



The effectiveness of high-resolution ultrasound in the assessment of the carotid intima–media thickness for postirradiated neck

Yu-Chun Yeh¹ · Kai-Min Fang² · Wan-Lun Hsu³ · Li-Jen Liao^{2,4,5}

Received: 25 October 2018 / Accepted: 16 January 2019 / Published online: 25 January 2019
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

Abstract

Objective The carotid intimal–medial thickness (CIMT) is a strong predictor of future cardiovascular events. We assessed the mean CIMT and evaluated associated factors in head and neck cancer (HNC) patients.

Materials and methods Between January 2016 and March 2018, 70 volunteers underwent automatic ultrasound measurement of the common carotid artery CIMT. A mean CIMT ≥ 1.0 mm was regarded as an elevated risk for cardiovascular disease (CVD). We aimed to investigate the risk factors for an increased mean CIMT.

Results We recruited 20 HNC survivors and 50 noncancer control individuals. Multiple linear regression analysis showed that old age ($\beta=0.006$, 95% confidence interval, CI 0.004–0.008), increased weight ($\beta=0.003$, 95% CI 0.001–0.005), hypertension ($\beta=0.10$, 95% CI 0.03–0.17), and prior irradiation ($\beta=0.13$, 95% CI 0.08–0.19) were positively correlated with the mean CIMT. From logistic regression analysis, it was shown that patients who underwent radiotherapy (OR 13.5, 95% CI 1.48–122.8) and who had higher bodyweight (OR 1.09, 95% CI 1.01–1.18) had a significantly higher risk of developing CVD.

Conclusion Measurement of the mean CIMT using ultrasound could be useful for assessing CVD risk in HNC survivors after neck irradiation.

Keywords Carotid intima–media thickness · Head and neck cancer · Irradiation · Cardiovascular disease

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00405-019-05302-1>) contains supplementary material, which is available to authorized users.

✉ Li-Jen Liao
liao lj@ntu.edu.tw; deniro@mail2000.com.tw

Yu-Chun Yeh
rambleurban@gmail.com

Kai-Min Fang
u701048@gmail.com

Wan-Lun Hsu
lun0112@ms26.hinet.net

- ¹ Department of Family Medicine, Far Eastern Memorial Hospital, New Taipei City, Taiwan, ROC
- ² Department of Otolaryngology Head and Neck Surgery, Far Eastern Memorial Hospital, No. 21, Sec. 2, Nanya S. Rd., Banqiao Dist, New Taipei City 220, Taiwan, ROC
- ³ Genomics Research Center, Academia Sinica, Taipei, Taiwan, ROC
- ⁴ Department of Electrical Engineering, Yuan Ze University, Taoyuan, Taiwan, ROC
- ⁵ Biomedical Engineering Office, Far Eastern Memorial Hospital, New Taipei City, Taiwan, ROC

Introduction

Head and neck cancer is increasing, and its survival rates are improving at the same time [1]. However, the treatment of head and neck cancer will lead to disability, even if the patient is cancer-free [2]. Radiation over the neck will increase the risk for stroke in head and neck cancer patients, and this risk from high-dose irradiation is doubled [3]. Further study of this association and possible interventions is warranted.

Recently, an increasing number of head and neck surgeons have used ultrasound (US) to assess the neck. US was mainly used to assess neck lumps, such as lymphadenopathy [4, 5], thyroid nodules [6, 7], and salivary gland tumors [8]. These surgeons may also use ultrasound to guide an aspiration procedure with very good performance and high safety [9]. However, very few head and neck surgeons use ultrasound to assess neck vessels and guide therapy.

Currently, cardiovascular disease (CVD) remains as the leading cause of death, inducing 17.3 million deaths per year and accounting for 31% of all deaths globally [10]. There are a substantial number of prediction models for CVD risk in

the general population, which are based on traditional risk factors, including hypertension, diabetes mellitus, hyperlipidemia, and tobacco use, as well as obesity. However, it takes years to develop CVD, and early intervention should be provided to prevent premature death. The carotid intimal–medial thickness (CIMT) has been adopted as a surrogate endpoint in many cardiovascular studies [11].

