Magnetic resonance imaging of the carotid artery in long-term head and neck cancer survivors treated with radiotherapy

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ABSTRACT

Background. In head and neck cancer (HNC) patients, long-term treatment-related complications include radiotherapy (RT)-induced carotid vasculopathy and stroke. The current study investigated the magnetic resonance imaging (MRI) characteristics of the carotid wall in long-term HNC survivors treated with RT.

Methods. MRI of the carotid arteries was performed within a prospective cohort of 42 HNC patients on average 7 years after RT. Two independent radiologists assessed maximal vessel wall thickness of common and internal carotid arteries. In case of wall thickening (>2 mm) the MRI signals as well as length of the thickened segment were assessed.

Results. Mean (SD) age of the 42 patients at baseline was 53 (13) years and mean (SD) follow-up time after RT was 6.8 (1.3) years. In total 62% were men and 60% had one or more cerebrovascular risk factors. Mean (SD) dose of RT on the common carotid arteries and internal carotid arteries was 57 Gy (11) and 61 Gy (10), respectively. Wall thickening was observed in 58% of irradiated versus 27% of non-irradiated common carotid arteries and 24% of irradiated versus 6% of non-irradiated internal carotid arteries (p < 0.05). Mean (SD) thickness of the irradiated and non-irradiated common carotid arteries was 2.5 (0.9) and 2 (0.7) mm (p = 0.02). Mean thickness of the irradiated and non-irradiated internal carotid arteries was 1.8 (0.8) and 1.5 mm (0.3) (n.s.). Mean length of the thickened vessel wall was 48 mm versus 36 mm in the irradiated versus non-irradiated common carotid arteries (p = 0.03) and 20 mm versus 15 mm in the irradiated versus non-irradiated internal carotid arteries (n.s.). No significant differences were observed for signal intensities of the vessel walls.

Conclusions. Our study showed significantly more vessel wall thickening in irradiated versus non-irradiated carotid arteries years after RT for HNC, while no differences in signal intensities were observed.

Cancer and cardiovascular diseases are the two leading causes of morbidity and mortality worldwide [1]. As a result of increased cancer survival rates long-term complications of treatment become more prevalent. In head and neck cancer (HNC) patients, such complications include radiotherapy (RT)-induced carotid artery vasculopathy and related ischemic strokes. In common carotid vasculopathy in the general population, the incidence of stroke is associated with the degree of stenosis and MRI characteristics of the atherosclerotic plaques, such as intra-plaque bleeding, lipid rich necrotic core and thinning of fibrous cap [2–4]. After unilateral RT of the neck, cross-sectional retrospective studies with duplex ultrasonography (DUS) showed an increased intima...
media thickness (IMT) of the irradiated compared to the non-irradiated carotid artery after a median follow-up period of 8–10 years [5,6]. In a prospective follow-up study, we earlier described a significant increase in IMT measured on DUS from baseline to follow-up with a mean of 7 years after RT [7].

Magnetic resonance imaging (MRI) studies investigating the incidence and characteristics of long-term complications of RT on carotid wall are lacking. The purpose of the present study therefore was to investigate the frequency, location and characteristics of RT-induced vasculopathy in long-term survivors of HNC.

Patients and methods

Study population

This study was part of a prospective multicenter cohort study, designed to investigate the long-term vascular and cerebral complications after RT of the neck, using DUS, MRI and neuropsychologic testing [8].

In short, patients who had undergone RT of the neck because of HNC were prospectively recruited between 2002 and 2008 in two centers in the Netherlands specialized in head and neck oncology [the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital (NCI/AvL), Amsterdam and the Radboud University Medical Center Nijmegen]. Patients with a history of cerebrovascular disease were excluded. Patients were assessed for cerebrovascular risk factors at baseline. At follow-up on average 7 years after start of RT all patients underwent a MRI of the carotid arteries. The Medical Ethics Review Committee region of Arnhem-Nijmegen approved the study (NL 41008.091.12), and all patients gave written informed consent.

