Chang RW, et al. Society for Vascular Surgery clinical practice guidelines for management of extracranial cerebrovascular disease. *J Vasc Surg*. 2022;75(1s):4s-22s. doi:10.1016/j.jvs.2021.04.073
11. Iliescu CA, Grines CL, Herrmann J, et al. SCAI Expert consensus statement: Evaluation, management, and special considerations of cardio-oncology patients in the cardiac catheterization laboratory (endorsed by the cardiological society of India, and sociedad Latino Americana de Cardiologıa intervencionista). *Catheter Cardiovasc Interv*. 2016;87(5):E202-E223. doi:10.1002/ccd.26375
12. Mitchell JD, Cehic DA, Morgia M, et al. Cardiovascular manifestations from therapeutic radiation: a multidisciplinary expert consensus statement from the International Cardio-Oncology Society. *JACC CardioOncol*. 2021;3(3):360-380. doi:10.1016/j.jaccao.2021.06.003
13. Goyal N, Day A, Epstein J, et al. Head and neck cancer survivorship consensus statement from the American Head and Neck Society. *Laryngoscope Investig Otolaryngol*. 2022;7(1):70-92. doi:10.1002/lio2.702
14. AIUM practice parameter for the performance of an ultrasound examination of the extracranial cerebrovascular system. *J Ultrasound Med*. 2016;35(9):1-11.
15. Lyon AR, López-Fernández T, Couch LS, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J*. 2022;43(41):4229-4361. doi:10.1093/eurheartj/ehac244
16. Qureshi AI, Janardhan V, Bennett SE, Luft AR, Hopkins LN, Guterman LR. Who should be screened for asymptomatic carotid artery stenosis? Experience from the Western New York Stroke Screening Program. *J Neuroimaging*. 2001;11(2):105-111. doi:10.1111/j.1552-6569.2001.tb00019.x
17. Derdeyn CP, Powers WJ. Cost-effectiveness of screening for asymptomatic carotid atherosclerotic disease. *Stroke*. 1996;27(11):1944-1950. doi:10.1161/01.str.27.11.1944
18. Jacobowitz GR, Rockman CB, Gagne PJ, et al. A model for predicting occult carotid artery stenosis: screening is justified in a selected population. *J Vasc Surg*. 2003;38(4):705-709. doi:10.1016/s0741-5214(03)00730-4
19. Obuchowski NA, Modic MT, Magdinec M, Masaryk TJ. Assessment of the efficacy of noninvasive screening for patients with asymptomatic neck bruits. *Stroke*. 1997;28(7):1330-1339. doi:10.1161/01.str.28.7.1330
20. Texakalidis P, Giannopoulos S, Tsouknidas I, et al. Prevalence of carotid stenosis following radiotherapy for head and neck cancer: a systematic review and meta-analysis. *Head Neck*. 2020;42(5):1077-1088. doi:10.1002/hed.26102
21. Lin PY, Cheng PC, Hsu WL, et al. Risk of CVD following radiotherapy for head and neck cancer: an updated systematic review and meta-analysis. *Front Oncol*. 2022;12:820808. doi:10.3389/fonc.2022.820808
22. Zheng Z, Zhao Q, Wei J, et al. Medical prevention and treatment of radiation-induced carotid injury. *Biomed Pharmacother*. 2020;131:110664. doi:10.1016/j.biopha.2020.110664
23. Lam WW, Liu KH, Leung SF, et al. Sonographic characterisation of radiation-induced carotid artery stenosis. *Cerebrovasc Dis*. 2002;13(3):168-173. doi:10.1159/000047771
24. Liao W, Zheng Y, Bi S, et al. Carotid stenosis prevalence after radiotherapy in nasopharyngeal carcinoma: a meta-analysis. *Radiother Oncol*. 2019;133:167-175. doi:10.1016/j.radonc.2018.11.013
25. Liang H, Zhou Y, Xiong W, Zheng S. Impact of radiotherapy for nasopharyngeal carcinoma on carotid stenosis risk: a meta-analysis. *Braz J Otorhinolaryngol*. 2022;88(Suppl 4):S98-s107. doi:10.1016/j.bjorl.2022.03.001
26. Howard DPJ, Gaziano L, Rothwell PM. Risk of stroke in relation to degree of asymptomatic carotid stenosis: a population-based cohort study, systematic review, and meta-analysis. *Lancet Neurol*. 2021;20(3):193-202. doi:10.1016/s1474-4422(20)30484-1
27. Arthurs E, Hanna TP, Zaza K, Peng Y, Hall SF. Stroke after radiation therapy for head and neck cancer: what is the risk? *Int J Radiat Oncol Biol Phys*. 2016;96(3):589-596. doi:10.1016/j.ijrobp.2016.07.007

