Ultrasound Evaluation of Carotid Artery Intima-Media Thickness: Effective Early Marker of Carotid Artery Disease in Adult Head and Neck Cancer Patients After Neck Radiation?

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Abstract

Radiation is a recommended front-line treatment for many adult head and neck cancer (HNC) patients. Early identification of radiation-associated carotid artery disease (CAD), a well-known phenomenon, can minimize long-term sequelae. This integrative literature review assesses the use of ultrasound measured carotid artery intima-media thickness (IMT) as an early marker of CAD in adult HNC patients after neck radiation. A search of PubMed and Scopus databases in December 2020 yielded 475 unique articles published between January 2011 and December 2020, of which eight met inclusion criteria. Carotid IMT, measured by ultrasound, was significantly increased after neck radiation in all reviewed publications. Ultrasound was able to detect IMT measurements exceeding or at risk of exceeding pathologic IMT, indicating higher risk for future cardiovascular events. Findings suggest that radiation-associated carotid IMT increase occurs early and persists for years. Ultrasound adequately detects post-radiation carotid IMT changes and is a reliable early marker for radiation-associated CAD. Initiation of ultrasound screening should be considered prior to neck radiation for a baseline and at 1 year post treatment to optimize medical management.

Radiation, either alone or with chemotherapy, is the recommended front-line treatment for many adult head and neck cancer (HNC) patients and has improved overall survival (National Comprehensive Cancer Network, 2021; Pulte & Brenner, 2010). Critical vascular structures, including the carotid artery, are often within the radiation treatment field due to their proximity to cervical chain lymph nodes, a common site of metastasis. Although the exact mechanism of radiation-induced large vessel injury is not well defined, radiation exposure is believed to cause endothelial damage, leading to intimal layer proliferation, necrosis of the media layer, periadventitial fibrosis, and accelerated atherosclerotic progression (Bashar et al., 2014; Fernández-Alvarez et al., 2018; Gujral et al., 2014; Venkatesulu et al., 2018; Xu & Cao, 2014).

The 2020 National Comprehensive Cancer Network (NCCN) Survivorship Guideline update highlights cardiovascular disease as "the most common cause of noncancer death for survivors of most cancer types" and encourages development of new strategies to improve cardiovascular outcomes in survivors (Denlinger et al., 2020; Zaorsky et al., 2017). The relationship between prior neck radiation, early development of carotid atherosclerosis, and increased risk for ischemic stroke is widely accepted. In a systematic review, Texakalidis and colleagues (2020) noted the yearly incidence of carotid stenosis of > 50% increased annually for the first 3 years following radiation, rising from 4% after 12 months to 21% after 36 months. Greco and colleagues (2012) reported a four-fold greater risk of progression to a higher stenosis grade in patients after neck radiation when compared with a control group receiving surgery alone. Prior neck radiation is also associated with substantially increased risk of ischemic stroke or transient ischemic attack, with one study demonstrating age of onset up to 10 years earlier than in matched controls (Arthurs et al., 2016; Chen et al., 2019; Huang, et al., 2019). The NCCN Survivorship Guidelines, along with multiple other head and neck cancer and radiation survivorship guidelines, note carotid stenosis as a well-known late effect of neck radiation, but stop short of making specific screening recommendations (Chen et al., 2016; Cohen et al., 2016; Werning, n.d.).

Ultrasound evaluation of carotid artery intima-media thickness (IMT) is established as a marker of carotid artery disease (CAD) and stroke risk in multiple populations, as well as a tool to evaluate the effectiveness of cardiovascular interventions (Intersocietal Accreditation Commission [IAC], 2021; Willeit et al., 2020). In a meta-analysis of 16 studies with 36,984 participants, Lorenz and colleagues (2007) noted that an absolute carotid IMT increase of 0.1 mm increases future risk of myocardial infarction by 10% to 15% and stroke by 13% to 18%, with a 1.18 relative risk of stroke. Den Ruijter and colleagues (2012) showed that the addition of common carotid IMT measurements improved the Framingham Risk Score 10-year risk prediction for first-time atherosclerotic cardiovascular disease events and particularly for participants in the intermediate risk category, although the authors cited minimal clinical utility with this finding. In The Multi-Ethnic Study of Atherosclerosis, Polak and colleagues (2017) later created normative values for carotid IMT based on age, sex, and race/ethnicity and assigned an IMT percentile to each patient. When added to the Framingham Risk Score, IMT percentile significantly improved event prediction and net risk group reclassification (Polak et al., 2017).