Magnetic resonance imaging (MRI) protocol

MRI studies were performed on a 3 Tesla MR-scanner (Skyra, Siemens Erlangen) with a 3T TIM neck coil (Siemens AG, Head Neck 20, Munich, Germany). MRI protocol of the carotids included a 3 dimensional time of flight angiography (TOF), phase-contrast angiography (PCA), transversal T1, T2 and proton density (PD) sequences from the thoracic outlet to the skull base, and a sagittal oblique T2 of the carotid bifurcation. Finally, a maximum intensity projection (MIP) of the TOF and PCA sequences was reconstructed. Supplementary Table I (available online at: http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1023901) shows the parameters for the imaging sequences. The complete scanning protocol took approximately 30 minutes.

Image review

All ratings were performed separately by two experienced neuro-radiologists. Image-quality was rated per sequence (3D TOF, T1, T2, PD) on a four-point scale (1 = not assessable, 4 = best) at four standard locations: right and left common carotid artery (CCA) and right and left internal carotid artery (ICA). The dose of RT on the four locations was extracted from the planning CT scan used for the RT dose calculations. Vessel walls with an image quality of one were excluded from analysis. Thickening of the vessel wall was defined according to previous studies, as a thickness of the vessel wall of at least 2 mm observed on the combination of sequences [9,10]. Characteristics of thickened vessel walls were scored as follows: greatest wall thickness (mm), length of thickening and distance from carotid bifurcation (mm) by visual inspection and extension along the circumference of the vessel wall on a four-point scale (1 = 0–90°, 2 = 90–180°, 3 = 180–270° and 4 = 270–360°). Disruption of the fibrous cap and ulceration were scored on 3D TOF. Signal intensity (SI) of vessel wall thickening was scored on 3D TOF, T1, T2 and PD separately with the adjacent sternocleidomastoid muscle as reference (decreased, similar, increased). Stenoses were measured according to NASCET criteria [11]. The thickness of the carotid wall measured by the two neuroradiologists separately was averaged to obtain one measure of vessel wall thickness and a separation of thickened versus non-thickened vessel walls. For all other scores, consensus was reached by both observers in case of inconsistencies.

Statistical analysis

Categorical variables were analyzed by the Fisher exact test. Differences in continuous variables were analyzed by independent t-test and expressed as mean differences (SD).

Results

A total of 103 patients were included in the study during initial inclusion between 2002 and 2008. After a mean follow-up time of 7 years (SD 1.3) after start of RT 42 patients underwent MRI (Supplementary Figure 1, available online at: http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1023901). Baseline characteristics are reported in Table I. At a median of 7 years, 51 patients had a follow-up visit. Another 14 patients underwent a follow-up by telephone only, because of refusal or physical inability to travel to the hospital. From the 38 patients out of follow-up, 24 died, mostly because of a secondary tumor (n = 9) or progression of primary oncologic
ICAs. One ICA was occluded due to dissection and hence measurement was not possible. No vessels had to be excluded because of insufficient image quality.

**Carotid wall thickening**

From the total of 84 assessed CCAs, 62 (74%) were located within and 22 (26%) outside the RT portal. From the irradiated CCAs 58% had a thickening of the vessel wall versus 27% of the non-irradiated CCAs ($p < 0.05$, Table II). In total 34 (41%) of the ICAs were located within the RT portal and 49 (59%) outside the RT portal. From the irradiated ICAs 24% had a thickening of the vessel wall versus 6% of the non-irradiated ICAs ($p < 0.05$). From the irradiated CCAs, 45% had a vessel wall thickness $\geq 2.5$ mm versus 18% of the non-irradiated CCAs ($p < 0.05$). From the irradiated ICAs, 12% had a vessel wall thickness $\geq 2.5$ mm versus 0% of the non-irradiated ICAs ($p < 0.05$). Mean (SD) thickness of the irradiated and non-irradiated CCAs was 2.5 (0.9) and 2 (0.7) mm ($p < 0.02$). Mean thickness of the irradiated and non-irradiated ICAs was 1.8 (0.8) and 1.5 mm (0.3) (n.s.).

