Risk of ischaemic cerebrovascular events in head and neck cancer patients is associated with carotid artery radiation dose

van Aken, Evert S M; Paul van der Laan, Hans; Bijl, Hendrik P; Van den Bosch, Lisa; van den Hoek, Johanna G M; Dieters, Margriet; J H M Steenbakkers, Roel; Langendijk, Johannes A

Published in:
Radiotherapy and Oncology

DOI:
10.1016/j.radonc.2021.01.026

Publication date:
2021

Radiotherapy and Oncology 157 (2021) 182–187

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Risk of ischaemic cerebrovascular events in head and neck cancer patients is associated with carotid artery radiation dose

Evert S.M. van Aken, Hans Paul van der Laan *, Hendrik P. Bijl, Lisa Van den Bosch, Johanna G.M. van den Hoek, Margriet Dieters, Roel J.H.M. Steenbakkers, Johannes A. Langendijk

Department of Radiation Oncology, University of Groningen, University Medical Center Groningen, The Netherlands

ARTICLE INFO

Article history:
Received 3 September 2020
Received in revised form 13 January 2021
Accepted 18 January 2021
Available online 3 February 2021

Keywords:
Head and neck cancer
Radiotherapy
Carotid arteries
Stroke
Transient ischemic attack

ABSTRACT

Background and purpose: Radiotherapy in the head and neck area may cause vascular damage to the carotid arteries, increasing the risk of anterior circulation ischaemic cerebrovascular events (ICVEs). However, limited data exists on the relationship between radiation dose to the carotid arteries and risk of ICVE. The purpose of this study was therefore to determine the relationship between radiation dose to the carotid arteries and anterior circulation ICVE risk.

Materials and methods: A retrospective analysis of a prospective study cohort of 750 head and neck cancer patients treated with definitive (chemo)radiotherapy was performed. Carotid arteries were delineated, and dose–volume parameters of the treatment plans were calculated. ICVEs were scored prospectively and checked retrospectively by analysing all patient records. Cox proportional hazards analysis was performed to analyse the dose–effect relationships.

Results: The median follow-up period was 3.4 years, 27 patients experienced an ICVE and the 5-year cumulative risk was 4.6%. ICVE risk was significantly associated with dose to the carotid arteries. Multivariable analysis showed that the absolute volume (cm^3) of the carotid arteries that received at least a radiation dose of 10 Gy was the most important prognostic factor for ICVE (HR = 1.11, AUC = 0.68, $p < 0.001$).

Conclusion: This is the first large prospective cohort study that demonstrates an independent dose–effect relationship between radiation dose to the carotid arteries and the risk of ICVE. These findings may be used to identify patients at risk for ICVE after radiotherapy who may benefit from primary or secondary preventive measures.

Radiotherapy is recommended in around 80% of patients with malignancies in the head and neck area and often combined with surgery or systemic treatment [1,2]. Since survival rates are gradually improving due to more intensified regimens, there is increasing attention to the prevention of long-term side effects caused by (chemo)radiation [3]. In the head and neck region, the salivary glands and the swallowing structures are the most important organs at risk for developing long-term side effects, such as xerostomia, sticky saliva and dysphagia [2,4]. Although the main focus is to prevent xerostomia and dysphagia, radiotherapy in the head and neck region is also associated with an increased risk of ischaemic cerebrovascular events (ICVEs), including ischaemic strokes and transient ischaemic attacks [5]. The ICVE risk at least doubles after radiotherapy in the head and neck area [5–7], which indicates that ICVE should be considered as a clinically relevant side effect whose implications on quality of life may be devastating [8].

The majority of ICVEs affect the anterior circulation, which is supplied by the carotid arteries [9–11]. The posterior circulation is mainly supplied by the vertebral arteries [9,10] and ICVEs in this posterior territory are located in the brainstem, cerebellum and areas of the occipital lobe and temporal lobe [9,10,12]. However, arterial territories may vary widely among individual patients [10].

Although there is consensus that radiotherapy in the head and neck area causes vascular damage to the carotid arteries, leading to an increased ICVE risk [6,13], information on the relationship between carotid artery radiation dose and the risk of ICVE is lacking. Considering the current epidemiological and pathophysiological evidence [14–17], it is likely that there is a dose–effect relationship. Identifying the most clinically relevant dose–volume parameters is important for radiotherapy treatment planning opti-

Abbreviation: ICVE, ischaemic cerebrovascular event.

* Corresponding author at: University of Groningen, University Medical Center Groningen, Department of Radiation Oncology, PO Box 30001, 9700 RB Groningen, The Netherlands.
E-mail address: h.p.van.der.laan@umcg.nl (H.P. van der Laan).

https://doi.org/10.1016/j.radonc.2021.01.026
0167-8140/

misation, which is a critical component in the primary prevention of radiation-induced toxicity, such as ICVE [18].

Therefore, the purpose of this study is to determine the dose–effect relationship between radiation dose to the carotid arteries and the risk of anterior circulation ICVEs, to identify the most relevant dose–volume parameters and to develop an NTCP (normal tissue complication probability) model to predict the ICVE risk after radiotherapy.