To date, the CIMT has evolved into one of the most utilized and most validated atherosclerosis imaging techniques, and it has been a strong predictor for future cardiovascular events since its first description in 1986 [12]. Its advantages of noninvasiveness, safety, and reproducibility has made it highly accessible to both clinical practice and research studies. While radiation-induced microvascular damage has been well-studied, increasing amounts of evidence show that radiation can induce carotid artery atherosclerosis and increase the CIMT [13]. An observational study showed significant CIMT increase 6 month after RT without corresponding narrowing of the carotid lumen, but both the values reach significance difference at 12-month follow-up after RT [14]. Another study reported the similar result, showing RT produced greater CIMT and narrower carotid artery lumen. It also proved that the carotid plaques in irradiated head and neck cancer survivors do not differ from those arising from spontaneous atherosclerosis in the general population. Both the CIMT and the carotid plaque character were of prognostic importance for HNC patients [15]. Therefore, post-radiotherapy patients may benefit from a vascular assessment using CIMT to prevent further CVD.

Although the previous studies indicated that radiation could lead to an increased CIMT [13–16], the potential confounding factors, such as age and lifestyle, were never adjusted in these studies. In addition, the effect size of the factors related to carotid vasculopathy is not clarified. In our study, we aimed to test the utility of US in neck carotid assessment and used high-resolution US to assess the mean carotid intimal–medial thickness (mCIMT). In addition, we tried to evaluate the associated risk factors for carotid vasculopathy.

Methods

Study population and design

This study was approved by the institutional review board (IRB 104180-E). Between January 2016 and March 2018, 70 volunteers underwent US for measurement of the mCIMT. Twenty of the eligible participants were head and neck cancer (HNC) survivors who had received treatment including either neck radiotherapy alone or concurrent chemoradiotherapy. The other 50 participants composed the noncancer

control group. Written informed consent was obtained from all participants.

Data collection and carotid ultrasound measures

The mCIMT was assessed by automated measurement over the bilateral carotid arteries using a Toshiba Aplio 500 ultrasound system (Otawara, Japan) with a 5–14 MHz L probe. All assessments of the CIMT were performed by a single experienced sonographer who is also a head and neck surgeon (LJ Liao). Images with a plaque-free area at least 1.0 cm in length of the far wall of common carotid artery (CCA) were obtained from at least 1.0 cm proximal to the origin of the carotid bulb. The IMT was defined as the distance from the lumen–intimal interface to the medial–adventitial interface (the “double-line pattern”) in the far walls of the vessels (Fig. 1). We measured the CIMT three times and averaged the results of the CIMT values, which we termed the mCIMT [17]. A mean CIMT greater than 1.0 mm was

