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Vascular morbidity

Progression of carotid intima media thickness after radiotherapy: A long-term prospective cohort study

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ABSTRACT

Background and purpose: Carotid artery vasculopathy is a long-term complication of radiotherapy (RT) of the neck. We investigated the change in carotid intima media thickness (IMT) and the incidence of ischemic stroke in the first 7 years after radiotherapy (RT) of the neck.

Materials and methods: A multicentre prospective cohort study among patients treated for Head and Neck Cancer (HNC) assessed carotid IMT at baseline (before RT) and after a median of 7 years follow-up. We also screened for cerebrovascular risk factors and events.

Results: 48 patients underwent IMT measurement at baseline and follow-up (median age 61 years, range 29–87). Mean IMT of the irradiated common carotid arteries was 0.64 mm at baseline and 0.74 mm at follow-up ($p = 0.002$). Mean delta IMT in the irradiated and non-irradiated common carotid arteries were 0.11 and 0.02 mm ($p = 0.03$). Incidence rate of stroke in our cohort, compared to the Dutch population was 8.9 versus 1.5 per 1.000 person years.

Conclusions: IMT in irradiated carotid arteries was significantly increased in the first 7 years after RT. The incidence rate of stroke was six fold increased. Patients treated with RT for HNC have sustained risk for developing atherosclerosis of the carotid arteries and future stroke.

Cancer and cardiovascular disease are the leading causes of mortality and morbidity worldwide [1]. Successful treatment options for cancer result in more long-term survivors prone to long-term complications. Radiotherapy (RT) induced carotid artery vasculopathy is a potential long-term complication after RT of the neck, with enhanced risk of ischemic stroke (IS) [2–4]. To find diagnostic and preventive strategies, more insight in the underlying pathophysiology is needed. The current study investigated the characteristics of these long-term vascular changes by measurement of the intima media thickness (IMT) in a unique cohort of patients treated for head and neck cancer (HNC) with 7 years follow-up.

The IMT of the carotid artery is a widely used, validated and reliable measure of atherosclerosis, and is associated with future cardio- and cerebrovascular events [5]. Prior retrospective studies showed a larger IMT in the irradiated, compared to the non-irradiated carotid artery after a median follow-up period of 8–10 years after unilateral RT of the neck. Increased IMT was associated with an increased risk of ischemic stroke [2,6,7]. Prior small prospective studies with a limited follow-up time between 3 months and 3 years showed conflicting results [8–10]. In the current study cohort, we previously showed no increase in carotid IMT in the first 2 years after RT [11]. In this long-term prospective follow-up study we investigated the change in carotid IMT and the incidence of IS in the first 7 years after RT.

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Patients and methods

Study design and patients

This study was part of a prospective multicentre cohort study, designed to investigate the long-term vascular and cerebral complications after RT of the neck. The detailed study protocol was described earlier [12]. In short, study subjects were recruited in two university medical centers in The Netherlands (The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital (NKI/AvL) and the Radboud University Medical Center). At baseline, patients were eligible for inclusion if they received RT of the neck because of a T1/T2 (N0M0) laryngeal carcinoma, T1/T2 (N0M0) parotid carcinoma/pleomorphic adenoma, T1/2 (N1/2M0) naso/oro/hypopharynxcarcinoma or non-Hodgkin/Hodgkin lymphoma. (Table 1). The Medical Ethics Review Committee region of Arnhem-Nijmegen approved the study (NL 41008.091.12). Originally, the study was designed as an open-label multicentre Prospective Randomized Open Blinded Endpoint (PROBE) study to assess the effect of an HMG-coA reductase inhibitor (atorvastatin) on carotid IMT in the first years after irradiation of the neck. Because of dwindling accrual the study was redesigned to a prospective cohort study. Among the initial exclusion criteria was history of cerebrovascular disease. All patients gave written informed consent.

Patients were assessed at baseline (before RT) for height, weight and blood pressure, underwent a neurological examination, and the following cerebrovascular risk factors were assessed: 1. Cigarette smoking. 2. Hypertension, defined as using antihypertensive medication or blood pressure >130/80 mmHg. 3. Diabetes mellitus, defined as using anti-diabetic medication or a non-fasting serum glucose >11.1 mmol/L. Medication prescription was checked in the pharmacy database. 4. Hypercholesterolemia, defined as serum total cholesterol >6.5 mmol/L. 5. Obesity, defined as Body Mass Index (BMI) >30 kg/m^2.