Materials and methods

Study design and population

This is a retrospective analysis within a prospective cohort study of 750 patients with squamous cell carcinoma, originating in the nasopharynx, oropharynx, hypopharynx, oral cavity or larynx. All patients were treated between January 2007 and June 2016 with curatively intended definitive radiotherapy, chemoradiotherapy or cetuximab with radiotherapy. Treatment details are described in previous studies [19–21]. Baseline patient, tumour and treatment characteristics were prospectively collected. The Adult Comorbidity Evaluation-27 (ACE-27) questionnaire was used for patient-reported baseline comorbidity.

Outcome measures

The primary endpoint was the event of an ischaemic cerebrovascular accident or a transient ischaemic attack in the anterior circulation after completion of radiotherapy. Posterior circulation ICVEs were not counted as an event, as we aimed at explicitly analysing the influence of radiation-induced vascular injury to the carotid arteries. Also, ICVEs as a direct complication of a surgical procedure after completion of radiotherapy were not counted as an event. The specification 'anterior circulation' will generally be omitted in the results and the discussion of this study.

Patient data considering ICVE were prospectively collected as part of the prospective data registration of our department. Additionally, all patient records were retrospectively analysed to register all ICVEs and to collect missing survival data. Follow-up was analysed until 2018 or earlier due to loss to follow-up or shorter survival.

Delineation of organs at risk

Before the start of radiotherapy, every patient underwent a contrast-enhanced planning CT scan. The carotid arteries were delineated on these CT-scans according to consensus guidelines, as described by Brouwer et al., using Mirada (Mirada Medical Ltd., UK) [22]. Additionally, the carotid arteries were divided into the common carotid artery (CCA), bifurcation and internal carotid artery (ICA). The bifurcation was defined as the part of the artery 1 cm caudally to 1 cm cranially from the point where the CCA divides into the ICA and external carotid artery (which was not delineated). Relative (%) and absolute (cm^3) volumes receiving more than a particular dose (relative and absolute *V*-values), in addition to the mean dose (D_{mean}) and maximum dose (D_{max}) in the whole structure, were analysed per 10 Gy. These were derived for each structure from the clinical dose data, which were available for all patients.

Statistical analysis

Multivariate imputation by chained equations was performed for missing patient comorbidity data in order to use all available patient data and to minimise the risk of biased results [23,24]. Multiple imputation was performed 10 times, according to the protocol described by Van den Bosch et al. [24]. Univariable Cox proportional hazards analysis was performed to analyse different dose–volume parameters (including mean dose and relative and absolute *V*-values) of the carotid arteries and carotid artery substructures, together with patient comorbidity factors in relation to the endpoint. Dose volume parameters and clinically relevant comorbidity factors ($p < 0.2$) were selected for multivariable Cox proportional hazards analysis. In case of a Spearman's rank correlation > 0.8 between candidate variables, the dominant variable (lowest Bayesian information criterion (BIC) value) was selected as best candidate. Dose parameters of the carotid arteries were preferred over dose parameters of the carotid artery substructures when the BIC values were comparable. Multivariable Cox proportional hazards analysis was performed following a stepwise backward BIC-based selection procedure. After the final model was established, the model predictors of the multivariable Cox model were fitted using logistic regression to develop an NTCP model. The binary endpoint of this model was the cumulative ICVE incidence at 5 years. Finally, both the Cox and NTCP model were internally validated by bootstrapping (1000 bootstrap samples) and the model parameters were corrected for the estimated optimism, to prevent overfitting [24]. The following equation was used for the NTCP model:

$$\mathrm{NTCP} = 1/(1 + e^{-s})$$

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM corp., Armonk, NY, USA) and R version 3.4.2.

Results

Most patients (75%) in this study were male. The mean age at start of radiotherapy was 63 years. Tumours were primarily located in the larynx (45%) and the oropharynx (36%). Concurrent systemic treatment was given in 41% of the patients. These and further patient and treatment characteristics are listed in Table 1.

The median follow-up period after the end of radiotherapy was 3.4 years (0.1–10.6 years) (total observation time (range), regardless of an event). During follow-up, 27 patients (3.6%) experienced an ICVE: 18 patients experienced an ischaemic cerebrovascular accident and 9 patients experienced a transient ischaemic attack. Of these events, 18 were left-sided, 6 right-sided, while in 3 patients, laterality was unknown. The median time to event in patients with ICVE was 1.9 years. The 5-year and 8-year cumulative incidence of ICVE was 4.6% and 7.4%, respectively (Fig. 1).

No significant associations were found between patient and treatment characteristics and the cumulative incidence of ICVE (Table 2). However, a trend was seen for IMRT (intensity-modulated radiotherapy) ($p = 0.101$), current smokers ($p = 0.106$), patients with angina pectoris ($p = 0.061$), patients with heart failure ($p = 0.130$) and patients with a prior ICVE ($p = 0.082$) at baseline. The percentage of missing data before imputation is shown in the Supplementary data, Table 1.