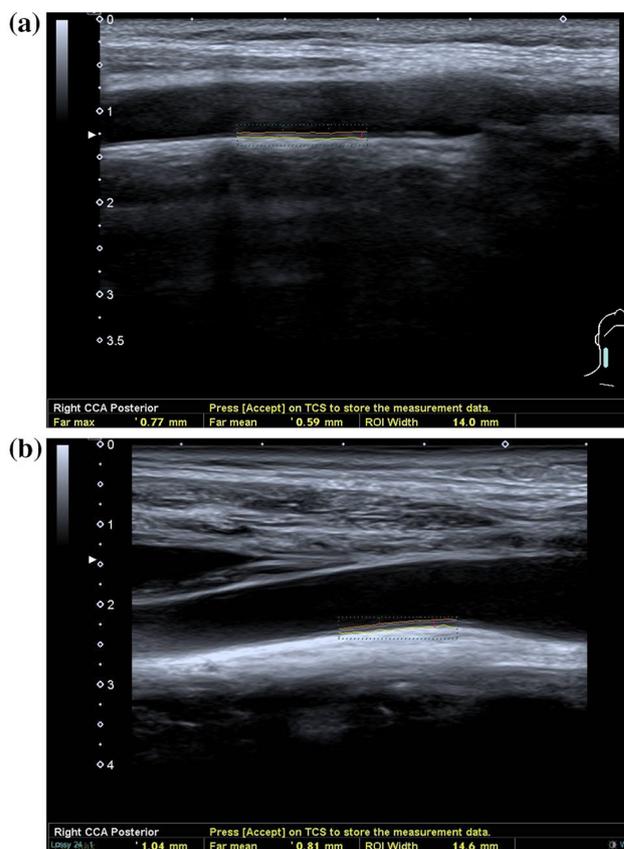


Fig. 1 **a** Longitudinal ultrasound of the right CCA in a 27-year-old female without any comorbidity showed a right CCA far mean CIMT=0.59 mm. **b** Longitudinal ultrasound of the right CCA in a 61-year-old male with tongue cancer and hypertension showed a right CCA far mean CIMT=0.81 mm

regarded as an indicator of abnormality and elevated risk for CVD [18].

Statistical analysis

Univariate and multivariate linear regression analyses were used to assess the associations between the mCIMT and the following variables: age, gender, body mass index (BMI), weight, height, smoking status, hypertension, diabetes mellitus, hyperlipidemia, and prior cervical irradiation. When collinearity between covariates was suspected, the variables most strongly correlated with the mCIMT were selected for the analysis. All statistically significant variables in the univariate analysis were selected for inclusion in the multivariate linear regression. Logistic regression was used to investigate the risk for an abnormal mCIMT result. Moreover, we divided the variables into two groups and performed the difference of the mCIMT using an independent *t* test and evaluated the magnitude of the difference between groups by the “effect size” using Cohen’s *d* [19]. Effect size estimates can provide information for judgments of practical significance. A Cohen’s *d* greater than 0.8 is considered “large”. A *p* value < 0.05 was considered statistically significant. All statistical analyses were carried out using Stata software, version 12.0 (Stata Corp. LP, College Station, TX).

Results

The demographic data of the recruited volunteers are shown in Table 1. Among the 70 participants recruited for the study, the mean participant age was 43.1 ± 14.7 years, and 56% of the participants were men and 29% were HNC patients. One-fourth of the HNC patients were oral cancer patients (Table 1).

In the univariate linear regression, the mCIMT was positively correlated with age ($\beta = 0.009$ 95% CI 0.007–0.01),

weight ($\beta = 0.005$ 95% CI 0.002–0.007), BMI ($\beta = 0.02$ 95% CI 0.01–0.03), hypertension ($\beta = 0.21$ 95% CI 0.14–0.28), diabetes mellitus (DM) ($\beta = 0.16$ 95% CI 0.04–0.28), hyperlipidemia ($\beta = 0.14$ 95% CI 0.08–0.26), smoking history ($\beta = 0.16$ 95% CI 0.04–0.28), prior irradiation ($\beta = 0.24$ 95% CI 0.18–0.30), and chemotherapy ($\beta = 0.20$ 95% CI 0.13–0.27). (Table 2). In the multivariate linear regression, after all adjustments were made, elder age ($\beta = 0.006$ 95% CI 0.004–0.008), higher weight ($\beta = 0.003$ 95% CI 0.001–0.005), hypertension ($\beta = 0.10$ 95% CI 0.03–0.17), and prior irradiation ($\beta = 0.13$ 95% CI 0.08–0.19) were associated with a higher mCIMT. Due to multicollinearity, BMI, weight and chemotherapy were removed in the multivariate linear regression.