28. Gaitini D, Soudack M. Diagnosing carotid stenosis by Doppler sonography: state of the art. *J Ultrasound Med*. 2005;24(8):1127-1136. doi:10.7863/jum.2005.24.8.1127
29. Jahromi AS, Cinà CS, Liu Y, Clase CM. Sensitivity and specificity of color duplex ultrasound measurement in the estimation of internal carotid artery stenosis: a systematic review and meta-analysis. *J Vasc Surg*. 2005;41(6):962-972. doi:10.1016/j.jvs.2005.02.044
30. Cassola N, Baptista-Silva JC, Nakano LC, et al. Duplex ultrasound for diagnosing symptomatic carotid stenosis in the extracranial segments. *Cochrane Database Syst Rev*. 2022;7(7):Cd013172. doi:10.1002/14651858.cd013172.pub2
31. Tzoumas A, Xenos D, Giannopoulos S, et al. Revascularization approaches in patients with radiation-induced carotid stenosis: an updated systematic review and meta-analysis. *Kardiol Pol*. 2021;79(6):645-653. doi:10.33963/kp.15956
32. Sun L, Brody R, Candelieri D, et al. Risk of cardiovascular events among patients with head and neck cancer. *JAMA Otolaryngol Head Neck Surg*. 2023;149(8):717-725. doi:10.1001/jamaoto.2023.1342
33. Wardlaw JM, Chappell FM, Stevenson M, et al. Accurate, practical and cost-effective assessment of carotid stenosis in the UK. *Health Technol Assess*. 2006;10(30):1-182. iii-iv, ix-x. doi:10.3310/hta10300
34. Hackam DG. Optimal medical management of asymptomatic carotid stenosis. *Stroke*. 2021;52(6):2191-2198. doi:10.1161/strokeaha.120.033994
35. Rothwell PM, Goldstein LB. Carotid endarterectomy for asymptomatic carotid stenosis: asymptomatic carotid surgery trial. *Stroke*. 2004;35(10):2425-2427. doi:10.1161/01.str.0000141706.50170.a7
36. Roffi M, Kulcsár Z, Carrera E, Cremonesi A. Carotid artery stenting. *Heart*. 2016;102(13):1059-1069. doi:10.1136/heartjnl-2015-307638
37. Howard VJ, Meschia JF, Lal BK, et al. Carotid revascularization and medical management for asymptomatic carotid stenosis: protocol of the CREST-2 clinical trials. *Int J Stroke*. 2017;12(7):770-778. doi:10.1177/1747493017706238
38. Shah Z, Masoomi R, Thapa R, et al. Optimal medical management reduces risk of disease progression and ischemic events in asymptomatic carotid stenosis patients: a long-term follow-up study. *Cerebrovasc Dis*. 2017;44(3-4):150-159. doi:10.1159/000477501
39. Reiff T, Eckstein HH, Mansmann U, et al. Carotid endarterectomy or stenting or best medical treatment alone for moderate-to-severe asymptomatic carotid artery stenosis: 5-year results of a multicentre, randomised controlled trial. *Lancet Neurol*. 2022;21(10):877-888. doi:10.1016/s1474-4422(22)00290-3
40. Whitty CJ, Sudlow CL, Warlow CP. Investigating individual subjects and screening populations for asymptomatic carotid stenosis can be harmful. *J Neurol Neurosurg Psychiatry*. 1998;64(5):619-623. doi:10.1136/jnnp.64.5.619
41. Halliday A, Mansfield A, Marro J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet*. 2004;363(9420):1491-1502.
42. Simpson MC, Massa ST, Boakye EA, et al. Primary cancer vs competing causes of death in survivors of head and neck cancer. *JAMA Oncol*. 2018;4(2):257-259. doi:10.1001/jamaoncol.2017.4478
43. Bytyçi I, Shenouda R, Wester P, Henein MY. Carotid atherosclerosis in predicting coronary artery disease: a systematic review and meta-analysis. *Arterioscler Thromb Vasc Biol*. 2021;41(4):e224-e237. doi:10.1161/atvbaha.120.315747
44. Chowdhury R, Khan H, Heydon E, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. *Eur Heart J*. 2013;34(38):2940-2948. doi:10.1093/eurheartj/eht295
45. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK, Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *N Engl J Med*. 1999;340(1):14-22.
46. Kalyanasundaram A, Lincoff AM. Managing adverse effects and drug-drug interactions of antiplatelet agents. *Nat Rev Cardiol*. 2011;8(10):592-600. doi:10.1038/nrcardio.2011.128
47. Kashani A, Phillips CO, Foody JM, et al. Risks associated with statin therapy: a systematic overview of randomized clinical trials. *Circulation*. 2006;114(25):2788-2797. doi:10.1161/circulationaha.106.624890