The mean dose to the carotid arteries was 39.8 ± 0.5 Gy (mean ± SEM). Among the dose–volume parameters, the absolute V10Gy–V50Gy, relative V10Gy–V30Gy and maximum dose were significantly associated with ICVE risk (Table 3). The absolute V10Gy was the most significant predictor ($p < 0.001$) with the lowest BIC and an area under the curve (AUC) of 0.69. In patients with and patients without an ICVE after radiotherapy the absolute V10Gy of the carotid arteries was 19.0 ± 1.2 Gy and 15.8 ± 0.2 Gy, respectively. A dose–volume histogram illustrating the difference between patients with and without an ICVE after radiotherapy is shown in the Supplementary data, Fig. 1.

Table 1
Patient and treatment characteristics.

Characteristics		Total cohort number (n = 750)	%
Sex	Male	560	75%
	Female	190	25%
Age	≤65 years	457	61%
	>65 years	293	39%
Tumour location	Nasopharynx	30	4%
	Oropharynx	271	36%
	Hypopharynx	71	9%
	Larynx	334	45%
	Oral cavity	44	6%
T-classification	Tis	4	1%
	T1	123	16%
	T2	236	32%
	T3	182	24%
	T4	205	27%
N-classification	N0	333	44%
	N1	64	9%
	N2	330	44%
	N3	23	3%
Treatment technique	3D-CRT	86	12%
	IMRT	546	73%
	VMAT	106	14%
	IMRT + VMAT	12	2%
Treatment modality	Conventional radiotherapy	149	20%
	Accelerated radiotherapy	294	39%
	Concurrent chemotherapy	242	32%
	Concurrent cetuximab	65	9%
Smoking	Yes, currently	402	54%
	Yes, in the past	254	34%
	No	94	13%
Alcohol use (currently or in the past)	Yes	567	76%
	No	183	24%
HPV status (oropharyngeal patients tested only)	Positive	104	14%
	Negative	646	86%
Diabetes Mellitus	Yes	88	12%
	No	662	88%
Hypertension	Yes	231	31%
	No	519	69%
Angina pectoris	Yes	14	2%
	No	736	98%
Cardiac arrhythmia	Yes	60	8%
	No	690	92%
Heart failure	Yes	39	5%
	No	711	95%
Prior ICVE	Yes	74	10%
	No	676	90%
Re-irradiation during follow-up	Yes	44	6%
	No	706	94%

Abbreviations: 3D-CRT = three-dimensional conformal radiotherapy, IMRT = intensity-modulated radiotherapy, VMAT = volumetric modulated arc therapy, HPV = human papillomavirus, ICVE = ischaemic cerebrovascular event.

In the multivariable analysis, the absolute V10Gy of the carotid arteries was selected as sole predictor in the model for ICVE risk. After internal validation, the model had an hazard ratio (HR) of 1.11 and an AUC of 0.68 ($p < 0.001$).

The final NTCP model was fitted to estimate the cumulative ICVE risk within 5 years after radiotherapy. This resulted in the following linear predictor for the NTCP model: −5.938 + 0.138 * (absolute V10Gy of the carotid arteries). The AUC of this model was 0.68. A visualisation of this model is shown in Fig. 2. The calibration plot after bootstrapping can be found in the Supplementary data, Fig. 2.

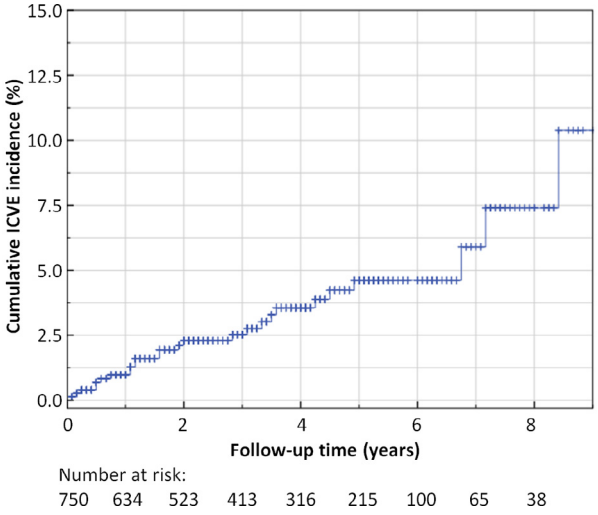

Fig. 1. Cumulative anterior circulation ICVE incidence over time. *Abbreviation:* ICVE = ischaemic cerebrovascular event.

Discussion

This study demonstrates a dose–effect relationship between radiation dose to the carotid arteries and the risk of anterior circulation ICVE in head and neck cancer patients treated with curatively intended definitive radiotherapy, including when combined with systemic treatment. The absolute volume of the carotid arteries that received at least 10 Gy was the most important prognostic factor for ICVE.

To the best of our knowledge, no other studies have shown a direct relationship between carotid artery radiation dose and ICVE risk. Carpenter et al. analysed the dose–effect relationship between carotid artery radiation dose and the combined endpoints strokes, transient ischaemic attacks and asymptomatic carotid artery stenosis, but they did not find a significant dose–effect relationship [25]. This might be caused by the combination of these three endpoints, the smaller cohort size (n = 366) or the absence of a radiation dose analysis below V40Gy.