We further evaluated the risk for CVD (defined as a mean CCA CIMT ≥ 1.0 mm) using the logistic regression method (Table 3). In the univariate analysis, age (OR 1.06, 95% CI 1.01–1.12), weight (1.07, 1.01–1.13), BMI (1.26, 1.05–1.51), prior irradiation (24.8, 2.98–205.5), and chemotherapy (5.05, 1.27–20.1) were associated with a higher risk for CVD. Irradiation (13.5, 1.48–122.8) and increased weight (1.09, 1.01–1.18) were independent risk factors for CVD in the multivariate analysis after adjusting for other variables.

In the effect size estimation (Table 4), the mCIMT was higher in the patients with an age ≥ 65 years (mean 0.86 mm vs. 0.63 mm; $p < 0.01$; effect size: 1.19), body-weight ≥ 65 kg (mean 0.69 mm vs. 0.61 mm; $p < 0.01$; effect size: 0.45), BMI ≥ 23 (mean 0.72 mm vs. 0.57 mm; $p < 0.01$; effect size: 0.73), hypertension (0.81 mm vs. 0.60 mm; $p < 0.01$; effect size: 1.06), DM (0.79 mm vs. 0.63 mm; $p < 0.01$; effect size: 0.79), hyperlipidemia (0.77 mm vs. 0.64 mm; $p = 0.04$; effect size: 0.68) smoking history (0.79 mm vs. 0.63 mm; $p < 0.01$; effect size: 0.80), prior irradiation (0.82 mm vs. 0.58 mm, $p < 0.01$; effect size: 1.22), and previous chemotherapy (0.81 mm vs. 0.60 mm, $p < 0.01$; effect size: 1.03).

Table 1 Demographic data of the volunteers

	Volunteers (<i>n</i> = 70)	Noncancer volunteers (<i>n</i> = 50)	Head and neck cancer survivors ^a (<i>n</i> = 20)
Male gender, [<i>n</i> (%)]	39 (56%)	25 (50%)	14 (70%)
Age, (years)	43 ± 15	39 ± 14	53 ± 10
Weight, (kg)	65 ± 14	63 ± 13	71 ± 14
Height, (cm)	166 ± 9	166 ± 8	166 ± 10
BMI, (kg/m ²)	24 ± 4	23 ± 4	26 ± 3
HTN, [<i>n</i> (%)]	16 (23%)	8 (16%)	8 (40%)
DM, [<i>n</i> (%)]	6 (9%)	2 (4%)	4 (20%)
Hyperlipidemia, [<i>n</i> (%)]	5 (7%)	3 (6%)	2 (10%)
Smoking, [<i>n</i> (%)]	6 (9%)	3 (6%)	3 (15%)

^aOral cancer: 5; nasopharyngeal cancer: 4; oropharyngeal cancer: 3; hypopharyngeal cancer: 3; parotid cancer: 2; submandibular gland cancer: 1; laryngeal cancer: 1; other (unknown primary cancer): 1

Table 2 Univariate and multivariate linear regression analyses using the mean CIMT of the CCA as the dependent variable

	Univariate		Multivariate	
	β coef. (95% CI)	<i>p</i>	β coef. (95% CI)	<i>p</i>
Male gender	0.02 (−0.05 to 0.09)	0.551		
Age	0.009 (0.007 to 0.01)	<0.01	0.006 (0.004 to 0.008)	<0.01
Weight	0.005 (0.002 to 0.007)	<0.01	0.003 (0.001 to 0.005)	<0.01
Height ^a	−0.0003 (−0.004 to 0.003)	0.843		
BMI ^a	0.02 (0.01 to 0.03)	<0.01		
HTN	0.21 (0.14 to 0.28)	<0.01	0.10 (0.03 to 0.17)	<0.01
DM	0.16 (0.04 to 0.28)	0.008	−0.08 (−0.19 to 0.02)	0.11
Hyperlipidemia	0.14 (0.08 to 0.26)	0.038	−0.01 (−0.12 to 0.10)	0.86
Smoking	0.16 (0.04 to 0.28)	0.008	−0.02 (−0.12 to 0.09)	0.77
Irradiation	0.24 (0.18 to 0.30)	<0.01	0.13 (0.08 to 0.19)	<0.01
Chemotherapy ^a	0.20 (0.13 to 0.27)	<0.01		

