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Increased carotid wall thickening after radiotherapy on the neck

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Abstract

Patients treated for head and neck tumours with local radiotherapy (RT) on the neck harbour an increased risk of stroke. This may be due to accelerated atherosclerotic changes within the RT-field; however, the real impact of local RT on the carotid artery remains debatable. The aim of the present study was to assess the difference in carotid wall thickness (intima-media thickness) in 42 unilaterally irradiated parotid tumour patients by performing B-mode ultrasonography. A mean difference in intima-media thickness (IMT) of the irradiated compared with the non-irradiated carotid artery of 0.30 mm ($P = 0.031$) was found. A significant correlation was established with a longer post-RT interval ($P = 0.008$). RT on the neck is associated with increased thickening of carotid IMT. Screening and treatment of additional cerebrovascular risk factors which contribute to further IMT thickening and stroke development is recommended, especially in radiotherapy patients with a favourable prognosis.

Keywords: Carotid artery; Radiotherapy; Injurious complications of therapeutic radiology; Head and neck tumours; B-mode ultrasound; Intima-media thickness

1. Introduction

Patients treated for head and neck tumours with local radiotherapy (RT) harbour an increased risk of stroke [1,2]. The underlying mechanism has not been completely identified, but accelerated atherosclerosis of the vessels in the RT-field is thought to play an important role [3]. This mechanism is corroborated by others [4,5] who show a significantly higher risk of carotid artery stenosis in patients irradiated on the neck compared with age- and sex-matched controls. In these studies, however, the effect of RT on the degree of carotid artery stenosis was compared with a healthy control group and could therefore give an overestimation of the effect of RT on vascular changes. This is caused by the fact that patients with head and neck tumours generally have more risk factors for atherosclerosis, especially nicotine abuse.

B-mode ultrasonography is a reliable and non-invasive technique for assessing the inner wall thickness of the carotid artery. The inner wall is usually expressed as the intima-media thickness (IMT) [6]. Carotid plaques and increase of carotid IMT are shown to be independent predictors of cerebrovascular disease [7–9]. We therefore studied the effect of RT on the carotid artery IMT in unilaterally irradiated patients, allowing the

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patient's contra-lateral carotid artery to serve as an internal control.

2. Patients and methods

2.1. Patients

We studied 42 consecutive patients from whom follow-up could be obtained. All patients had received postoperative unilateral RT on the neck. Two types of patients were studied: (i) patients with parotid carcinoma and (ii) patients with pleomorphic adenoma in whom massive uncontrolled tumour spill or incomplete resection necessitated RT. All patients gave written consent to participate in the study. Patients who had also been treated with chemotherapy were excluded.

2.2. Intima-media thickness

Two-dimensional carotid imaging studies were performed with a 7.5-MHz linear array transducer [10]. The IMT was defined as the distance between the echogenic line representing the blood–intima interface and the echogenic line representing the media–adventitia interface. The IMT was measured on the posterior wall in the longitudinal plane in an anterolateral approach with the transducer head perpendicular to the vessel. IMT was measured either at the internal carotid artery (ICA) or at the bifurcation, or both, depending on the anatomical borders of the RT-field (Fig. 1). The difference in IMT was calculated as the IMT at the irradiated side minus the IMT at the non-irradiated side. If the bifurcation was also located in the RT-field, the difference in IMT was also calculated at this level. The mean

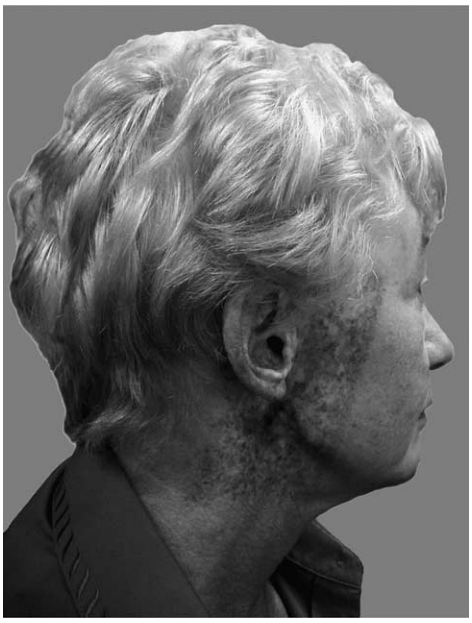

Fig. 1. Lateral view of the neck and face of a patient irradiated for a parotid carcinoma on the right side, illustrating the skin changes in the former RT-field. Note the demarcation of the RT-field and the association with the carotid artery.