The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) and IAC acknowledge the utility of carotid IMT measurements; however, neither currently recommends routine ultrasound IMT screening in the asymptomatic general population due to limitations in available data, low CAD prevalence in this population, or unclear clinical benefit (Brott et al., 2011; Goff et al., 2014; IAC, 2021). Alternatively, the European Society of Cardiology position paper for primary and secondary cardiovascular disease prevention endorses ultrasound evaluation of carotid IMT and carotid plaque with a level IIa/A recommendation (Vlachopoulos et al., 2015).

High incidence of CAD and involvement of the intima-media layers in the accelerated development of radiation-associated CAD provides a unique opportunity for studying ultrasound carotid IMT measurements in this adult HNC population after radiation (Carpenter et al., 2018). In a 2014 systematic review, which included 14 studies from 1991 to 2010 measuring carotid IMT changes after neck radiation, Gujral and colleagues (2014) noted an overall post-treatment carotid IMT increase of 18% to 40% for all cancer types, and up to 36% in HNC patients.

This review synthesizes current evidence evaluating the use and timing of carotid IMT ultrasound measurements as an early marker of CAD in adult HNC patients after neck radiation.

Establishing evidence-based guidelines for early identification of radiation-associated cardiovascular toxicities is central to minimizing long-term sequelae. Ultrasound assessment was chosen as the focus of this review due to its relative accessibility, affordability, and reliability with the use of standardized methodology and edge-detection software.

METHODS

A literature search of English language articles published between January 2011 and December 2020 was conducted on PubMed and Scopus databases in December 2020. The time frame extends findings from the Gujral and colleagues (2014) systematic review, which included 14 studies from 1991 to 2010, and reflects the evolution of radiation treatment modalities in the past decade. Search terms included (head OR neck OR cervical) AND (radiation* OR irradiation OR radiotherapy) AND (stenosis OR restenosis OR atherosclerosis OR intima-media OR "intima media") in the title or abstract. The terms "stent" and "revascularization" in the title were excluded because treatment options are not the focus of this review.

The search generated 475 unique articles. Titles and abstracts were individually reviewed for all articles, and those meeting inclusion criteria were selected for full-text review. Both retrospective and prospective studies conducted after 2010 that utilized ultrasound for evaluation of carotid IMT in adult HNC patients treated with neck radiation were included. Case studies and case reports were excluded. Publications were excluded if they were a duplicate, had an irrelevant title, had differing outcomes of interest, reported mid-study results when a final study was already published, or used other radiographic modalities to evaluate carotid arteries, such as MRI or CT scan. Eight original research articles met inclusion criteria and were evaluated in this study (Figure 1).

RESULTS

A total of eight articles were reviewed, including four prospective studies (Faruolo et al., 2013; Pereira Lima et al., 2011; Toprak et al., 2012; Wilbers et al., 2014) and four retrospective studies (Gujral et al., 2016; Strüder et al., 2020; Yeh et al., 2019; Yuan et al., 2017; Table 1). Although these studies varied in design and included differing secondary endpoints, all reported post-radiation carotid IMT values and compared them to an external control population, an internal contralateral control, or internal control with measurements over time.

Two variables emerged that address the effectiveness of ultrasound as an early marker of carotid atherosclerosis in adult HNC patients. The first evaluated whether there is an increase in post-radiation carotid IMT, which can be measured by ultrasound to serve as an early marker for CAD. The second assessed whether data supports a specific timepoint for initiating post-radiation ultrasound screenings. Results are organized by these variables.

Ultrasound Measured Radiation-Associated Increase in Carotid IMT

All eight studies showed statistically significant increases in carotid IMT after neck radiation (Table 2). Faruolo and colleagues (2013), Pereira Lima and colleagues (2011), and Toprak and colleagues (2012) each conducted prospective cohort studies following adult HNC patients over short post-radiation follow-up intervals, whereas Wilbers and colleagues (2014) evaluated their subjects at mean 6.7 years (range 4.5–9.6 years) post treatment.