Table 1
Patient and treatment related characteristics at baseline.

Characteristic	n = 65
Demographics	
Men (%)	60
Age at baseline, years (mean, SD)	54.3 (13.3)
Follow-up post RT, years (mean, range)	6.7 (4.5–9.6)
Cancer diagnosis (%)	
Carcinoma of larynx	45
Carcinoma of parotid	14
Pleiomorphic adenoma of parotid	15
Carcinoma of nasopharynx	2
Carcinoma of oropharynx	17
Carcinoma of hypopharynx	2
Lymphoma	6
Radiotherapy	
Dose on irradiated carotid arteries (Gy, mean, min–max, (SD))	
CCA	58, 30–70, (12)
ICA	61, 30–70, (12)
Bilateral (%)	63
CV risk factors at baseline (%)	
Smoking	
Current smoker or stopped <3 years ago	51
Former smoker or stopped >3 years ago	23
Never smoked	25
Hypertension	26
Diabetes mellitus	5
Hypercholesterolemia	9
Obesity	8
Number CV risk factors at baseline[‡] *(%)*	
0	32
1	43
⩾2	25

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

If patients reported an incident of IS or TIA at follow-up detailed medical information was collected from their neurologist and reassessed by one vascular neurologist (EvD). From the patients out of follow-up the reason, cause of death and occurrence of stroke were checked at the general practitioner, the patient or family members.

Radiation therapy

Radiotherapy was usually given with a linear accelerator and 4–6 MV photons linear accelerator with the patient immobilized using a thermoplastic mask. The target area of the patients entered in this study included at least the ipsilateral neck, including part of the carotid artery system (e.g. in case of parotid tumors or well lateralized oropharyngeal carcinomas). In other patients, both sides of the neck and the vascular system were irradiated (e.g. in case of laryngeal or hypopharyngeal carcinoma).

The radiation treatment was delivered with external beam radiotherapy using either standard techniques (parallel opposing beams or wedge-pair techniques) or Intensity-Modulated Radiotherapy (IMRT), depending on resources.

The radiation dose given was typically 30–36 Gy for lymphoma, 50–60 Gy for parotid tumors (pleiomorphic adenoma or parotid carcinoma), 60–70 Gy for laryngeal carcinoma and 70 Gy for oropharyngeal and hypopharyngeal carcinoma. In the majority of cases, 2 Gy per fraction was delivered up to the specified total dose. For patients with lymphoma, parotid tumors or T1N0 oropharyngeal carcinoma, a standard once-daily fractionation schedule was used. Accelerated fractionation according to the DAHANCA schedule [13] was used for patients with T2 or N1 oropharyngeal carcinomas, hypopharyngeal carcinomas and larynx carcinoma patients beyond stage T1N0. In patients with T1N0 glottic laryngeal carcinomas the fractionation schedule was 60 Gy in 25 fractions over 5 weeks to the larynx only, using 2 lateral opposing fields.

IMT measurements

IMT measurements were performed using the same protocol at baseline (before RT) and at follow-up. IMT was assessed at the common carotid artery (CCA) and the internal carotid artery (ICA) of both the left and right side. The location of measurement in the irradiated arteries was selected according to the high dose RT field. The IMT was assessed in the highest quality ultrasonography approximate to the bifurcation. The dose of RT on the four IMT locations was extracted from the planning CT scan used for RT dose calculations.

IMT was measured with one of the following linear array transducers: L17-5 connected to an iU22 Philips and UST-5539-7.5 MHz connected to an ALOKA 5000. IMT pictures were digitally stored on the ultrasound machine or printed in case digital storage was not available. Printed images were then scanned at high resolution and interpolated (using Matlab 2010a) to obtain the same resolution as the digitally stored images. For all data, IMT was automatically measured by two investigators (JW, WR), using QLAB (Version 4.2.1, Philips). An edge-detection algorithm identified the lumen-intima and the media-adventitia interface within a region of interest (selected by the operator) over a maximally 10 mm long segment and calculated the mean IMT (Fig. 1).

Firstly, IMT at baseline, follow-up and delta IMT were calculated for irradiated (within the irradiated volume) and non-irradiated CCA and ICA apart. In case left and right carotid artery were both within the irradiated volume, mean IMT was calculated.

Secondly, in the subgroup of unilateral irradiated patients IMT at baseline, follow-up and delta IMT of CCA and ICA were compared between the irradiated and the non-irradiated side within the same patient.