Radiation induced vascular disease and ischemic stroke

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Radiation induced vascular disease and ischemic stroke

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op het gebied van de Medische Wetenschappen

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Voor Jeroen, Julia en Nanne

Table of contents

Chapter 1

General introduction and outline of the thesis

Radiation therapy, a risk factor for ischemic stroke?

Adapted from:
Lucille D.A. Dorresteijn, Henri A.M. Marres, Harry Bartelink, L. Jaap Kappelle, Willem Boogerd en Arnoud C. Kappelle

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Radiation-induced vascular disease is a well known phenomenon, which has already been described in 1899.[1] Thereafter, several reports and cohort studies have documented the local vascular consequences of radiation therapy (RT).[2-6] Acute vascular sequelae consist e.g. of (carotid) artery rupture, that is seen sporadically after RT on the neck in patients with head and neck cancer or lymphoma.[7] Late delayed vascular complications are more frequent and generally occur many years after RT (range 1 to > 20 years).[3,8] These late complications can occur at different locations than those of classical atherosclerosis and are related to the former RT-field. Among these, femoral artery and subclavian artery occlusions can occur after RT on the pelvis and the supraclavicular region, respectively. However, the relation between an ischemic stroke and previous RT on the neck is not always appreciated. To illustrate this entity, the clinical vignette of a patient with radiation-induced ischemic stroke is presented.

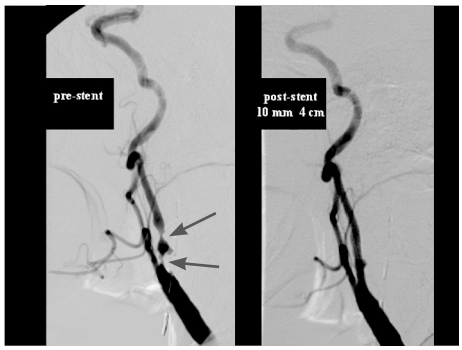
Patient A, a 78-year-old man, noticed sudden-onset weakness of the right side of his body in December 2003. In early 1997, he was curatively treated for a T2N0M0 laryngeal carcinoma with RT (66 Gy in 33 fractions). No recurrence had occurred during the oncological follow-up. He had stopped smoking since the diagnosis of laryngeal carcinoma in 1997. No other cardiovascular risk factors were present. At the emergency room, neurological examination showed a normal level of consciousness and unimpaired language functions, slight weakness of the right arm and face, and no other abnormalities.

He was admitted to the stroke care unit under the suspicion of a stroke located in the territory of the medial cerebral artery (MCA). A cerebral CT-scan confirmed a recent small cortical infarction in the left parietal lobe. The patient was then given aspirin 300 mg daily for two weeks after which it was lowered to the permanent dose of 100 mg daily.

Duplex examination and MR-angiography of the cerebropetal arteries showed a significant stenosis (more than 70%) of the left internal carotid artery (ICA). Extensive screening of other risk factors did not reveal any abnormalities.

His right-sided weakness recovered during the admission. Considering the RT in the past, carotid endarterectomy (CEA) was deferred because of extensive fibrotic changes in the neck. In order to treat the symptomatic high-grade ICA stenosis, it was decided to perform a carotid angioplasty with stent placement (CAS) (figure 1). The procedure was performed without complications and during repeated outpatient visits, the patient did not report any new neurological deficits.

Figure 1. Left: Digital subtraction angiogram of the left internal carotid artery with a stenosis of more than 70% (arrow) distal to the bifurcation. Right: A clear improvement is visible after carotid angioplasty with stent placement.



Due to more successful RT and chemotherapy, the survival of many oncological patients has improved substantially.[9,10] The downside of this success is the occurrence of long-term treatment related complications. Vascular disease, like ischemic stroke, is one of the most important determinants of late morbidity and mortality after RT. The magnitude of a possibly increased risk of future stroke and TIA due to RT on the neck can not be extracted from the data and cases published so far. Evidence for an increased risk of stroke was provided by a cohort study by Elerding et al.; although they were not able to accomplish a definite relation between RT on the neck and increased risk of stroke.[11]