Several studies have shown a dose–effect relationship between radiation dose and vascular injury. The first radiation-induced visible change is an increase in the intima-media thickness, which is an ultrasound-assisted measure of the thickness of the artery wall [6,14,26,27]. This measure can be used as an early marker of atherosclerosis [28]. Gianicolo et al. demonstrated a linear relationship between radiation dose to the neck and carotid intima media thickness (CIMT) [14]. Martin et al. suggested a threshold dose of 35 Gy, based on CIMT measurements [15], but Vatanen et al. showed that radiation doses of 10–12 Gy (total body irradiation) already cause vascular damage [16]. In atomic bomb survivors, a study by Shimizu et al. even showed an increased risk of stroke and heart disease at estimated doses above 0.5 Gy, as well as a relative risk increase per Gy [17]. Some studies have suggested that atherosclerotic plaques caused by radiotherapy are less dense and calcified than 'classical' atherosclerosis, thus probably carrying an even higher risk of ICVEs [27,29–31].

The HR found in this study is in line with results found by Dorth et al., who analysed the relationship between radiation dose to the bifurcation and the risk of carotid artery stenosis [32]. In our study,

Table 2
Univariable analysis: patient and treatment characteristics.

Characteristics	HR	95% CI	AUC	BIC	*p*
Sex (female)	1.13	0.50–2.60	0.499	321.7	0.764
Age	1.02	0.98–1.06	0.504	320.8	0.324
Accelerated radiotherapy	0.77	0.35–1.68	0.507	321.3	0.509
Concurrent systemic treatment	0.85	0.38–1.88	0.529	321.6	0.681
Concurrent chemotherapy	0.64	0.26–1.59	0.552	320.8	0.336
Concurrent cetuximab	1.87	0.56–6.26	0.523	320.9	0.310
IMRT	2.48	0.84–7.36	0.565	318.5	0.101
VMAT	0.73	0.17–3.19	0.526	321.6	0.679
Smoking (currently)	1.94	0.87–4.31	0.582	319.0	0.106
Smoking (>10 pack years)	1.46	0.38–5.62	0.527	320.7	0.579
Alcohol (>21 units/week)	0.80	0.21–3.01	0.518	321.3	0.742
HPV status	0.01	0.00 - ∞	0.564	315.9	0.615
Diabetes mellitus	1.25	0.42–3.68	0.527	321.5	0.692
Hypertension	0.92	0.39–2.16	0.515	321.6	0.851
Angina pectoris	4.00	0.94–17.05	0.522	319.3	0.061
Cardiac arrhythmia	1.19	0.32–4.42	0.512	321.5	0.800
Heart failure	2.79	0.74–10.50	0.537	319.6	0.130
Prior ICVE	2.37	0.90–6.28	0.542	319.3	0.082
Re-irradiation during follow-up	1.35	0.32–5.74	0.508	321.6	0.681

Abbreviations: HR = hazard ratio, CI = confidence interval, AUC = area under the curve, BIC = Bayesian information criterion, IMRT = intensity-modulated radiotherapy, VMAT = volumetric modulated arc therapy, HPV = human papillomavirus, ICVE = ischaemic cerebrovascular event.

Table 3
Univariable analysis: carotid artery dose–volume parameters.

Dose–volume parameters: carotid arteries	HR	95% CI	AUC	BIC	*p*
Volume (cm^3)	1.09	1.02–1.16	0.664	315.8	*0.011
Dmean (Gy)	1.03	1.00–1.07	0.603	317.5	0.057
Dmax (Gy)	1.14	1.01–1.29	0.634	315.8	*0.034
V10Gy (%)	1.02	1.00–1.05	0.609	316.7	*0.045
V20Gy (%)	1.02	1.00–1.05	0.615	316.4	*0.040
V30Gy (%)	1.02	1.00–1.04	0.613	316.7	*0.044
V40Gy (%)	1.02	1.00–1.04	0.601	317.1	0.054
V50Gy (%)	1.02	1.00–1.04	0.592	317.3	0.054
V60Gy (%)	1.01	0.98–1.03	0.562	321.5	0.572
V70Gy (%)	1.02	0.97–1.07	0.589	321.2	0.398
V10Gy (cm^3)	1.14	1.06–1.22	0.694	307.7	*<0.001
V20Gy (cm^3)	1.14	1.06–1.22	0.695	307.9	*<0.001
V30Gy (cm^3)	1.13	1.06–1.21	0.693	308.6	*<0.001
V40Gy (cm^3)	1.13	1.05–1.20	0.690	309.5	*0.001
V50Gy (cm^3)	1.12	1.04–1.20	0.664	310.6	*0.001
V60Gy (cm^3)	1.06	0.97–1.15	0.600	320.5	0.227
V70Gy (cm^3)	1.06	0.88–1.27	0.597	321.4	0.520

Abbreviations: HR = hazard ratio, CI = confidence interval, AUC = area under the curve, BIC = Bayesian information criterion.
*$p < 0.05$.