β coef. β coefficient, 95% CI 95% confidence interval, SE standard error, BMI body mass index, HTN hypertension, DM diabetes mellitus

^aDue to multicollinearity, BMI, BH, and chemotherapy are removed

Table 3 Logistic regression analysis of risk for an abnormal CIMT result (mean CIMT \geq 1.0 mm)

Risk factor	Univariate		Multivariate	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Male gender	1.64 (0.39–6.84)	0.498		
Age	1.06 (1.01–1.12)	0.019	1.07 (0.99–1.16)	0.077
Weight ^a	1.07 (1.01–1.13)	0.016	1.09 (1.01–1.18)	0.027
Height	1.05 (0.97–1.14)	0.219		
BMI ^a	1.26 (1.05–1.51)	0.014		
HTN	2.94 (0.74–11.69)	0.125		
DM	3.46 (0.63–18.90)	0.152		
Hyperlipidemia	1.69 (0.19–15.08)	0.636		
Smoking	1.36 (0.16–11.93)	0.779	0.22 (0.02–2.93)	0.252
Irradiation	24.75 (2.98–205.52)	0.003	13.50 (1.48–122.81)	0.021
Chemotherapy ^a	5.05 (1.27–20.13)	0.022		

OR odds ratio, 95% CI 95% confidence interval, SE standard error, BMI body mass index, HTN hypertension, DM diabetes mellitus

^aDue to multicollinearity, BMI, BH and chemotherapy are removed

Discussion

In our study, we found the previous irradiation as a factor that is strongly associated with an increased CIMT after controlling for multiple associated factors, such as DM, hypertension, hyperlipidemia, and smoking. The effect size of the previous irradiation was as large as 1.22 (Table 4). The CIMT measurements using high resolution US provided a more visualized way to evaluate the risk stratification of CVD beyond traditional risk factors for CVD, including age, hypertension, and bodyweight, which

were also significantly associated with an increased CIMT in our study.

We highlight the importance of the assessment of the CIMT by US for head and neck cancer survivors with prior neck radiation.

In recent years, several studies have examined the relationship between the CIMT and future adverse events, including myocardial infarction (MI), angina pectoris, coronary intervention, and stroke, as well as transient ischemic attack (TIA). In the general population, for an absolute carotid IMT difference of 0.1 mm, the future risk for MI increases by 10–15%, and the stroke risk increases by 13–18% [11]. Though the CIMT had been widely used as a predictor for CVD in the general population, there is a scarcity of the literature that evaluates the CIMT in irradiated patients.

Currently, multimodality including surgery, chemotherapy, and radiotherapy is the mainstay for treatment of malignancies of the head and neck. Successful treatment increases survival, but also puts the patient at risk for radiation-related side effects, such as radiation vasculopathy. The complex and broad ranges of the effects of radiation on vessels may cause cerebrovascular events, which are often under-recognized [20]. Vascular injury is believed to be associated initially with endothelium dysfunction and subsequently with abnormal proliferation and fibrosis after radiation [21]. Furthermore, radiation was thought to accelerate atherosclerosis and augment the initial injury [22, 23]. Both short-term and long-term effects of radiotherapy have been shown in recent studies. Although a longer latency period is required to develop a symptomatic cerebrovascular event, vascular changes can take place as soon as 90 days after the end of radiation treatment [24].