The underlying pathogenetic mechanism in RT-related vascular changes is partly different from classical atherosclerosis.[12] Whereas classical atherosclerosis is merely a disease of the intimal layer predominated by inflammation and lipid storage; RT-related vascular changes affect the 3 arterial layers (i.e. the intima, the media and the adventitia). On the one hand, already existing atherosclerotic lesions seem to worsen by RT, but RT itself can also induce atherosclerotic changes in atherosclerotic-naive, young patients. Histological examination showed endothelial damage in an early post-RT stage.[13] In the chronic phase, this probably leads to a cascade of inflammatory reactions that result in the proliferation of the endothelial (i.e. intima) layer, fibrosis of the medial layer, and obliteration of the vasa vasorum in the adventitial layer. The combination of these changes will eventually lead to narrowing of the arterial lumen. Correspondingly, thickening of the inner wall, expressed as the intima-media thickness (IMT), seems to be an independent predictor of cerebrovascular disease.[14-16] RT could lead to enhancement of the IMT progression which in turn can result in carotid artery stenosis and consequently to ischemic cerebrovascular disease. Until now, the real impact of RT on IMT progression after neck irradiation is unknown.

Duplex examination of the cerebropetal arteries is performed in patients with a transient ischemic attack or ischemic stroke. In case of a symptomatic stenosis of the ICA of more than 50-70%, it is advised to confirm this with MR-angiography or a conventional angiography. Patients who have undergone RT often show occlusive carotid disease at different locations compared to patients with classic age-related atherosclerosis. In general, these occlusive lesions are more extensive after RT[17-19] and are often found outside the bifurcation: in the common carotid artery, the distal internal carotid artery, or the external carotid artery, which corresponds to the full radiation area.[4] The best treatment of RT-related symptomatic ICA stenosis is unknown. In line with the extensive studies that have been performed in patients with a stenosis based on atherosclerosis, a CEA is advised in case of a symptomatic ICA stenosis with a luminal reduction of more than 70%.[20] However, the neck area of these patients is also called "hostile neck" because of the fibrotic abnormalities and the disrupted anatomy (figure 2).[21] Therefore CEA can be a technically difficult and thus a risk-bearing procedure. In fact, in the extensive North American Symptomatic Carotid Endarterectomy Trial (NASCET), these patients were excluded from the study because of the high surgical risk.[20] CAS could offer a good alternative for these "hostile neck" patients. This technique consists of a percutaneous balloon dilatation followed by stent placement. The value of this intervention compared to CEA in patients with classic atherosclerosis is the topic in randomized studies at present.[22] Endovascular treatment in patients who have undergone RT on the neck has not been studied sufficiently to establish the utility in this specific patient population.

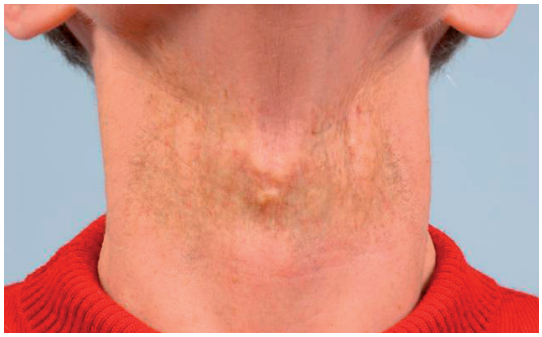
To prevent is better than to heal also applies for irradiated patients; from this view, preventive measurement should become available for patients who will undergo irradiation on large arteries, like the carotid and coronary arteries. Until now, no study has focused on prevention of RT-related vascular changes. The best advise for the treating physicians is to consider risk reducing strategies since additional cerebrovascular risk factors contribute to RT induced vasculopathy.

Aims and outline of the thesis

General aims of the present thesis were (I) to evaluate the long-term risk of radiation induced vasculopathy and (ischemic) cerebrovascular disease in cancer survivors who have been treated with radiotherapy on the neck, (II) to assess the outcome of endovascular treatment of radiation induced carotid stenosis, and (III) to initiate a randomized, multicenter trial on the prevention of radiation related vasculopathy.