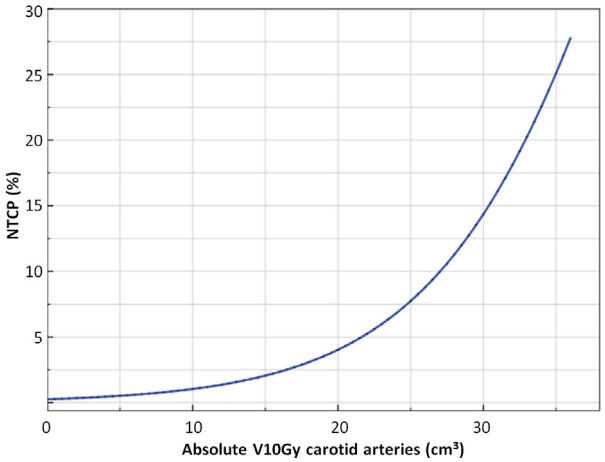

Fig. 2. NTCP model for cumulative anterior circulation ICVE risk within 5 years after radiotherapy. *Abbreviations:* NTCP = normal tissue complication probability. ICVE = ischaemic cerebrovascular event.

the HR of the mean dose to the carotid arteries was 1.37 for every 10 Gy and the HR of the mean dose to the bifurcation was 1.27 for every 10 Gy, but neither variable reached statistical significance. Dorth et al. found that every 10 Gy increase of the mean dose to the bifurcation leads to an HR for carotid artery stenosis of 1.4, which is within the 95% CI of the current study, despite the fact that they delineated the bifurcation differently [32].

According to the NTCP model, the baseline ICVE risk (without radiotherapy) within 5 years is only 0.26%, which may be an underestimation of the actual risk in these patients [33], because in logistic regression time-to-event and shorter survival is not accounted for. The lower baseline ICVE risk might also be caused by only counting anterior circulation events and by the distribution of ICVEs when plotted against the absolute V10Gy (Supplementary data, Fig. 3).

The results of this study indicate that carotid artery volume might play a role in ICVE risk. The incidence of stroke [34] and cardiovascular events [35–37] is associated with the outer diameter of the CCA, which is possibly caused by chronically elevated blood pressure [34,38]. However, in our study (patient-reported) hypertension was not associated with increased ICVE risk. Also, a higher

CIMT may lead to a larger carotid artery diameter [38,39]. An alternative option is that in radiotherapy patients, ICVE risk is associated with the carotid volume, because a larger carotid volume leads to a larger area at risk for developing radiation-induced vascular damage.

Among the carotid artery substructures, the dose–volume parameters of the bifurcation and in particular the CCA showed the most substantial dose–effect relationship (Supplementary data, Tables 2–4). These findings are in line with studies showing that radiotherapy-induced vascular changes particularly occur in the CCA [30,40].

The current study was based on a large cohort, included in a standardised follow-up programme. However, the median follow-up period was only 3.4 years, which is relatively short for this endpoint. Dorresteijn et al. reported a median interval between radiotherapy and stroke of 10.9 years [41] and there is consensus that the latency period between radiotherapy and these symptoms can be long [6]. In contrast, some studies report early vascular changes after radiotherapy [27,42]. In our study, haemorrhagic events, events during or directly after a surgical procedure and posterior circulation events were not counted, in order to merely analyse ICVEs that are most likely related to carotid artery injury. Despite extensive patient record analysis, our method might lead to underestimation of events because of missing information of other hospitals.

Some studies suggest that common vascular risk factors may have a limited influence on ICVE risk after head and neck radiotherapy [6,29,43]. In our study, the impact of patient characteristics and systemic therapy was low, although a trend was seen for risk factors for cardiovascular events such as smoking, angina pectoris, heart failure and prior ICVE ($p < 0.2$). However, baseline comorbidity was reported by patients and the finding that no significant effect of comorbidities on ICVE risk was observed may be related to the power of the study (the limited number of events combined with the low prevalence of some of the comorbidities). In other studies, age [44-46], hyperlipidaemia [44], smoking [47], platelet counts [46], cholesterol levels [40], diabetes [40], prior cerebrovascular symptoms [45] and the number of Framingham risk factors [32] were associated with the development of vascular changes after radiotherapy.

The role of patient characteristics in other studies implies that it remains important to enter patient comorbidity, lifestyle factors and medication use (e.g. anticoagulants) in future studies on cardiovascular events after radiotherapy. Also, new voxel-based data mining techniques may enhance identification of different dose distributions and levels of radiosensitivity within organs at risk, to further improve NTCP predictions [48,49].

The results of this study may be used for primary prevention by optimising treatment plans, although the applicability is expected to be limited as the inclusion of elective nodal areas in the target volumes almost always includes the full circumference of carotid arteries following adequate margins from CTV to PTV. However, in unilateral irradiation and treatment of early glottic cancer without elective nodal irradiation, reduction of the V10Gy is possible and may decrease the risk of ICVE. Secondary prevention may be accomplished by identifying patients at risk and subsequent regular screening or pharmacological treatment [6]. Some studies suggest a beneficial effect of statin use, but this needs further investigation [50–52].

In conclusion, this is the first prospective cohort study that demonstrates a dose–effect relationship between radiation dose to the carotid arteries and the risk of ICVE. Our results implicate that the absolute V10Gy to the entire carotid arteries is an independent prognostic factor for anterior circulation ICVE risk after radiotherapy in head and neck cancer patients. These findings may lead to more adequate ICVE risk prediction in order to identify patients that may benefit from either primary or secondary preventive measures.