In the sub-group of patients with unilateral RT mean thickness in irradiated versus non-irradiated CCAs ($n = 14$) and ICAs ($n = 17$) was 2.24 versus 2.20 mm (n.s.) and 1.72 versus 1.45 mm (n.s.).

The length of the thickened CCA wall was 48 mm in the irradiated and 36 mm in the non-irradiated arteries ($p < 0.05$). In the thickened ICAs this was 20 and 15 mm, respectively (n.s.). In total 20% of the irradiated and thickened CCA vessel walls had a circumferential thickening of $\geq 180^\circ$ versus 0% in the non-irradiated CCAs. In the thickened ICAs this was 26% and 0%, respectively. Rupture of the cap or signs of ulceration were not seen. In 91% of the irradiated and 67% of the non-irradiated CCAs grade of stenosis was 0%–50%. There were no CCAs with a stenosis of $\geq 50%$. In the ICAs 86% of the irradiated and 50% of the non-irradiated arteries had 0%–50% stenosis. One irradiated ICA had a stenosis of $> 50%$ (Table III). Pattern of intensities on each of four sequences was not different between the irradiated and the non-irradiated arteries.

**Table I. Patient- and treatment-related characteristics.**

| Characteristic | n = 42 |
|---------------|--------|
| **Demographics** | |
| Men, % | 62 |
| Age at baseline, years (mean, SD) | 53 (13) |
| Follow-up post RT, years (mean, SD) | 6.8 (1.3) |
| **Cancer diagnosis** | |
| Carcinoma of the larynx, % | 36 |
| Carcinoma of the parotid, % | 14 |
| Adenoma of the parotid, % | 19 |
| Carcinoma of the nasopharynx, % | 2 |
| Carcinoma of the oropharynx, % | 21 |
| Carcinoma of the hypopharynx, % | 2 |
| Lymphoma, % | 5 |
| **Radiotherapy** | |
| Dose on irradiated carotid arteries [Gy, mean, min-max, (SD)] | |
| CCA | 57, 30–70 (11) |
| ICA | 61, 30–70 (10) |
| Bilateral, % | 57 |
| Length of carotid in RT portal, cm [mean, min-max, (SD)] | 9, 4–16 (3) |
| **CV risk factors at baseline** | |
| Smoking | |
| Current smoker or stopped < 3 years ago, % | 43 |
| Former smoker or stopped > 3 years ago, % | 29 |
| Never smoked, % | 29 |
| Hypertension, % | 21 |
| Diabetes mellitus, % | 2 |
| Hypercholesterolemia, % | 10 |
| Obesity, % | 5 |
| Number CV risk factors at baseline (%) | |
| 0 risk factors, % | 41 |
| 1 risk factors, % | 41 |
| $\geq$ 2 risk factors % | 19 |

CCA, common carotid artery; ICA, internal carotid artery.

*a Cerebrovascular (CV) risk factors at baseline consists of: hypertension, diabetes, hypercholesterolemia, overweight and current smoking.

**Table II. Vessel wall thickening on MRI.**

| CCA (n = 84) | ICA (n = 83) |
|-------------|-------------|
| **RT+ (n = 62)** | **RT− (n = 22)** | **RT+ (n = 34)** | **RT− (n = 49)** |
| Mean thickness, mm (SD) | 2.5 (0.9) | 2.0 (0.7)* | 1.8 (0.8) | 1.5 (0.3)* |
| Thickness $\geq 2$ mm, n (%) | 36 (58) | 6 (27)* | 8 (24) | 3 (6)* |
| Thickness $\geq 2.5$ mm, n (%) | 28 (45) | 4 (18)* | 4 (12) | 0 (0)* |

CCA, common carotid artery; ICA, internal carotid artery; RT, radiotherapy. *Independent t-test for difference between irradiated and non-irradiated CCA, $p = 0.02$ and ICA, $p = 0.09$; *Fischer exact test for difference between % irradiated and non-irradiated CCA and ICA, $p < 0.05$. 