For this purpose we examined the risk of ischemic stroke in head and neck cancer patients who received irradiation on the neck before the age of 60 years.
The incidence was compared with stroke rates of the general population, together with the cumulative risk of stroke **(chapter 2.1)**.
Since we were interested in the occurrence of cerebrovascular disease as a consequence of irradiation in other cancer survivors; we performed treatment specific analysis in the Late Effects Breast Cancer Study **(chapter 2.2)** and in Hodgkin's lymphoma survivors **(chapter 2.3)**. Treatment specific risk factors of radiation fields were studied, as well as the etiology of ischemic cerebrovascular disease.
To study the real impact of radiotherapy on the carotid artery we performed a cross-sectional study in patients irradiated unilaterally on the neck. A duplex ultrasonographic comparison of the intima-media thickness of the irradiated versus the unirradiated carotid artery was performed **(chapter 3.1**).
To evaluate the possibility of endovascular treatment of radiation induced carotid stenosis we assessed the outcome in terms of the occurrence of cerebrovascular disease and restenosis after stenting **(chapter 4.1)**.
In an attempt to prevent radiation induced vasculopathy, we initiated a randomized, multicenter trial. The effect of atorvastatin, a cholesterol-lowering drug on reducing the intima-media thickness progression is evaluated within patients who will receive radiotherapy on the neck region **(chapter 5.1)**.

Figure 2. Extensive fibrotic abnormalities and teleangiectasia in the neck.
The neck abnormalities are usually referred to as "hostile neck".



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Chapter 2

Epidemiology of cerebrovascular events after radiation therapy

Chapter 2.1

Increased risk of ischemic stroke after radiotherapy on the neck in patients younger than 60 years

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Abstract

Purpose
To estimate the risk of ischemic stroke in patients irradiated for head and neck tumors.

Patients and methods
The incidence of ischemic stroke was determined in 367 patients with head and neck tumors (162 larynx carcinoma, 114 pleomorphic adenoma, and 91 parotid carcinoma) who had been treated with local radiotherapy (RT) at an age younger than 60 years. Relative risk (RR) of ischemic stroke was determined by comparison with population rates from a stroke-incidence register, adjusted for sex and age. Other risk factors for stroke (hypertension, smoking, hypercholesterolemia, diabetes mellitus (DM)) were registered. The median follow-up time after RT was 7.7 years (3,011 person-years of follow-up).

Results
Fourteen cases of stroke occurred (expected 2.5; RR 5.6; 95% confidence interval (CI) 3.1-9.4): eight in patients with laryngeal carcinoma (expected 1.56; RR 5.1; 95% CI 2.2-10.1), four in patients with pleomorphic adenoma patients (expected 0.71; RR 5.7; 95% CI 1.5-14.5), and two in parotid carcinoma patients (expected 0.24; RR 8.5; 95% CI 1.0-30.6). Five of six strokes in patients irradiated for a parotid tumor occurred at the ipsilateral side. Analysis of other risk factors for cerebrovascular disease showed hypertension and DM to cause an increase of the RR after RT. After more than 10 years' follow-up, the RR was 10.1 (95% CI 4.4-20.0). The 15-year cumulative risk of stroke after RT on the neck was 12.0% (95% CI 6.5%-21.4%).

Conclusion
This is the first study to demonstrate an increased risk of stroke after RT on the neck. During medical follow-up, preventive measures should be taken to reduce the impact of the risk factors for cerebrovascular disease, to decrease stroke in these patients.

Introduction

Radiotherapy (RT) is a common curative treatment modality for head and neck malignancies and may serve as adjuvant therapy in post-operative conditions for some benign tumors. Successful treatment increases survival but also puts the patient at risk for radiation-related side effects. In this respect, vascular side effects are serious and may be life threatening. Already in 1899 Gassmann reported effects of RT on vascular tissue.[1] Thereafter several studies described radiation-induced atheromatous disease of major arteries in a variety of locations.[2-4] Similar changes have also been reported involving the carotid artery after neck irradiation.[5-9]

Long-term vascular complications are usually contributed to accelerated atherosclerosis of the irradiated vessels, which increases the risk of vascular stenosis and thromboembolism. The main sequelae of carotid atherosclerosis include transient ischemic attacks, ischemic strokes and amaurosis fugax.[10] The reported intervals between irradiation and first symptoms range from 6 months to more than 20 years.[10,11]

Case reports combined with histopathological studies suggest a possible relationship between RT and occurrence of stroke.[6-8] However, the extent of a possible increase of risk due to RT can not be assessed from reports published so far. Moreover, most reported patients had also received surgical therapy for their head and neck tumors, which might have contributed to the carotid artery pathology.[12] In only one study was the incidence of stroke in patients irradiated on the neck compared with the expected incidence in a population of similar age and sex.[13] No significant increase of the risk of stroke after previous RT on the neck was found. However, inclusion of operated, not-operated patients, and elderly patients makes those study results hard to interpret. With this background, we investigated a consecutive series of patients protocollary treated for head and neck tumors at relatively young age (< 60 years), to assess the relative risk (RR) of stroke after irradiation on the neck.