Conflict of interest notification

The authors state that the research presented in this manuscript is free of conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.01.026.

References

[1] Borras JM, Barton M, Grau C, Corral J, Verhoeven R, Lemmens V, et al. The impact of cancer incidence and stage on optimal utilization of radiotherapy: Methodology of a population based analysis by the ESTRO-HERO project. Radiother Oncol 2015;116:45–50. https://doi.org/10.1016/j.radonc.2015.04.021.

[2] Strojan P, Hutcheson KA, Eisbruch A, Beitler JJ, Langendijk JA, Lee AWM, et al. Treatment of late sequelae after radiotherapy for head and neck cancer. Cancer Treat Rev 2017;59:79–92. https://doi.org/10.1016/j.ctrv.2017.07.003.

[3] Grégoire V, Langendijk JA, Nuyts S. Advances in radiotherapy for head and neck cancer. J Clin Oncol 2015;33:3277–84. https://doi.org/10.1200/JCO.2015.61.2994.

[4] Beetz I, Schilstra C, Visink A, van der Schaaf A, Bijl HP, van der Laan BFAM, et al. Role of minor salivary glands in developing patient-rated xerostomia and sticky saliva during day and night. Radiother Oncol 2013;109:311–6. https://doi.org/10.1016/j.radonc.2013.06.040.

[5] Plummer C, Henderson RD, O'Sullivan JD, Read SJ. Ischemic stroke and transient ischemic attack after head and neck radiotherapy: A review. Stroke 2011;42:2410–8. https://doi.org/10.1161/STROKEAHA.111.615203.

[6] Fernández-Alvarez V, López F, Suárez C, Strojan P, Eisbruch A, Silver CE, et al. Radiation-induced carotid artery lesions. Strahleninduzierte Läsionen der Karotisarterie 2018;194:699–710. https://doi.org/10.1007/s00066-018-1304-4.

[7] Huang R, Zhou Y, Hu S, Ren G, Cui F, Zhou P-K. Radiotherapy exposure in cancer patients and subsequent risk of stroke: A systematic review and meta-analysis. Front Neurol 2019;10:1–12. https://doi.org/10.3389/fneur.2019.00233.

[8] Carod-Artal FJ, Egido JA. Quality of life after stroke: The importance of a good recovery. Cerebrovasc Dis 2009;27:204–14. https://doi.org/10.1159/000200461.

[9] Merwick A, Werring D. Posterior circulation ischaemic stroke. BMJ 2014;348. https://doi.org/10.1136/bmj.g3175. g3175–g3175.

[10] van Laar PJ, Hendrikse J, Golay X, Lu H, van Osch MJP, van der Grond J. In vivo flow territory mapping of major brain feeding arteries. Neuroimage 2006;29:136–44. https://doi.org/10.1016/j.neuroimage.2005.07.011.

[11] Floßmann E, Rothwell PM. Prognosis of vertebrobasilar transient ischaemic attack and minor stroke. Brain 2003;126:1940–54. https://doi.org/10.1093/brain/awg197.

[12] Searls DE, Pazdera L, Korbel E, Vysata O, Caplan LR. Symptoms and signs of posterior circulation ischemia in the new England medical center posterior circulation registry. Arch Neurol 2012;69:346–51. https://doi.org/10.1001/archneurol.2011.2083.

[13] Lee JY, Kim YA, Kim HS, Back JH, Jung YH, Lee D-H, et al. Radiotherapy can increase the risk of ischemic cerebrovascular disease in head and neck cancer patients: A Korean population-based cohort study. Radiother Oncol 2020;142:85–91. https://doi.org/10.1016/j.radonc.2019.09.025.

[14] Gianicolo ME, Gianicolo EAL, Tramacere F, Andreassi MG, Portaluri M. Effects of external irradiation of the neck region on intima media thickness of the common carotid artery. Cardiovasc Ultrasound 2010;8:8. https://doi.org/10.1186/1476-7120-8-8.

[15] Martin JD, Buckley AR, Graeb D, Walman B, Salvian A, Hay JH. Carotid artery stenosis in asymptomatic patients who have received unilateral head-and-neck irradiation. Int J Radiat Oncol Biol Phys 2005;63:1197–205. https://doi.org/10.1016/j.ijrobp.2005.04.017.

[16] Vatanen A, Sarkola T, Ojala TH, Turanlahti M, Jahnukainen T, Saarinen-Pihkala UM, et al. Radiotherapy-related arterial intima thickening and plaque formation in childhood cancer survivors detected with very-high resolution ultrasound during young adulthood. Pediatr Blood Cancer 2015;62:2000–6. https://doi.org/10.1002/pbc.25616.

[17] Shimizu Y, Kodama K, Nishi N, Kasagi F, Suyama A, Soda M, et al. Radiation exposure and circulatory disease risk: Hiroshima and Nagasaki atomic bomb survivor data, 1950–2003. BMJ 2010;340. https://doi.org/10.1136/bmj.b5349. b5349–b5349.