In the shortest interval follow-up, Toprak and colleagues (2012) evaluated bilateral carotid arteries in 50 HNC patients immediately before and on the final day of a 6-week course of bilateral neck radiation, with total radiation dose < 6,000 centigray (cGy) in 18 patients (36%) and > 6,000 cGy in 32 patients (64%). A significant increase in carotid IMT (0.68 ± 0.11 mm vs. 0.87 ± 0.16 mm, $p < .001$) was found, although no statistical significance was noted when comparing IMT to gender, cardiovascular risk factors, adjuvant chemotherapy, surgery, or radiation dose. Additionally, the researchers noted development of new, soft, hypoechoic plaques and changes in size and echogenicity to preexisting plaques during the 6-week study period, suggesting that radiation induces inflammatory changes in this population earlier than previously thought.

Faruolo and colleagues (2013) prospectively assessed 50 HNC patients before neck radiation with a median dose of 62 gray (Gy, range 50–70

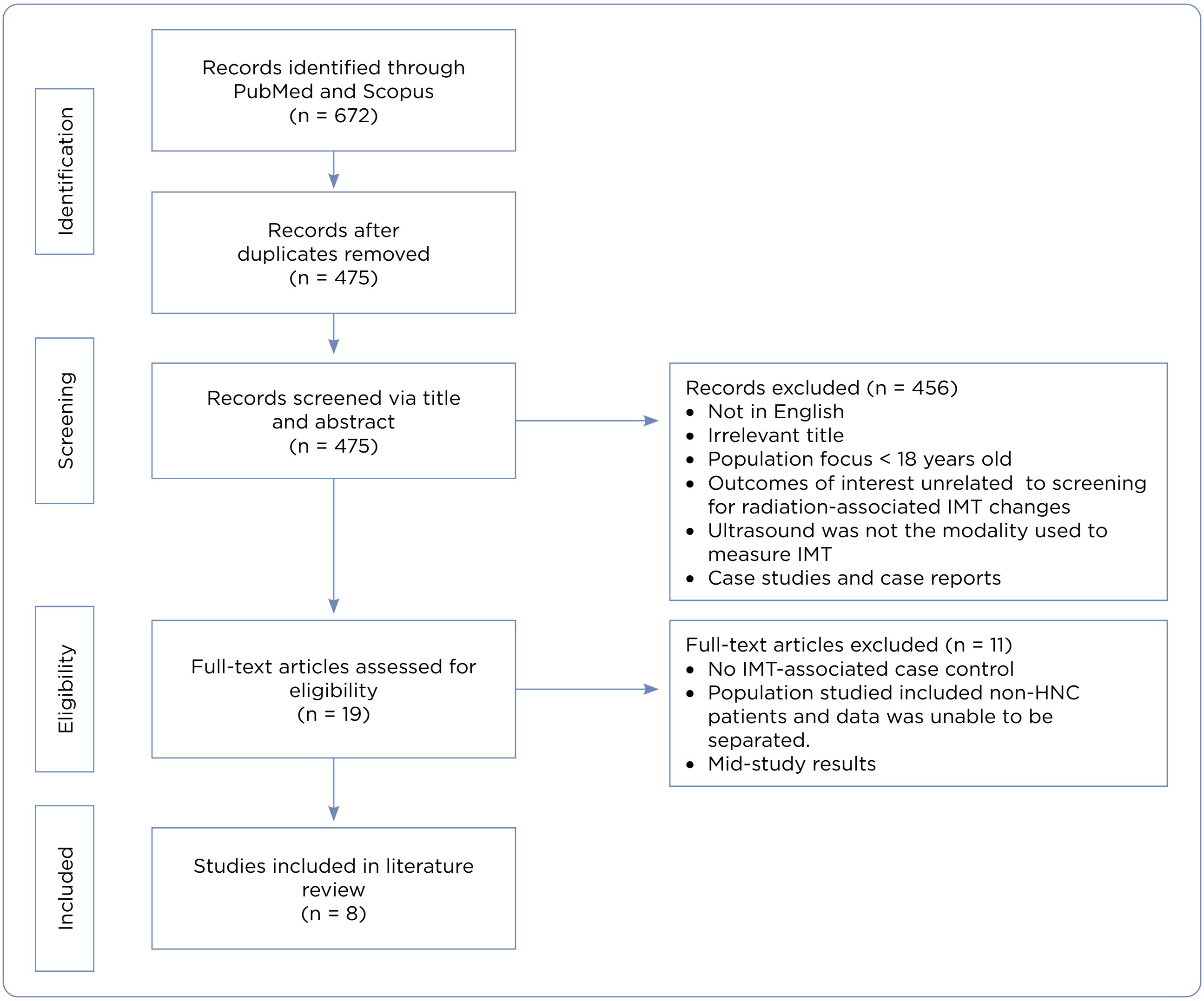

Figure 1. PRISMA diagram. Adapted from Moher et al. (2009).