Patients and Methods

Patients

The study group consisted of two categories of patients; those with laryngeal carcinoma primarily treated with RT, i.e. T1 and T2 carcinomas, and patients with parotid gland tumors i.e. pleomorphic adenoma and parotid carcinoma. This patient selection was made in order to constitute a homogeneous study population with approximately the same treatment protocol, and with an expected long term survival and follow-up. Patients with T3 and T4 laryngeal carcinomas and patients with oro-pharyngeal carcinomas were excluded because of their limited survival time, and because of

operative intervention in the carotid area . Patients with laryngeal carcinoma received RT with a curative intent. Patients with pleomorphic adenomas underwent a superficial parotidectomy, and postoperative RT was indicated by tumor spill and/or incomplete microscopic clearance. Parotid carcinomas were surgically removed by performing a total (conservative) parotidectomy followed by RT.

A retrospective cohort study was performed of patients treated between January 1977 and January 1998 at the Netherlands Cancer Institute/ Antoni van Leeuwenhoekhuis. Patients older than 60 years were excluded in order to constitute a relatively young study population with low risk of cerebrovascular disease. A minimal follow-up time of 0.5 year was required in order to exclude acute complications of treatment, which might harbor a different pathogenesis.[8] During the period from January 1, 1977, January 1, 1998, 383 patients fulfilled the inclusion criteria. Records were untraceable for 16 patients. Thus, this study was restricted to the 367 patients who received RT on the neck.

From each patient chart, the following data were collected: sex, age, primary tumor, timing of RT, RT dosage and fraction size, risk factors of cerebrovascular disease, interval from RT to stroke occurrence, interval from start of RT to last visit during follow-up, and date and cause of death. The recorded risk factors included smoking, hypertension, diabetes mellitus (DM) and hypercholesterolemia. Hypertension was defined as either treatment for high blood pressure or a blood pressure that twice exceeded the limit of 95 mm Hg diastolic blood pressure. Smoking was scored positive when the patient was currently smoking or had quit smoking less than 2 years before last follow-up. Each patient treated for DM was scored as positive. The cut-off value for hypercholesterolemia was 6.5 mmol/L. Criteria for cerebrovascular symptoms were a fixed neurological deficit lasting for more than 24 hours (subarachnoidal and intracerebral haemorrhage, transient ischemic attack, and amaurosis fugax were excluded). In all cases, the clinical diagnosis was based on a neurological examination and in most cases it was confirmed by a computed tomography or magnetic resonance imaging scan.

In case of incomplete follow-up data in the patient record, the general practitioner was requested to provide relevant data by a questionnaire that elicited risk factors and history of cerebrovascular disease.

Radiotherapy

Patients with laryngeal carcinoma were irradiated with a total dose of 60 to 66 Gy delivered in fractions of 2 to 2.4 Gy (five fractions per week). Two lateral fields, 5 x 5 cm in size, were treated each day. Wedges and a plastic shell were used to immobilize patients. Linear accelerators with 8-MV and 4-MV photons replaced the cobalt-60 machine in the later years. The RT portal included both carotid areas. The estimated dose of RT at the carotid artery level was 95% to 100% of the administered total dose. The dose of RT in patients with pleomorphic adenoma was 50 Gy in fractions of 2 Gy,

and the post-operative treatment for patients with parotid carcinoma consisted of 60 Gy in fractions of 2 Gy (five fractions per week). The radiation technique used was two lateral oblique-wedged fields with 4- to 8-MV photons encompassing the parotid gland area and upper neck nodal regions in patients with malignant tumors. Typically these fields included the ipsilateral carotid artery over an average length of 10 cm. The estimated dose at the carotid level was 95% to 100% of the administered dose.