disease ($n = 7$). Three patients died because of a carotid bleeding, one because of a gastrointestinal bleeding, one because of complications after hip fracture, one because of pneumonia and two had an unknown cause of death. From all patients out of follow-up, two had suffered from a stroke. MRI examinations of the carotid arteries resulted in 84 measurements of CCAs and 83 measurements of ICAs.
fusely involved and the stenosis were more frequently tandem and bilateral. No significant differences in MRI signal intensities were observed between the thickened vessel walls in irradiated and non-irradiated arteries. An explanation of this finding could be that RT-induced atherosclerosis is an accelerated age-related atherosclerosis with similar vessel wall composition and hence similar MRI signal intensity changes. Another explanation could be underpowering of the current study for this observation. Moreover, at the time of the study a dedicated high resolution coil for the carotids was not available, and images were acquired using a standard neck coil. At last, the relatively small degree of stenosis in this study may indicate an early stage of long-term vascular changes after RT, which may become more evident over time.

Although this study involved only 42 patients at follow-up, this is the largest prospective cohort of HNC survivors with the longest follow-up period described up to now. However, a methodological limitation of the current study was the lack of a baseline MRI, which prevents us from studying changes over time and hence from making causal inferences about the effect of RT. Another limitation is the lack of an external control group. The ideal external control group would consist of HNC patients not treated with RT matched for cardiovascular risk factors. Since RT is the treatment of choice in locally advanced HNC, this control group does not exist.

### Table III. Characteristics of carotid walls if thickness ≥ 2 mm.

| Measurements, mean mm (SD) | CCA (n = 42) | ICA (n = 11) |
|----------------------------|--------------|--------------|
| Length of thickened part   | RT+ (n = 36) | RT− (n = 6)  |
| Distance from bulbus       | 48 (12)      | 36 (13)     |
| Degree of circumferential thickening, number (%)       | 20 (12)      | 15 (8)      |
| 90–180 degree              | 29 (81)      | 6 (100)     |
| 180–270 degree             | 6 (17)       | 1 (13)      |
| 270–360 degree             | 1 (3)        | 1 (13)      |
| Intact cap, number (%)     | 36 (100)     | 6 (100)     |
| Ulceration, number (%)     | 0 (0)        | 0 (0)       |
| Stenosis grade, number (%) | 0%           | 3 (8)       |
| 0–50%                      | 33 (92)      | 4 (67)      |
| 50–99%                     | 0 (0)        | 1 (33)      |

CCA, common carotid artery; ICA, internal carotid artery; RT, radiotherapy. Data are expressed as number (%). Unmarked variables are not statistically significant between the irradiated and the non-irradiated arteries. *Independent t-test for difference between irradiated and non-irradiated CCA, p 0.03. Unmarked results are not significant different between the irradiated and non-irradiated arteries.
subgroup of unilateral irradiated patients, the non-irradiated carotid artery could serve as an internal control within a single patient. Although this subgroup was too small to reach significant level, we found a trend towards more pathologic vessel wall changes in the irradiated arteries. Figure 1 shows an example of a MRI of one participant treated with unilateral sided RT. Unfortunately, it was not possible to study the influence of RT dose and/or other cardiovascular risk factors on vessel wall changes, because subgroups were too small and power insufficiently.

No guidelines exist to prevent long-term vascular and cerebral changes after RT in HNC. However, the current study appeals for the need of preventive strategies. Patients need to be informed about the potential vascular long-term complications and other concomitant cerebrovascular risk factors associated with increased risk of stroke, like smoking, physical inactivity, atrial fibrillation, hypertension and diabetes should be checked regularly and treated were possible. Future studies focusing on preventive strategies should comprise a larger patient cohort, with longer follow-up duration after RT.

In conclusion, our MRI study showed significantly more vessel wall thickening over a longer trajectory in irradiated carotid arteries 7 years after RT as compared to the non-irradiated carotid arteries in the same patient group. Survivors of HNC treated with neck RT have to be informed about the increased risk of carotid artery pathology and potential long-term complications and should be instructed about other modifiable cerebrovascular risk factors. Future studies should focus on potential preventive strategies.

Acknowledgments

We thank C. Frentz for designing the MRI protocol.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary material available online

Supplementary Table I and Figure 1, available online at: http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1023901.