Gy) and at 6-, 12-, and 18-month follow-ups. They reported significant IMT increase at 6 months post radiation without corresponding carotid lumen narrowing (n = 50, 0.9 to 1.02 mm, p = .0001) and significant IMT increase with corresponding carotid lumen narrowing at 12 and 18 months post therapy (n = 15, 0.81 to 1.06 mm, p = 0.001; and n = 6, 0.8 to 1.1 mm, p = .01, respectively). Their analysis was limited by significant cohort attrition with each subsequent follow-up.

Pereira Lima and colleagues (2011) prospectively compared local vs. distant radiation effects on carotid IMT in 19 patients receiving bilateral neck radiation for various HNC (M = 66 Gy ± 6) and in 24 patients receiving radiation for prostate cancer (M = 70 Gy ± 3). In early post-radiation follow-up of less than 90 days, carotid IMT was significantly increased in the HNC group compared with the prostate cancer control (r = 0.62, p = 0.027). However, carotid IMT increase measured 6 months after the early follow-up measurement was not statistically significant in either group. This lends evidence to support early and local radiation-associated vascular injury and decreases suspicion that distant prostate radiation impacts changes to the carotid IMT.

In a multicenter prospective cohort study, Wilbers and colleagues (2014) performed ultrasound carotid IMT evaluations in 48 adult patients without significant cardiovascular history who received neck radiation for primary HNC (common carotid artery, M = 58 Gy ± 12, range 30–70 Gy;

Table 1. Evidence Summary

Author (year)	Sample	Control	Radiation dose	Time since radiation	Control IMT M ± SD (mm)	Treatment IMT M ± SD (mm)	*p* value
Faruolo et al. (2013)	HNC	Internal Self over time	Mdn = 62 Gy (50–70 Gy)		Pre-RT:	Post-RT:	
	n = 50			6 months	0.9 ± 0.3	1.02 ± 0.3	.0001
	n = 15			12 months	0.8 ± 0.2	1.06 ± 0.2	.001
	n = 6			18 months	0.8	1.10	.01
Gujral et al. (2016)	HNC N = 50	Internal Self over time Hemineck	M = 53 Gy ± 13	M = 53.9 months (42.5–90.5, IQR)	Unirradiated Hemineck	Radiated Hemineck	
					Prox CCA: 0.68 ± 0.14	Prox CCA: 0.76 ± 0.15	< .0001
					Med CCA: 0.68 ± 0.16	Med CCA: 0.74 ± 0.2	.01
					Distal CCA: 0.68 ± 0.15	Distal CCA: 0.77 ± 0.2	.004
					Bifurcation: 0.72 ± 0.17	Bifurcation: 0.85 ± 0.25	.001
Pereira Lima et al. (2011)	HNC n = 19	Prostate cancer n = 24	To neck: M = 66 Gy ± 6 To prostate: M = 70 Gy ± 3	Early post-RT: M = 42 days ± 33 Late post-RT: M = 167 days ± 51	Pre-RT: 0.73 ± 0.04	Early post-RT: 0.80 ± 0.05	.029
Strüder et al. (2020)	HNC RT n = 96	HNC surgery n = 21	Bilateral RT M = 62.5 Gy ± 7.9	M = 3 years ± 3.1 (1 month–12 years)	Healthy control: 0.64 ± 0.11	Post-RT: 0.77 ± 0.18	< .05
	Boost: n = 40 bilateral neck; n = 55 with boost	Healthy ENT n = 20	Bilateral RT with tumor side boost: M = 61.1 Gy ± 9.7 Contralateral without boost: M = 49.3 Gy ± 15.8		Surgery control: 0.69 ± 0.10		< .05
					Contralateral: 0.73 ± 0.16	Boost: 0.78 ± 0.20	< .05
Toprak et al. (2012)	HNC n = 50	Internal Self over time	Bilateral	Final day of RT	Pre-RT: 0.68 ± 0.11	Post-RT: 0.87 ± 0.16	< .001
Wilbers et al. (2014)	HNC N = 48	Internal Self over time	CCA: M = 58 Gy ± 12 (30–70 Gy)	Mdn = 6.7 years (4.5–9.6)	Pre-RT: 0.64	Post-RT: 0.74	.002
	Bilateral: RT 63% Unilateral: RT 37%		ICA: M = 61 Gy ± 12 (30–70 Gy)		Mean delta: 0.02 ± 0.06	0.11 ± 0.2	.03
Yeh et al. (2019)	HNC n = 20	Healthy control n = 50			Healthy control: 0.58 ± 0.15	Post-RT: 0.82 ± 0.2	.01
Yuan et al. (2015)	NPC n = 69	T2DM n = 70 Healthy w/o CV risk factors n = 76	M = 66.87 Gy ± 3.45 (58–73.72 Gy)	> 4 years	DM: 0.70 ± 0.126	Post-RT: 0.68 ± 0.13	.732
					Healthy control: 0.527 ± 0.159		.001