Statistical Analysis

A person-time analysis was carried out in which the incidence of ischemic stroke in the study population was compared with the incidence in the general population. In this type of analysis, accumulation of person-time at risk for stroke began at start of first treatment with RT, and ended at date of diagnosis of stroke, date of death, or date of most recent medical follow-up examination, whichever came first.

Expected numbers of ischemic stroke were computed by multiplying the accumulated age- and sex-specific person-years with corresponding age- and sex-specific incidence rates from the Oxfordshire Community Stroke Project (OCSP).[14] This British study was used because it covers much more detailed age- and sex-specific incidence rates than the smaller and less detailed Dutch Tilburg study, which is the only available one in the Netherlands.[15] From a thorough inspection of both studies on differences in incidence rates, we learned that ischemic stroke rates appeared quite comparable in the two countries.

Thus, with survival experience (person-years) of the population of the irradiated patients taken into account, RRs were calculated as observed/expected ratios overall, and for separate categories of primary tumor, sex, follow-up interval, and several risk factors. Confidence limits of the ratios were obtained with the use of the Poisson distribution of observed cases.[16] The results were also used to calculate the absolute excess risk, by subtracting the expected number of cases from the number of observed, multiplying by 1,000, and finally divided by person-years at risk. This risk, which estimates the excess number of strokes per 1,000 patients per year, is the most appropriate measure to judge which factors contribute most to the excess risk.

Cumulative proportions of stroke incidence were estimated as a function of time since initial treatment. A life-table analysis was carried out according to the product-limit method first described by Kaplan and Meier.[17]

Results

The characteristics of the 367 patients according to the type of tumor are described in table 1. Thirty patients with laryngeal carcinoma underwent laryngectomy, including neck dissection, for recurrent disease.

Table 1. Patients characteristics

	Overall	Larynx carcinoma	Pleomorphic adenoma	Parotid carcinoma
Number of patients	367	162	114	91
Male	224	134	42	48
Female	143	28	72	43
Person years	3011	1270	1114	626
Male	1755	1108	358	288
Female	1256	162	756	338
Median age at treatment (years)	49.3	53.7	41.5	43.0
Median follow-up (years)	7.8	7.6	9.7	6.0
Range follow-up (years)	0.5-22.6	0.5-22.4	0.7-22.6	0.6-21.4
Dose of RT (Gy)	50-66	60-66	50	60

Overall 14 out of 367 patients experienced a first ischemic stroke after RT. The overall risk of stroke after RT was significantly increased compared with the general population (RR 5.6; 95% CI 3.1-9.4). The median age at stroke was 62.7 years. The median interval from RT to occurrence of stroke was 10.9 years (range 1.3 to 21.0 years). The absolute excess risk (AER), which estimates the excess number of strokes per 1,000 patients per year, amounted to 3.8 in the whole group.
Table 2 shows the number of stroke cases, expected numbers, RR and AER for the whole group and the separate groups.

Table 2. Observed and expected cases, relative and absolute excess risk of ischemic stroke after RT

	Overall	Larynx-carcinoma	Pleomorphic adenoma	Parotid carcinoma
Observed numbers of stroke	14	8	4	2
Expected strokes	2.50	1.56	0.71	0.24
Relative Risk	5.6	5.1	5.7	8.5
95% Confidence Interval	3.1-9.4	2.2-10.1	1.5-14.5	1.0-30.6
Median age at stroke (years)	62.7	62.7	63.0	58.2
Median interval treatment to stroke (years)	10.9	7.1	13.6	8.5
Range treatment to stroke (years)	1.3-21.0	1.3-13.4	10.9-21.0	2.1-14.9
Absolute excess risk (per 1,000/year)	3.8	5.1	3.0	2.8

Table 3 lists the stroke characteristics and the outcome of the patients after the occurrence of stroke. The two strokes observed in the group of patients with parotid carcinoma were both on the irradiated side. In the group of patients with pleomorphic adenoma, one out of four stroke patients experienced a stroke on the contralateral, unirradiated side. One out of eight patients with stroke in the group of laryngeal carcinoma had been treated 5 years after irradiation with a total laryngectomy and neck dissection for a local recurrence. The interval between the operation and the ischemic stroke was 6 years. In all 14 cases, the infarction area was in the carotid artery territory. Angiography revealed carotid artery stenosis or occlusion localized to the irradiated level, typically without signs of atherosclerosis at the non-irradiated segments (figure 1).