[18] Lyman JT, Wolbarst AB. Optimization of radiation therapy, IV: A dose-volume histogram reduction algorithm. Int J Radiat Oncol Biol Phys 1989;17:433–6. https://doi.org/10.1016/0360-3016(89)90462-8.

[19] van der Laan HP, Gawryszuk A, Christianen MEMC, Steenbakkers RJHM, Korevaar EW, Chouvalova O, et al. Swallowing-sparing intensity-modulated radiotherapy for head and neck cancer patients: Treatment planning

optimization and clinical introduction. Radiother Oncol 2013;107:282–7. https://doi.org/10.1016/j.radonc.2013.05.004.
[20] van Dijk LV, Brouwer CL, van der Schaaf A, Burgerhof JGM, Beukinga RJ, Langendijk JA, et al. CT image biomarkers to improve patient-specific prediction of radiation-induced xerostomia and sticky saliva. Radiother Oncol 2017;122:185–91. https://doi.org/10.1016/j.radonc.2016.07.007.
[21] van Rijn-Dekker MI, van den Bosch L, van den Hoek JGM, Bijl HP, van Aken ESM, van der Hoorn A, et al. Impact of sarcopenia on survival and late toxicity in head and neck cancer patients treated with radiotherapy. Radiother Oncol 2020;147. https://doi.org/10.1016/j.radonc.2020.03.014.
[22] Brouwer CL, Steenbakkers RJHM, Bourhis J, Budach W, Grau C, Grégoire V, et al. CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines. Radiother Oncol 2015;117:83–90. https://doi.org/10.1016/j.radonc.2015.07.041.
[23] van Buuren S, Groothuis-Oudshoorn K. mice: multivariate imputation by chained equations in R. J Stat Softw 2011;45:1–67. https://doi.org/10.18637/jss.v045.i03.
[24] Van den Bosch L, Schuit E, van der Laan HP, Reitsma JB, Moons KGM, Steenbakkers RJHM, et al. Key challenges in normal tissue complication probability model development and validation: towards a comprehensive strategy. Radiother Oncol 2020;148:151–6. https://doi.org/10.1016/j.radonc.2020.04.012.
[25] Carpenter DJ, Mowery YM, Broadwater G, Rodrigues A, Wisdom AJ, Dorth JA, et al. The risk of carotid stenosis in head and neck cancer patients after radiation therapy. Oral Oncol 2018;80:9–15. https://doi.org/10.1016/j.oraloncology.2018.02.021.
[26] Gujral DM, Chahal N, Senior R, Harrington KJ, Nutting CM. Radiation-induced carotid artery atherosclerosis. Radiother Oncol 2014;110:31–8. https://doi.org/10.1016/j.radonc.2013.08.009.
[27] Toprak U, Aytaş İL, Ustuner E, Habiboğlu R, Aslan N, Paşaoğlu E, et al. Sonographic assessment of acute changes in plaque size and echogenicity and in intima-media thickness of carotid arteries after neck radiation therapy. J Clin Ultrasound 2012;40:566–71. https://doi.org/10.1002/jcu.v40.910.1002/jcu.21971.
[28] Gujral DM, Shah BN, Chahal NS, Bhattacharyya S, Hooper J, Senior R, et al. Carotid intima-medial thickness as a marker of radiation-induced carotid atherosclerosis. Radiother Oncol 2016;118:323–9. https://doi.org/10.1016/j.radonc.2015.11.025.
[29] Thalhammer C, Husmann M, Glanzmann C, Studer G, Amann-Vesti BR. Carotid artery disease after head and neck radiotherapy. Vasa 2015;44:23–30. https://doi.org/10.1024/0301-1526/a000403.
[30] Lam WWM, Liu KH, Leung SF, Wong KS, So NMC, Yuen HY, et al. Sonographic characterisation of radiation-induced carotid artery stenosis. Cerebrovasc Dis 2002;13:168–73. https://doi.org/10.1159/000047771.
[31] Reilly LM, Lusby RJ, Hughes L, Ferrell LD, Stoney RJ, Ehrenfeld WK. Carotid plaque histology using real-time ultrasonography. Clinical and therapeutic implications. Am J Surg 1983;146:188–93. https://doi.org/10.1016/0002-9610(83)90370-7.
[32] Dorth JA, Patel PR, Broadwater G, Brizel DM. Incidence and risk factors of significant carotid artery stenosis in asymptomatic survivors of head and neck cancer after radiotherapy. Head Neck 2014;36:215–9. https://doi.org/10.1002/hed.v36.210.1002/hed.23280.
[33] 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;96:589–96. https://doi.org/10.1016/j.ijrobp.2016.07.007.
[34] Polak JF, Sacco RL, Post WS, Vaidya D, Arnan MK, O'Leary DH. Incident stroke is associated with common carotid artery diameter and not common carotid artery intima-media thickness. Stroke 2014;45:1442–6. https://doi.org/10.1161/STROKEAHA.114.004850.
[35] Kozakova M, Morizzo C, La Carrubba S, Fabiani I, Della Latta D, Jamagidze J, et al. Associations between common carotid artery diameter, Framingham risk score and cardiovascular events. Nutr Metab Cardiovasc Dis 2017;27:329–34. https://doi.org/10.1016/j.numecd.2017.01.001.