Note. ENT = ear, nose, throat; HNC = head and neck cancer; Gy = gray; cGy = centigray; NPC = nasopharyngeal cancer; RT = radiation therapy; T2DM = type 2 diabetes mellitus; CCA = common carotid artery; ICA = internal carotid artery.

internal carotid artery mean dose 61 Gy ± 12, range 30–70 Gy). At mean follow-up (average time between completion of neck radiation to ultrasound IMT assessment) of 6.7 years (range 4.5–9.6 years), a statistically significant carotid IMT increase was associated with radiation to the neck (0.64 mm vs. 0.74 mm, $p = .002$). Additionally, when evaluating patients who received unilateral neck radiation,

Table 2. **Ultrasound Measured Radiation-Associated IMT Changes and Evaluation Interval**

Author (year)	US-measured radiation-associated change in carotid IMT[a]	Post-radiation US IMT interval
Faruolo et al. (2013)	Increase	6, 12, 18 months[a]
Gujral et al. (2016)	Increase	No effect
Pereira Lima et al. (2011)	Increase	Early and late[a]
Strüder et al. (2020)	Increase	No effect
Toprak et al. (2012)	Increase	Final day of RT[a]
Wilbers et al. (2014)	Increase	–
Yeh et al. (2019)	Increase	–
Yuan et al. (2017)	Increase	–

Note. IMT = intima-media thickness; US = ultrasound; RT = radiation therapy.
[a]$p < .05$

the common carotid artery mean delta IMT (the difference between the pre- and post-radiation mean IMT) in the nonirradiated neck was 0.2 mm per 7 years, which corresponds with normal age-related increase in patients described previously (Overgaard et al., 2003). When the mean delta IMT in the irradiated neck was compared with the nonirradiated side, radiation was correlated with a greater than five-fold increase at mean 6.7-year follow-up ($p = .03$), and the absolute value exceeded the 0.1 mm IMT increase threshold set by Lorenz and colleagues (2007), indicating greater relative risk of stroke.

Strüder and colleagues (2020) designed a cross-sectional study analyzing ultrasound measured carotid IMT in 96 irradiated HNC patients (M = 3.1 ± 3.1 years post radiation), 21 HNC patients receiving neck dissection alone, and 20 nonirradiated controls that included both HNC patients receiving surgery only and routine otorhinolaryngology patients. Of those treated with radiation, 41 patients received bilateral neck radiation (M = 62.5 Gy ± 7.9), while 55 patients received tumor side boost (M = 61.1 Gy ± 9.7) with contralateral side receiving a lower dose (M = 49.3 Gy ± 15.6). Strüder and colleagues (2020) reported ultrasound measured a 13% mean carotid IMT increase in HNC patients after neck radiation vs. receiving neck dissection alone, and a 20% increase over healthy controls (radiation: n = 96, 0.77 mm ± 0.18; surgery: n = 21, 0.69 mm ± 0.10; control: n = 20, 0.64 mm ± 0.12; $p < 0.05$). This increase in carotid IMT was maintained over 10 years of follow-up.

In a cross-sectional study, Gujral and colleagues (2016) studied 50 HNC patients who received hemineck radiation at least 2 years previously, utilizing the contralateral unirradiated neck as an internal control and a normal reference population as an external control. Four segments of the common carotid artery were measured using ultrasound, and significant carotid IMT increases were noted in all segments of the treated artery (M = 53 Gy ± 13) when compared with the same segments on the untreated artery ($p < .01$). Chemotherapy, surgery, age, and smoking status had no significant effect, lending support to the hypothesis that radiation was the primary risk factor for IMT increase.