Table 3. Patient case histories and stroke characteristics

Pt	Sex	Age at stroke (years)	Tumor	Side of RT	Infarction Territory	Outcome
1	F	62	Larynx carcinoma	Both	Right and Left hemisphere	Good
2	F	66	Pleomorphic adenoma	Right	Right hemisphere	Good
3	M	72	Larynx carcinoma	Both	Left hemisphere	Good
4	F	53	Pleomorphic adenoma	Right	Right hemisphere	Good
5	F	70	Larynx carcinoma	Both	Right hemisphere	Moderately disabled
6	M	76	Larynx carcinoma	Both	Right hemisphere	Severely disabled
7	M	65	Larynx carcinoma	Both	Left hemisphere	Mildly disabled
8	F	61	Pleomorphic adenoma	Right	Right hemisphere	Good
9	M	50	Larynx carcinoma	Both	Left hemisphere	Mildly disabled
10	F	55	Larynx carcinoma	Both	Right hemisphere	Mildly disabled
11	M	63	Larynx carcinoma	Both	Left hemisphere	Mildly disabled
12	M	72	Pleomorphic adenoma	Left	Right hemisphere	Good
13	F	51	Parotid carcinoma	Right	Right hemisphere	Mildly disabled
14	F	65	Parotid carcinoma	Left	Left hemisphere	Dead

In table 4 the distribution of other risk factors for cerebrovascular disease is shown. Table 5 lists the RR and AER of stroke according to the risk profile. The RR was higher

in patients with hypertension (RR 12.5; 95% CI 4.6-27.2) than in patients without hypertension (RR 4.3; 95% CI 1.8-8.4), although the difference was not statistically significant. The same tendency was seen in patients with DM. Smokers and nonsmokers had approximately similar RRs of stroke.

Figure 1. Angiogram of the right carotid artery demonstrates (at the level of C4-C5) occlusion of the internal carotid artery about 2 cm distal to the bifurcation, but with a normal aspect of the proximal carotid artery (patient no. 10).

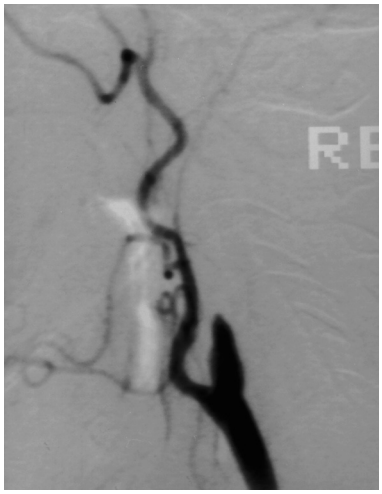


Table 4. Distribution of other risk factors for stroke

Risk factor		Overall (%)
Hypertension	Yes	15.5
	No	78.2
	Unknown	6.3
Diabetes Mellitus	Yes	3.8
	No	85.0
	Unknown	11.2
Smoking	Yes	43.6
	No	44.1
	Unknown	12.3

According to table 5, we found that patients with hypertension or DM who were irradiated on the neck had an AER of stroke of 11.6 and 17.7 per 1,000 patients per year, respectively, compared to the general population.

Table 5. Analysis of other risk factors

Risk factor		Observed strokes	Expected strokes	RR	95% CI	AER /1,000/yr*
Overall		14	2.50	5.6	3.1-9.4	3.8
Hypertension	No	8	1.87	4.3	1.8-8.4	2.6
	Yes	6	0.48	12.5	4.6-27.2	11.6
Diabetes mellitus	No	12	2.07	5.8	3.0-10.1	
	Yes	2	0.17	12.1	1.5-43.5	17.7
Smoker	No	8	1.26	6.4	2.7-12.5	4.5
	Yes	6	1.04	5.7	2.1-12.5	4.3

* Absolute excess risk (AER) per 1,000 patients per year

An analysis by duration of follow-up revealed increased RR and AER during follow-up time (table 6). After more than 10 years' follow-up, the RR was 10.1 (95% CI 4.4-20.0) and the AER was 14.0 per 1,000 patients per year. In the group of patients younger than 50 years during RT, the RR was 9.8 (95% CI 3.2-22.9) compared with 4.5 (95% CI 2.1-8.6) in the group of patients older than 50 years during RT.