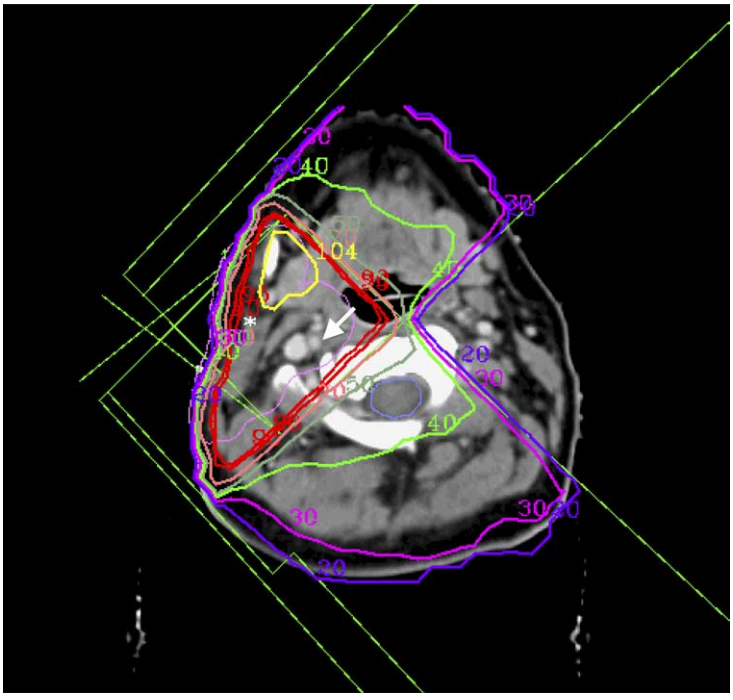

Fig. 2. Contrast-enhanced computed tomography (CT)-scan at the level of the upper neck of a patient with a right-sided parotid carcinoma, illustrating the position of the carotid artery (white arrow) next to the jugular vein within the radiation fields (red lines represent 90% dose).

difference in IMT at both locations was used for this group of patients.

2.3. Radiation therapy

The radiation technique was two lateral oblique-wedged fields that encompass the parotid gland and upper neck nodal regions with 4 or 8-MV photons. These fields included the unilateral carotid artery. The estimated dose of RT was 90–100% of the total administered dose (Fig. 2). RT-variables including time of RT, dose and fractionation schedule were assessed. Post-RT interval was determined as the time span between RT and IMT measurement (years).

2.4. Measurements of other covariates

All patients completed a standardised questionnaire to assess patients' and family history of cerebrovascular disease. Blood pressure was measured twice on the right arm in a sitting position using a mercury sphygmomanometer. Hypertension was defined when systolic blood pressure $\geqslant$160 mmHg and/or a diastolic blood pressure $\geqslant$95 mmHg in both measurements; and/or the patient was taking blood pressure-lowering medication. Diabetes mellitus was considered present if the patient was taking oral anti-diabetics or insulin. Hypercholesterolaemia was present if the patient was taking cholesterol-lowering drugs. Smoking was considered present if the patient was a current smoker or had quit smoking less than 3 years ago.

2.5. Statistical analysis

A paired *t*-test was conducted for comparison of the IMT at the irradiated versus the non-irradiated side. Stepwise linear regression analysis was used to examine the association between age at RT, sex, the post-RT interval, other covariates and the difference in IMT. We performed post-RT interval stratified analysis to investigate the effect of the post-RT interval on the IMT.

3. Results

3.1. Patients

Forty-two patients (20 males, 22 females) were included in the study, consisting of 43% patients with a parotid carcinoma and 57% patients with a pleomorphic adenoma. The median age at RT was 47.4 years (range 23–77 years). The median post-RT interval was 9.8 years (range 3.4–27.2 years).

The total therapeutic radiation dose ranged from 40 to 66 Gy and was delivered in fractions of 2 Gy. Patient characteristics and an outline of other covariates are summarised in Table 1.

3.2. Intima-media thickness

Overall, the mean IMT on the irradiated side was 1.13 mm (standard deviation (SD) ± 0.85 mm) and 0.83 mm (SD ± 0.51 mm) on the non-irradiated side. The mean difference in IMT was 0.30 mm (95% CI 0.03–0.57, paired *t*-test, $P = 0.031$, Table 2).

There was a linear correlation between the IMT difference and the duration of the post-RT interval (unstandardised β(SE) = 0.062 IMT-increase/year post-RT (0.020), $P = 0.008$). Adjustment for other covariates did not alter the magnitude of the association.

Stratification for post-RT interval showed a mean difference in IMT of 0.67 mm during a post-RT interval of more than 10 years ($P = 0.007$), whereas there was no difference in IMT during the first 10 years (Table 2).