In a retrospective cohort study, Yuan and colleagues (2017) measured ultrasound carotid IMT between three cohorts: adult nasopharyngeal cancer patients at least 4 years post radiation without cardiovascular risk factors (mean dose 66.87 ± 3.45 Gy), adults with type 2 diabetes and no prior radiation, and healthy controls without cardiovascular risk factors or prior radiation. After adjusting for age and gender, the post-radiation cohort had a 29.3% carotid IMT increase over healthy controls (681.7 ± 132.2 mm vs. 527.1 ± 159.1 mm, $p < 0.001$) with a follow-up interval greater than 4 years.

Yeh and colleagues (2019) retrospectively evaluated 20 HNC survivors who received neck radiation alone or with chemotherapy, along with 50 healthy subjects. After statistically controlling for multiple known cardiovascular disease risk factors, including diabetes mellitus, hypertension, hyperlipidemia, and smoking, prior neck irradiation was independently associated with ultrasound-evaluated carotid IMT increase (0.82 ± 0.20 mm vs. 0.58 ± 0.15 mm, effect size 1.22, $p < 0.01$) and higher risk for developing cardiovascular disease.

Four of the eight articles also identified the presence of pathological IMT at the final ultrasound assessment or calculated an increased risk for developing pathological IMT in their post-radiation treatment groups. Pathological carotid IMT is defined as IMT > 0.9 mm or > 75th percentile of a reference population matched for age, sex, and race/ethnicity, and carries a significantly higher risk for future cardiovascular events in the general population (Greenland et al., 2010; Stein et al., 2008). Faruolo and colleagues (2013) reported unirradiated mean IMT ≤ 0.9 mm prior to radiation, followed by an absolute increase to > 0.9 mm in each of three short follow-up periods. Gujral and colleagues (2016) illustrated that carotid IMT measurements above the 75th percentile of a normal reference population occurred more frequently in all four segments of irradiated arteries than in unirradiated segments. Yeh and colleagues (2019) subscribed to a higher-risk threshold of IMT > 1.0 mm, yet noted prior radiation was still independently associated with higher risk of cardiovascular events (odds ratio 13.5, 95% confidence interval [CI] = 1.48–122). Strüder and colleagues (2020) noted exposure to neck radiation, and not chemotherapy or neck dissection, increased the risk for developing pathologic IMT, with a relative risk of 1.19 (95% CI = 1.04–1.34) and attributable risk of 6.47 (95% CI = 3.42–17.6).

Initiation of Post-Radiation Ultrasound Screenings

Each of the included studies noted significant post-radiation carotid IMT increase and broadly recommended ultrasound IMT evaluation to encourage early identification of CAD; however, specific screening recommendations were limited. Thus, it is important to establish when ultrasound evaluation should be initiated, and whether the adult HNC population would benefit from routine screenings.

Two retrospective studies found no association between time from treatment and carotid IMT increase. Strüder and colleagues (2020) studied the post-radiation interval of a subset of patients who received tumor side radiation boost (n = 55) and compared boost side to contralateral neck, which received a lower radiation dose. The data were analyzed by separating these patients into four groups based on follow-up intervals of < 0.5 years, 0.5 to 2 years, 2 to 5 years, and > 5 years (n = 11, 23, 15, 6, respectively). Using simple linear regression, no correlation was found for time from radiation. Due to the retrospective design of their study, IMT was evaluated at a single timepoint instead of comparing change in each patient over time. Using multiple regression analysis, Gujral and colleagues (2016) also retrospectively found no effect between time from radiation and carotid IMT in any of the four measured arterial segments; however, the authors highlighted their study was not powered to demonstrate this link.

Three of the prospective studies utilized pre- and post-radiation measurements. The shortest ultrasound follow-up interval, performed by Toprak and colleagues (2012), measured carotid IMT prior to the first radiation treatment and on the final day of radiation 6 weeks later, and showed statistically significant carotid IMT increase ($p < .001$). Their study was ongoing with additional scheduled follow-up ultrasounds, so no screening recommendations were made at time of publication. Pereira Lima and colleagues (2011) noted statistically significant carotid IMT increase on initial short follow-up (M = 42 days ± 33 post radiation, $p = 0.027$), although they did not find significant increase in measurements 6 months after that initial post-radiation follow-up (M = 167 days ± 51). These results highlighted the early, local vascular effects of radiation. Pereira Lima and colleagues (2011) did not recommend a specific timepoint for initiating surveillance ultrasounds. After reporting significant carotid IMT increases at 6, 12, and 18 months post-neck radiation, Faruolo and colleagues (2013) recommended initiating ultrasound evaluation at 1 year post treatment. Yuan and colleagues (2017) did not make screening recommendations based on carotid IMT data but on the presence of plaques at the conclusion of radiation. Yuan and colleagues recommended annual monitoring in patients with demonstrated plaque or initiating screening at 4 years post radiation in patients without plaques present.