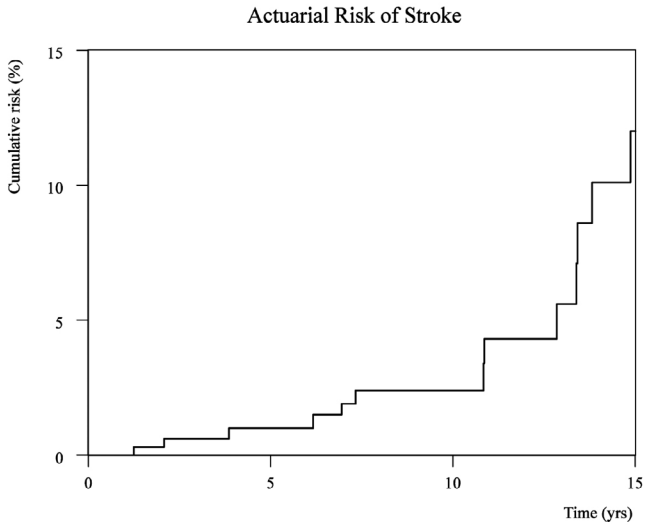
Table 6. Relative and absolute excess risks of stroke according to follow-up interval, age at radiotherapy and gender

	Person-years	Observed cases	Expected cases	RR	95% CI	AER/1,000/yr *
Follow-up time						
0-9 years	2,313	6	1.63	3.7	1.3-8.0	1.9
> 10 years	514	8	0.79	10.1	4.4-20.0	14.0
Age at RT						
< 50 years	1,659	5	0.51	9.8	3.2-22.9	2.7
> 50 years	1,351	9	1.99	4.5	2.1-8.6	5.2
Gender						
Male	1,755	8	1.91	4.2	1.8-8.2	3.5
Female	1,256	6	0.59	10.2	3.7-22.2	4.3

* Absolute excess risk (AER) per 1,000 patients per year

Figure 2 shows the cumulative risk of stroke by follow-up time. After 15 years of follow-up, the cumulative risk amounted to 12.0% (95% CI 6.5%-21.4%).

Figure 2. Cumulative risk of stroke after RT on the neck



Discussion

Several case reports and histopathological studies suggest a relation between RT and large vessel disease.[2,3,5,10,18,19] To the best of our knowledge, our study is the first to show a significant increased risk of ischemic stroke in an irradiated patient population with head and neck tumors. The risk of stroke after RT on the neck has already been investigated by Elerding et al.,[13] but they were not able to demonstrate a significant correlation between RT and stroke. In comparison with Elerding et al., we studied a more homogenous group of patients who were treated with approximately the same dose of RT and who had a relatively favorable prognosis for vascular events because of their age, i.e., below 60 years at RT. We excluded patients with T3 and T4 laryngeal carcinomas, oropharyngeal carcinomas and lymphomas because their treatment protocol consist of RT in combination with chemotherapy and/or operative intervention in the carotid area. These procedures may be associated with an increased incidence of vascular disease,[12,19,20] which could make the results hard to interpret.

Recently, a meta-analysis on the long-term survival of patients irradiated for early breast cancer showed a significantly increased vascular mortality after the first decade

following RT.[21] This study underlines the long term effect of RT on the development of radiation-induced vascular disease. In our study we also found a significantly increased risk of ischemic stroke after more than ten years of follow-up.

The assumed pathogenesis of radiation-induced vascular disease is an acceleration of the atherosclerotic process probably due to endothelial cell damage, fibrosis of the intima-media layer and development of atheromatous plaques, which is increased by occlusive changes in the vasa vasorum leading to ischemia of the arterial wall. This contributes to additional damage of the carotid artery.[5,18] The risk of ischemic stroke is presumably related to the increase of the intima-media thickness and narrowing of the vascular lumen. This is reflected in the high excess number of strokes of 14.0 per 1,000 patients per year after 10 years following RT on the large carotid artery compared to a 1.9 excess number of strokes when the interval from RT is shorter than 10 years. This seems also reflected in the more exponential curve of the actuarial risk of stroke from 10 years following RT (figure 2). Besides, an increased incidence of stroke in the control group of the same age probably contributes to the exponential course of the curve at advanced age.