Table 1
Characteristics of study population

Characteristics	*n*	%
Median age (range) (years)	47 (23–77)	
Gender		
Male	20	48
Female	22	52
Tumour type (%)		
Parotid carcinoma	18	43
Pleomorphic adenoma	24	57
Radiotherapy (%) (Gy)		
40–50	2	5
50–60	31	74
>60	9	21
Smoking		
Current smoker	12	29
Smoking past	12	29
Non-smoker	18	43
Hypertension	7	17
Diabetes mellitus	0	0
Hypercholesterolaemia	6	14
Atrial fibrillation	4	10
Family history of cardiovascular disease	11	26
History of cardiovascular disease	4	10

Table 2
Intima-media thickness (IMT) (mm) of the irradiated carotid artery and the non-irradiated carotid artery, overall and divided in 10-year post-RT intervals

Post-RT interval	Mean IMT (mm) carotid artery		ΔIMT (mm)	*P* value
	RT-side	Non-RT side		
Overall	1.13	0.83	+0.30	0.031
<10 years	0.91	0.96	−0.05	>0.05
$\geqslant$10 years	1.35	0.68	+0.67	0.007

RT: radiotherapy.

3.3. Occurrence of cerebrovascular accidents

Five patients had sustained a vascular ischaemic event (3 TIA, 2 infarction) at a median of 11 years (range 5.9–13.1 years) following RT. In 4 of these 5 patients, it occurred in the area of the irradiated carotid artery. The mean difference in IMT in these patients was 1.1 mm. One patient developed an infarction in the hemisphere contra-lateral to the side of irradiation. This patient showed no difference in IMT (0 mm).

4. Discussion

Our study demonstrates that RT causes a significant increase in IMT on the irradiated carotid artery compared with the non-irradiated side. The difference in IMT is especially pronounced after a longer post-RT interval. The strength of our study was the comparison of the irradiated carotid artery to the patient's contralateral non-irradiated carotid artery. In this way, we could eliminate all other risk factors and the difference can be ascribed to the effect of RT on the vascular tissue. However, it is necessary to mention that the presence of other vascular risk factors can aggravate the changes.

A limitation of this study was the cross-sectional design. Selection of patients with favourable oncology and a good vascular prognosis might have led to selective survival. This possible selection bias could be responsible for a smaller IMT on the non-RT side in patients studied more than 10 years post-RT (0.68 mm) in comparison to those studied within 10 years (0.96 mm). Those with a large IMT (higher degree of atherosclerosis) have presumably already died. Another restriction related to the cross-sectional design is the lack of follow-up within one patient. A longitudinal prospective study is needed to determine the development of radiation-related vascular changes over time within individual patients.

It has been postulated that RT induces acute endothelial damage, which in turn causes endothelial proliferation [11] as well as chronic fibrosis of the media and occlusive changes of the vasa vasorum of the adventitia. These changes will produce atherosclerotic-like plaques resulting in vascular stenosis and thromboembolic processes [3]. A large longitudinal study of 4466 (non-irradiated) subjects without a history of cardiovascular disease showed that an increment of 0.55 mm in wall thickness was associated with an approximate 40% increased risk of stroke [9]. The increase in IMT in irradiated patients can be one of the causal factors leading to stroke. Moreover, the high incidence of vascular events that occurred in the territory of the irradiated carotid artery in our cohort favours this hypothesis.

Our study group consisted of relatively young patients (median age 47 years at the time of RT) with a favourable prognosis. The vascular changes become increasingly prominent during the time period after RT. In general, these patients develop (cerebro) vascular ischaemic complications at an earlier age than indicated by the incidence rates of (cerebro) vascular disease in non-irradiated patients [2,12]. Both carotid endarteriectomy [13,14] and carotid stenting [15] comprise options for intervention therapy in case of symptomatic carotid stenosis, although long-time follow-up results have not been reported.

Next to the factor time, radiation dose contributes to the development of vascular changes after RT. Others showed that a minimum dose of 25–40 Gy is correlated with induction of these changes [16], but at doses of more than 40 Gy Chung *et al.* [17] could not detect a dose-dependent relationship when they compared high dose RT ($\geqslant$65 Gy) with lower dose RT (<60 Gy) and the severity of the post-RT carotid changes on MRI angiography. In our cohort of 42 patients, the RT doses varied from 40 to 66 Gy; 74% of patients had received a dose between 50 and 60 Gy. We were not able to detect a dose–response relationship.

Our data support the hypothesis that RT is an independent risk factor for vascular disease, particularly after a post-RT interval greater than 10 years. This finding has important implications for the pre-treatment screening and post-treatment follow-up of irradiated patients. Attention must be paid to identify and modify other risk factors that further increase the risk of stroke in these irradiated patients [2]. Longitudinal prospective studies are needed to analyse the IMT-changes over a longer time period and, to investigate whether treatment with thrombo-modulating agents, such as statins or ACE-inhibitors, can prevent or diminish these changes following RT.

Conflict of interest statement

None declared.

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