Prospective Cohort Study of Carotid Intima-media Thickness after Irradiation

Joyce Wilbers, MD,* Frank J. Hoebers, PhD,† Willem Boogerd, PhD,‡ Erik D. van Werkhoven, Msc,‡ Marlies E. Nowee, PhD,‡ Guus Hart, Msc,‡ Harry Bartelink, PhD,‡ Ewoud J. van Dijk, PhD,* Arnoud C. Kappelle, PhD,* and Lucille D. Dorresteijn, PhD§

Background: Carotid artery vasculopathy is a potential long-term complication after radiotherapy (RT) of the neck, resulting in cerebrovascular events. The underlying pathophysiology is not well understood and early markers are lacking. We aimed to study whether RT of the neck is associated with increase in carotid intima-media thickness (IMT) and stroke in the first 2 years after RT in patients with head and neck cancer (HNC). *Methods:* In this prospective cohort study patients treated with RT of the neck were assessed for measurement of IMT before and 2 years after RT. Endpoints were changed in IMT and incidence of first-ever stroke. *Results:* Between 2003 and 2008 we included 69 patients (median age, 57 years [25%-75% quartile, 51-64 years], median dose of RT 66 Gy [interquartile range, 60-70]) with baseline and follow-up measurement of IMT. Median IMT at baseline and follow-up was .60 and .62 mm (ratio of geometric means 1.01; 95% confidence interval, .96-1.08; $P = .63$). Four of 69 patients suffered from a stroke. Mean interval from RT to stroke was 6.8 months. *Conclusions:* Our study showed no increase of carotid IMT in the first 2 years after RT of the neck in patients treated for HNC. This indicates that the IMT is not a reliable early marker for postirradiation vasculopathy. However, a high rate of strokes was observed. A longer follow-up period is needed to find the starting point of RT-induced vascular changes. **Key Words:** Head and neck cancer—stroke—carotid artery—carotid intima media thickness—radiotherapy.

Introduction

Improving cancer treatment has resulted in more long-term survivors. The counterpart is an increase in late cytotoxic effects of both chemo and radiotherapy (RT). A potential devastating long-term side effect of postirradiation vasculopathy of the carotid arteries is the development of ischemic stroke (IS) or transient ischemic attack (TIA).[1-3] Although the exact pathophysiology is not well understood, the proposed explanations are induction or acceleration of carotid atherosclerosis.[4] It is unclear whether the composition and location of postirradiation plaques and stenosis are different from those of common atherosclerosis due to cardiovascular risk factors. The intima media thickness (IMT) of the carotid artery is a valid method to measure atherosclerosis and a predictor of

From the *Department of Neurology, Radboud University Nijmegen Medical Centre, Nijmegen; †Maastricht University Medical Center, Department of Radiation Oncology (MAASTRO clinic), GROW School for Oncology and Developmental Biology, Maastricht; ‡Department of Neurology/Radiotherapy/Biometrics, Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam; and §Department of Neurology, Medisch Spectrum Twente, Enschede, The Netherlands.

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Address correspondence to Ewoud J. van Dijk, PhD, Reinier Postlaan 4, 6525 G.C Nijmegen, Huispost 935, The Netherlands. E-mail: Ewoud.vanDijk@radboudumc.nl.

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future strokes.[5,6] Previous retrospective studies showed an increase in carotid IMT after a median follow-up period of 8-10 years after neck irradiation.[7-9] Moreover, irradiation of the neck was associated with an increased risk of IS.[2] Prospective studies with a follow-up period between 3 months and 3 years showed conflicting results.[10-12]

The current prospective cohort study aimed to evaluate the changes in carotid IMT in the first 2 years after RT in head and neck cancer (HNC) patients and whether potential change in carotid IMT is associated with an increased incidence of IS in these patients.

Methods

A prospective cohort study of HNC patients in 2 centers of The Netherlands (the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam and the Radboud University Nijmegen Medical Centre, Nijmegen) was initiated.

Inclusion criterion was cervical RT because of HNC. Originally, the study was designed as an open-label multicenter Prospective Randomized Open Blinded Endpoint study to assess the effect of an hydroxymethylglutarylco-enzyme A-reductase (HMG-CoA) reductase inhibitor (atorvastatin) on carotid IMT in the first 2 years after irradiation of the neck. Because of dwindling accrual, the study was redesigned to a prospective cohort study. The initial exclusion criteria were as follows: a history of cerebrovascular disease, pregnancy or breast feeding, ongoing treatment with an HMG-coA reductase or cytochrome P450 inhibitor, active liver disease or more than 3 times the upper limit of serum transaminases, 5 times the normal level of creatine phosphokinase, serum cholesterol more than 7 mmol/L, and a life expectancy less than 2 years. All patients gave written informed consent. The protocol was approved by the local ethics committees.

Baseline and Follow-up

Patients were assessed at baseline (before RT) and after 2 years. At every visit height, weight and blood pressure were noted, patients underwent a neurologic and laboratory (C-reactive protein) examination, and the following cerebrovascular risk factors were assessed: (1) cigarette smoking; (2) hypertension, defined as using antihypertensive medication or blood pressure more than 130/80 mm Hg; (3) diabetes mellitus, defined as using antidiabetic medication or a nonfasting serum glucose more than 11.1 mmol/L, medication prescription was checked in the pharmacy database; (4) hypercholesterolemia, defined as serum total cholesterol more than 6.5 mmol/L; and (5) obesity, defined as body mass index more than 30 kg/m^2. If patients had suffered from a IS or TIA, detailed medical information was collected from their neurologist and reassessed by one of the investigators (E.v.D.), including assessment of the etiology of stroke according to the Modified Trial of Org 10172 in Acute Stroke Treatment classification.[13]

Radiation Therapy

RT 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 (eg, in case of parotid tumors or well lateralized oropharyngeal carcinomas). In other patients, both sides of the neck and the vascular system were irradiated (eg, in case of laryngeal or hypopharyngeal carcinoma).

The radiation treatment was delivered with external beam RT using either standard techniques (parallel opposing beams or wedge-pair techniques) or intensity-modulated RT, depending on resources.

The radiation dose given was typically 30-36 Gy for lymphoma, 50-60 Gy for parotid tumors (pleomorphic adenoma or parotid carcinoma), 60-70 Gy for laryngeal carcinoma, and 70 Gy for oropharyngeal and hypopharyngeal carcinoma. In most of the 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 Danish Head and Neck Cancer Study Group (DAHANCA) schedule[14] 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.

In every patient separately, the total irradiation dose on the common carotid artery (CCA) and internal carotid artery (ICA) was calculated from the radiation treatment fields.

Carotid Ultrasound

In patients with laryngeal or hypopharyngeal carcinoma IMT was measured on the CCA, according to the RT field. In patients with other tumors, IMT was measured in both the CCA and the ICA, also according to the RT field.

IMT was measured with a linear array transducer (iU22 Philips NZE172 probe, L17-5 Bothell, WA; Hewlett Packard Sonos 2000 probe, 7.5/5.5 Andover, MA; ALOKA 5000 Tokyo, Japan; G.E LOGIQ E9, Wauwatosa, WI), as described earlier.[7] IMT pictures were digitally stored on the ultrasound machine or printed in case digital storage was not available. Printed images were then scanned with high resolution and interpolated (using Matlab 2010a, Natick, MA) to obtain the same resolution as the digitally stored images. IMT was automatically measured by 2 blinded investigators (W.R. and J.W.),