[36] Eigenbrodt ML, Sukhija R, Rose KM, Tracy RE, Couper DJ, Evans GW, et al. Common carotid artery wall thickness and external diameter as predictors of prevalent and incident cardiac events in a large population study. Cardiovasc Ultrasound 2007;5. https://doi.org/10.1186/1476-7120-5-11.
[37] Baldassarre D, Hamsten A, Veglia F, de Faire U, Humphries SE, Smit AJ, et al. Measurements of carotid intima-media thickness and of interadventitia common carotid diameter improve prediction of cardiovascular events. J Am Coll Cardiol 2012;60:1489–99. https://doi.org/10.1016/j.jacc.2012.06.034.
[38] Polak JF, Kronmal RA, Tell GS, O'Leary DH, Savage PJ, Gardin JM, et al. Compensatory increase in common carotid artery diameter. Relation to blood pressure and artery intima-media thickness in older adults. Cardiovascular Health Study. Stroke 1996;27:2012–5. https://doi.org/10.1161/01.STR.27.11.2012.
[39] Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med 1987;316:1371–5. https://doi.org/10.1056/NEJM198705283162204.
[40] Kim BJ, Kang HG, Lee SW, Jung J, Lee MH, Kang DW, et al. Changes in the common carotid artery after radiotherapy: wall thickness, calcification, and atherosclerosis. J Clin Neurol 2018;14:35. https://doi.org/10.3988/jcn.2018.14.1.35.
[41] Dorresteijn LDA, Kappelle AC, Boogerd W, Klokman WJ, Balm AJM, Keus RB, et al. Increased risk of ischemic stroke after radiotherapy on the neck in patients younger than 60 years. J Clin Oncol 2002;20:282–8. https://doi.org/10.1200/JCO.2002.20.1.282.
[42] Faruolo M, Fiorentino A, Gallucci G, Lapadula L, Fusco V. Intimal-medial thickness and carotid arteries lumen in irradiated patients for head and neck cancer: preliminary data of an observational study. Clin Transl Oncol 2013;15:861–4. https://doi.org/10.1007/s12094-013-1023-3.
[43] Gujral DM, Shah BN, Chahal NS, Bhattacharyya S, Senior R, Harrington KJ, et al. Do traditional risk stratification models for cerebrovascular events apply in irradiated head and neck cancer patients?. QJM 2016;109:383–9. https://doi.org/10.1093/qjmed/hcv120.
[44] Chang Y-J, Chang T-C, Lee T-H, Ryu S-J. Predictors of carotid artery stenosis after radiotherapy for head and neck cancers. J Vasc Surg 2009;50:280–5. https://doi.org/10.1016/j.jvs.2009.01.033.
[45] Cheng SWK, Wu LLH, Ting ACW, Lau H, Lam LK, Wei WI. Irradiation-induced extracranial carotid stenosis in patients with head and neck malignancies. Am J Surg 1999;178:323–8. https://doi.org/10.1016/S0002-9610(99)00184-1.
[46] Huang T-L, Hsu H-C, Chen H-C, Lin H-C, Chien C-Y, Fang F-M, et al. Long-term effects on carotid intima-media thickness after radiotherapy in patients with nasopharyngeal carcinoma. Radiat Oncol 2013;8:261. https://doi.org/10.1186/1748-717X-8-261.
[47] Cheng SW, Ting AC, Lam LK, Wei WI. Carotid stenosis after radiotherapy for nasopharyngeal carcinoma. Arch Otolaryngol Head Neck Surg 2000;126:517–21. https://doi.org/10.1001/archotol.126.4.517.
[48] Monti S, Palma G, D'Avino V, Gerardi M, Marvaso G, Ciardo D, et al. Voxel-based analysis unveils regional dose differences associated with radiation-induced morbidity in head and neck cancer patients. Sci Rep 2017;7. https://doi.org/10.1038/s41598-017-07586-x.
[49] Beasley W, Thor M, McWilliam A, Green A, Mackay R, Slevin N, et al. Image-based data mining to probe dosimetric correlates of radiation-induced trismus. Int J Radiat Oncol 2018;102:1330–8. https://doi.org/10.1016/j.ijrobp.2018.05.054.
[50] Boulet J, Peña J, Hulten EA, Neilan TG, Dragomir A, Freeman C, et al. Statin use and risk of vascular events among cancer patients after radiotherapy to the thorax, head, and neck. J Am Heart Assoc 2019;8. https://doi.org/10.1161/JAHA.117.005996.
[51] Addison D, Lawler PR, Emami H, Janjua SA, Staziaki PV, Hallett TR, et al. Incidental statin use and the risk of stroke or transient ischemic attack after radiotherapy for head and neck cancer. J Stroke 2018;20:71–9. https://doi.org/10.5853/jos.2017.01802.
[52] Gaugler M-H, Vereycken-Holler V, Squiban C, Vandamme M, Vozenin-Brotons M-C, Benderitter M. Pravastatin limits endothelial activation after irradiation and decreases the resulting inflammatory and thrombotic responses. Radiat Res 2005;163:479–87. https://doi.org/10.1667/RR3302.