Table 4 Comparisons of the mean CIMT and effect size among different variables

Variables	Mean CIMT \pm SD (mm)	Effect size	<i>p</i> value
Gender (male vs. female)	0.66 \pm 0.21 vs. 0.64 \pm 0.19	0.10	0.55
Age (\geq 65 vs. < 65)	0.86 \pm 0.14 vs. 0.63 \pm 0.19	1.19	< 0.01
Weight (kg) (\geq 65 vs. < 65)	0.69 \pm 0.22 vs. 0.61 \pm 0.17	0.45	< 0.01
Height (cm) (\geq 165 vs. < 165)	0.63 \pm 0.21 vs. 0.67 \pm 0.19	−0.23	0.18
BMI (kg/m ²) (\geq 23 vs. < 23)	0.72 \pm 0.21 vs. 0.57 \pm 0.16	0.73	< 0.01
HTN (yes vs. no)	0.81 \pm 0.19 vs. 0.60 \pm 0.18	1.06	< 0.01
DM (yes vs. no)	0.79 \pm 0.21 vs. 0.63 \pm 0.19	0.79	< 0.01
Hyperlipidemia (yes vs. no)	0.77 \pm 0.24 vs. 0.64 \pm 0.19	0.68	0.04
Smoking (yes vs. no)	0.79 \pm 0.23 vs. 0.63 \pm 0.19	0.80	< 0.01
Irradiation (yes vs. no)	0.82 \pm 0.20 vs. 0.58 \pm 0.15	1.22	< 0.01
Chemotherapy (yes vs. no)	0.81 \pm 0.21 vs. 0.60 \pm 0.17	1.03	< 0.01

SD standard deviation, BMI body mass index, HTN hypertension, DM diabetes mellitus

In addition to conventional two-dimensional RT, intensity-modulated radiotherapy (IMRT) is an innovative radiation technique to modify the radiation distribution and extricating normal tissue from radiation damage. Previous study in nasopharyngeal cancer patients revealed that IMRT could reduce the incidence of significant carotid stenosis compared to conventional RT [25]. However, it is not feasible to eliminate RT dose to carotid in most clinical scenario, even with advanced RT techniques, because the carotid arteries are often included in the clinically treatment volume [26]. Therefore, ultrasound measurement of the CIMT should also be considered for all head and neck cancer survivors after RT. Further research should be conducted on the function of the anatomic sites of malignancy that would determine the target tissues for radiotherapy.

A patient who had head and neck radiotherapy appears to have at least double the relative risk (RR) for a TIA or stroke than normal individuals [16, 27]. The exception is adjuvant neck radiotherapy for breast cancer due to the minimal carotid radiation exposure from this therapy [20]. A recent systematic review showed an increased relative risk (RR)/hazard ratio (HR) for stroke/TIA in patients with head and neck cancer, for whom it was 5.6, compared with patients with breast cancer, for whom it was 1.12 [16].

In our study, the mCIMT was significantly associated with age, bodyweight, hypertension, and prior irradiation. In the multiple logistic regression, prior irradiation (OR 13.5, 95% CI 1.48–122) was independently associated with higher CVD risk when we regarded a mean CIMT greater than 1.0 mm as an indicator of elevated risk for CVD [16].

Increasing numbers of otolaryngologist head and neck surgeons use US to evaluate the neck due to its advantages of noninvasiveness, feasibility, and reproducibility. Ultrasonography is widely utilized in the neck to assess the cervical lymph nodes, thyroid nodules, vocal fold, and other adjacent structures. HNC survivors usually receive regular follow-up at departments of otolaryngology. However, there are limited

studies using ultrasonography to assess the CIMT and limited studies that focus on the postirradiated neck. Our study adds novel insight to the importance of cervical ultrasonography in this high-risk group for otolaryngologists, though the efficacy and cost-effectiveness of routine screening still warrant further investigation.

People with hypertension, DM, or smoking habits were generally more likely to have an increased mean CIMT. After multivariate linear and logistic regression analyses were performed, our study demonstrated that HNC patients with prior radiotherapy were at higher risk for CVD, which is consistent with the results of prior studies [16, 20, 27] (Table 3). Therefore, in our opinion, previously irradiated patients who have multiple CVD risks, such as a higher bodyweight, hypertension, diabetes mellitus, and smoking status, should have strict lifestyle modifications to delay the progression of atherosclerosis and prevent both cardiac events and cerebrovascular events. In addition, it is of great importance to pay attention to further preventive strategies of the postirradiation group, since HNC patients may outlive their malignancies and may suffer from sequelae of treatment [28].