DISCUSSION

This integrative review demonstrates that radiation in adult HNC patients causes significant carotid IMT increase adequately measured by ultrasound, which is supported by similar findings in earlier studies. In a systematic review, Gujral and colleagues (2014) noted significant carotid IMT increase in irradiated arteries over shorter periods than the 5- to 15-year post-treatment intervals previously recorded (Brown et al., 2005; Cheng et al., 1999). Findings from one prospective study noted significant carotid IMT increase 1 (p < .001) and 2 years (p < .01) after neck irradiation (Muzaffar et al., 2000), thus supporting their recommendation for 1- to 2-year ultrasound follow-ups. In short interval follow-up, three prospective studies with timed assessments noted increased carotid IMT as early as the final day of a 6-week radiation course (Toprak et al., 2012) and within months post treatment (Faruolo et al., 2013; Pereira Lima et al., 2011). In the other five studies, mean follow-up intervals with large standard deviations were reported, thus making it difficult to extrapolate timing recommendations for later follow-ups. One prospective study by Wilbers and colleagues (2014) demonstrated the longest mean follow-up of 6.7 years after radiation, supporting the hypothesis that carotid IMT develops early after radiation and persists for years after treatment.

Although two studies found no association between post-radiation interval and carotid IMT increase, Gujral and colleagues' study (2016) was not powered to assess this link, and Strüder and colleagues (2020) retrospectively evaluated this in a smaller subset of their study population receiving tumor-side boost with varying interval follow-ups (< 0.5 years, n = 11; 0.5–2 years, n = 23; 2–5 years, n = 15; 5–15 years, n = 6). These findings do not negate the identification of short interval post-radiation increase in carotid IMT noted in the other studies and only further reinforces the need for additional adequately powered, prospective studies to further investigate the benefit of long-term routine carotid IMT screenings.

As a secondary endpoint, Toprak and colleagues (2012) also reported new, primarily hypoechoic, carotid plaque formation and changes in size and echogenicity of preexisting plaques on the final day of patients' 6-week radiation course. Calcified plaques tend to be more stable when compared with anechoic or hypoechoic plaques, and thus the presence of new hypoechoic plaques after radiation may signal increased risk for thromboembolic/ischemic stroke (Reilly et al., 1983). Toprak and colleagues (2012) demonstrated post-radiation plaque changes earlier than previously reported, further supporting the need for early carotid screenings for these patients.

For primary or secondary prevention of cardiovascular disease, the European Society of Cardiology endorses ultrasound evaluation of both carotid IMT and carotid plaque (Vlachopoulos et al., 2015). Den Ruijter and colleagues (2012) and Polak and colleagues (2017) both noted that the addition of carotid IMT to the Framingham Risk Score improved prediction of cardiovascular risk, although only Polak and colleagues reported a significant clinical benefit from these results. Inclusion of carotid IMT helped clarify intermediate risk stratification in patients who may have been low risk due to lack of other traditional cardiovascular risk factors like dyslipidemia, diabetes, or hypertension (Polak et al., 2017). Evidence shows that neck radiation leads to increased carotid IMT and adding carotid IMT improves the Framingham risk prediction, and thus future studies are warranted to assess the role of carotid IMT in risk stratification for this population.

Prior neck radiation is not currently included in cardiovascular risk algorithms despite evidence that radiation contributes to accelerated atherosclerosis and significantly greater risk for stroke and transient ischemic attack. Similarly, carotid IMT increase occurs years before the development of carotid stenosis, thus offering a strong option as an early marker of future risk and may allow clinicians to maximize medical management years before a cardiovascular event in patients who may otherwise appear to be low risk.