Limitations

The first limitation of this study is mainly related to the small sample size and all of the data being from patients at one institution. Second, this is a cross-sectional study using the CIMT as an earlier indicator for atherosclerosis. It is not a prospective cohort study that investigates stroke/TIA or coronary heart disease as direct endpoints. Third, because the design of this study did not include HNC patients without irradiation treatment, it remains unclear whether the observed increased CIMT can be fully explained by the effect of prior irradiation or whether malignancy itself may play a role. It could be expected that mCIMT might be greater for head and neck survivors with the previous neck

surgery than those without neck surgery. In our study, there are only 4 in the 20 cancer survivors have received neck dissection before RT. Although there was no difference of the mCIMT between patient who received neck dissection and those who did not (0.80 ± 0.30 mm vs. 0.76 ± 0.21 mm [Median \pm IQR], $p = 0.47$ by non-parametric $M-U$ test), surgical intervention still might be a potential confounding factor. Further studies are necessary to define the relation of neck dissection and CIMT in the future. Another limitation of our study is that most of our irradiated patients had a post-RT interval less than 5 years, so the longer post-RT interval may cause a higher risk for developing vascular disease [29]. We also found that the distribution of age and bodyweight is different between the cancer survivors and controls. We further selected an additional comparable control group, and the results from this analysis are summarized in Supplemental Table 1 for completeness. The results show that the mCIMT is still significantly different between these two groups.

Conclusion

In summary, we have provided evidence that irradiation was significantly associated with a higher risk for CVD. An automated measurement of the CIMT using high-resolution US can be an effective tool to assess this risk. Further studies are needed to establish preventive strategies against CVD for radiation-treated head and neck cancer (HNC) patients.

Acknowledgments This work was supported by grants from the Far Eastern Memorial Hospital Research Program (FEMH - 2017-C-012).

Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

- Pulte D, Brenner H (2010) Changes in survival in head and neck cancers in the late 20th and early 21st century: a period analysis. *Oncologist* 15(9):994–1001
- Funk GF, Karnell LH, Christensen AJ (2012) Long-term health-related quality of life in survivors of head and neck cancer. *Arch Otolaryngol Head Neck Surg* 138(2):123–133
- Haynes JC, Machtay M, Weber RS et al (2002) Relative risk of stroke in head and neck carcinoma patients treated with external cervical irradiation. *Laryngoscope* 112(10):1883–1887
- Liao LJ, Wang CT, Young YH, Cheng PW (2010) Real-time and computerized sonographic scoring system for predicting malignant cervical lymphadenopathy. *Head Neck* 32(5):594–598
- Lo WC, Cheng PW, Wang CT, Liao LJ (2013) Real-time ultrasound elastography: an assessment of enlarged cervical lymph nodes. *Eur Radiol* 23(9):2351–2357
- Cheng PW, Chou HW, Wang CT, Lo WC, Liao LJ (2014) Evaluation and development of a real-time predictive model for ultrasound investigation of malignant thyroid nodules. *Eur Arch Otorhinolaryngol* 271(5):1199–1206
- Fukuhara T, Matsuda E, Endo Y et al (2015) Impact of fibrotic tissue on shear wave velocity in thyroid: an ex vivo study with fresh thyroid specimens. *Biomed Res Int* 2015:569367
- Matsuda E, Fukuhara T, Donishi R et al (2017) Usefulness of a novel ultrasonographic classification based on anechoic area patterns for differentiating Warthin tumors from pleomorphic adenomas of the parotid gland. *Yonago Acta Med* 60(4):220–226
- Ahn D, Roh JH, Kim JK (2017) Ultrasound-guided core needle biopsy for head and neck mass lesions in patients undergoing antiplatelet or anticoagulation therapy: a preliminary report. *J Ultrasound Med* 36(7):1339–1346
- Laslett LJ, Alagona P Jr, Clark BA 3rd et al (2012) The worldwide environment of cardiovascular disease: prevalence, diagnosis, therapy, and policy issues: a report from the American College of Cardiology. *J Am Coll Cardiol* 60(25 Suppl):S1–S49
- Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M (2007) Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation* 115(4):459–467
- Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R (1986) Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. *Circulation* 74(6):1399–1406
- Shariat M, Alias NA, Biswal BM (2008) Radiation effects on the intima-media thickness of the common carotid artery in post-radiotherapy patients with head and neck malignancy. *Postgrad Med J* 84(997):609–612
- Faruolo M, Fiorentino A, Gallucci G, Lapadula L, Fusco V (2013) Intimal-medial thickness and carotid arteries lumen in irradiated patients for head and neck cancer: preliminary data of an observational study. *Clin Transl Oncol* 15(10):861–864
- Cheng SW, Ting AC, Wu LL (2002) Ultrasonic analysis of plaque characteristics and intimal-medial thickness in radiation-induced atherosclerotic carotid arteries. *Eur J Vasc Endovasc Surg* 24(6):499–504
- Gujral DM, Chahal N, Senior R, Harrington KJ, Nutting CM (2014) Radiation-induced carotid artery atherosclerosis. *Radiother Oncol* 110(1):31–38
- Liao LJ, Cho TY, Huang TW (2017) Assessment of carotid artery intima-media thickness in patients with obstructive sleep apnoea. *Clin Otolaryngol* 42(5):974–978
- Chambless LE, Heiss G, Folsom AR et al (1997) Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987–1993. *Am J Epidemiol* 146(6):483–494
- Sullivan GM, Feinn R (2012) Using effect size—or why the P value is not enough. *J Grad Med Educ* 4(3):279–282
- Plummer C, Henderson RD, O'Sullivan JD, Read SJ (2011) Ischemic stroke and transient ischemic attack after head and neck radiotherapy: a review. *Stroke* 42(9):2410–2418

21. Hopewell JW, Campling D, Calvo W et al (1986) Vascular irradiation damage: its cellular basis and likely consequences. *Br J Cancer Suppl* 7:181–191
22. Cheng SW, Ting AC, Lam LK, Wei WI (2000) Carotid stenosis after radiotherapy for nasopharyngeal carcinoma. *Arch Otolaryngol Head Neck Surg* 126(4):517–521
23. Xu J, Cao Y (2014) Radiation-induced carotid artery stenosis: a comprehensive review of the literature. *Interv Neurol* 2(4):183–192
24. Pereira Lima MN, Biolo A, Foppa M et al (2011) A prospective, comparative study on the early effects of local and remote radiation therapy on carotid intima–media thickness and vascular cellular adhesion molecule-1 in patients with head and neck and prostate tumors. *Radiother Oncol* 101(3):449–453
25. Liao W, Zhou H, Fan S et al (2018) Comparison of significant carotid stenosis for nasopharyngeal carcinoma between intensity-modulated radiotherapy and conventional two-dimensional radiotherapy. *Sci Rep* 8(1):13899
26. Dorth JA, Patel PR, Broadwater G, Brizel DM (2014) Incidence and risk factors of significant carotid artery stenosis in asymptomatic survivors of head and neck cancer after radiotherapy. *Head Neck* 36(2):215–219
27. Smith GL, Smith BD, Buchholz TA et al (2008) Cerebrovascular disease risk in older head and neck cancer patients after radiotherapy. *J Clin Oncol* 26(31):5119–5125
28. Jordan LC, Duffner PK (2009) Early-onset stroke and cerebrovascular disease in adult survivors of childhood cancer. *Neurology* 73(22):1816–1817
29. Cheng SW, Wu LL, Ting AC et al (1999) Irradiation-induced extracranial carotid stenosis in patients with head and neck malignancies. *Am J Surg* 178(4):323–328