Combined, these data support the hypothesis that radiation to the carotid arteries leads to early, acute inflammatory changes, impacting the carotid IMT in the near term, and contributes to plaque formation that may persist and later result in stroke or transient ischemic attack. Ultrasound provides an effective and noninvasive modality for measurement of carotid

IMT and can identify pathologic levels of IMT that are associated with increased future risk. Initiating ultrasound carotid IMT screening at 1 year post radiation would trigger earlier identification of asymptomatic patients at high risk for developing radiation-associated CAD, which is essential to optimizing medical management in this population and ultimately reducing cardiovascular sequelae.

After the completion of this review, the International Cardio-Oncology Society (ICOS) published a 2021 consensus statement that recommended adding carotid evaluation to baseline CT imaging obtained for disease staging or treatment planning, then initiating carotid ultrasound screening 1 year post radiation in high-risk patients, followed by carotid ultrasound every 3 to 5 years to guide preventive therapy (Mitchell et al., 2021). This integrative literature review and the ICOS consensus statement agree that initiating ultrasound screening 1 year post treatment would allow for early detection of radiation-associated CAD and thus increased risk for stroke.

Limitations

Varying designs and controls of the included studies limited the strength of this review. Four of the eight studies (Faruolo et al., 2013; Gujral et al., 2016; Toprak et al., 2012; Wilbers et al., 2014) did not include external control groups but instead utilized internal controls of self over time or compared bilateral carotids in patients receiving unilateral radiation. Four of the eight studies (Gujral et al., 2016; Strüder et al., 2020; Yeh et al., 2019; Yuan et al., 2017) reviewed were retrospective, and thus a lesser level of evidence. Of the four prospective studies, three (Faruolo et al., 2013; Pereira Lima et al., 2011; Toprak et al., 2012) addressed short-interval screenings of 18 months or less, thus limiting the scope of this review to early post-radiation screening data. Longer follow-up intervals would strengthen the quality of evidence for long-term screening recommendations. Attrition was also a factor in the prospective studies; therefore, future studies may consider including early stage HNC patients to improve retention. While ultrasound of carotid IMT was the focus of this review, analysis of new or emerging imaging techniques may also be useful.

Implications for Practice

Ultrasound adequately detects post-radiation changes in carotid IMT. Clinicians providing care to HNC patients should consider obtaining baseline carotid ultrasound with IMT measurements prior to the start of neck radiation and at 1 year post therapy. Gujral and colleagues (2014) and the 2021 ICOS consensus statement support this conclusion by recommending carotid ultrasound at 1 year post radiation. In the absence of strong longer-term data, subsequent screenings should be determined based on individual patient risk for developing pathologic IMT, such as other cardiovascular risk factors. Patients and community providers should be educated on the increased risk for early radiation-associated CAD and cardiovascular sequelae. The importance of optimizing medical management for other cardiovascular risk factors should also be emphasized. To minimize loss to follow-up, screening recommendations should be included in survivorship care plans, particularly because carotid atherosclerosis develops over years and may occur after survivorship care has been transferred to another provider or facility.

Future research should include adequately powered, prospective, case-controlled studies to further evaluate the benefit of routine, long-term post-radiation carotid IMT ultrasound screenings. Additionally, studies should assess the utility of adding prior radiation or pathologic carotid IMT to cardiovascular risk stratification tools, like Framingham Risk Score, QStroke, or Atherosclerotic Cardiovascular Disease Risk Estimator Plus (D’Agostino et al., 2001; Henderson et al., 2016; Hippisley-Cox et al., 2013; Den Ruijter et al., 2012). Consideration of other ultrasound assessments, like Doppler flow, coronary artery calcification scores, and nature of the plaque, could also be added in future studies, as these combined characteristics may provide a more comprehensive evaluation of risk.

CONCLUSION

Ultrasound-detected carotid IMT increase is an effective surrogate endpoint for carotid artery stenosis and future stroke risk in the post-radiation adult HNC population. It is reasonable to initiate baseline ultrasound carotid IMT imaging prior to neck radiation and at 1 year post treatment given the evidence of increased carotid IMT.

Limited data on the relationship between a longer-term post-radiation interval and carotid IMT in the data from this review precluded recommendations for subsequent screening timepoints, although they did not contradict the ICOS recommendation for screening every 3 to 5 years. Early identification of cardiovascular risk allows clinicians to optimize medical management and make patient-centered decisions on long-term screenings according to their cardiovascular risk factors. Additional prospective, adequately powered, case-controlled studies are needed to further evaluate the benefit of routine post-radiation ultrasound carotid IMT screenings. ●

Disclosure

The authors have no conflicts of interest to disclose.

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