Five out of six strokes occurring at the ipsilateral side of the irradiated parotid tumors corroborates the hypothesis that radiation-induced atherosclerosis of the carotid artery is the pathogenic factor.

Age at RT may be of importance. Hancock et al.[22] observed a highly significant increased risk of cardiovascular complications after mediastinal RT for Hodgkin's disease in patients treated before they were 20 years old compared with those treated when they were older than 50 years. In the present study, the RR of stroke was 9.8 in patients treated before 50 years old compared to 4.5 in older patients; the difference was not significant.

The applied radiation dose in the present study varied between 50 Gy and 66 Gy. The minimal dose for RT-damage of the cervical arteries is assumed to be 40 Gy.[23] Chung et al.,[11] evaluating the degree of carotid stenosis on post-radiation MR scans, found no dose-effect relationship when RT dose was increased to 60 Gy.

The risk factor hypertension increased the risk (RR 12.5) of stroke after RT. No difference in the RR of stroke was observed between smokers and nonsmokers. However, this finding should be interpreted with caution, because registration of smoking habits in a retrospective analysis is probably inaccurate. The statement that stroke in patients with head and neck tumors should be ascribed to their lifestyle, including excessive smoking, does not hold true for patients with a parotid tumor. Moreover, a significant proportion of the patients with laryngeal carcinoma stopped smoking at the diagnosis of cancer. In view of the median interval of 7 years between RT and occurrence of stroke in these patients, and the observed similar RR of stroke in patients with laryngeal carcinoma and parotid tumor, smoking habits in our population of patients presumably

did not play a significant role in the observed increased risk of stroke compared with the matched normal populations.

Hypercholesterolemia may also play a role in the development of stenosis after RT. Silverberg et al.[24] found hypercholesterolemia to be a contributory risk factor for radiation-accelerated atherosclerosis, as was also demonstrated in animal studies.[25,26] In our population, only a few patients (22.6%) were screened for cholesterol-levels, which made data inconclusive.

As treatment for malignancies becomes more effective, more patients will survive and long-term cerebrovascular disease will become more prominent. This highlights the need for long-term follow-up after curative treatment for head and neck cancer. During follow-up more attention should be paid to reduction of risk factors for atherosclerosis in patients who received RT on the neck. Routine performance of carotid non-invasive studies, like ultrasound may be worthwhile. In this respect, in case of amaurosis fugax, transient ischemic attack, or stroke, the patient needs neurological evaluation to investigate possible therapeutic interventions.

RT-induced carotid artery lesions, as seen on angiography can easily be differentiated from normal artherosclerotic lesions. The lesions appear to have a disproportionate involvement of the distal common carotid artery, according to the irradiated area, are usually long, and are not confined to the bifurcation.[27] In addition, they are often associated with occlusion of other cervical arteries within the radiated portal.[28]

Therapeutic options consist of percutaneous transluminal angioplasty (PTA), carotid endarteriectomy and, bypass surgery. However, these techniques remain difficult because of arterial, periarterial and cutaneous sclerosis. Complications are divers and included scar disruption, prosthetic infection, anastomotic breakdown, wound healing problems and restenosis.[28] Reports about carotid artery repair after neck radiation include less than 100 patients and most have been isolated cases. Recently, Kashyap et al.,[29] presented the results of two decades of follow-up of carotid artery repair in 24 patients. They concluded carotid surgery after neck radiation to be a safe and durable treatment. Furthermore, they found this intervention to guarantee the protection against neurologic events similar to the results obtained in endarterectomy in the absence of RT. Although surgery is an option for intervention, we would rather emphasize prevention of cerebrovascular disease after RT, which can be achieved in part by reduction of risk factors. The benefit of prophylactic antiplatelet therapy and the use of statins or angiotensin-converting-enzyme inhibitors remain uncertain in this matter. Indications for post-operative RT in case of incomplete surgical removal of pleomorphic adenoma and/or tumor spill should be re-evaluated and weighed against the increased risk of neurological complications.[30]

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Chapter 2.2

Decreased risk of stroke among 10-year survivors of breast cancer

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Abstract

Purpose
To assess treatment-specific risk of cerebrovascular events in early breast cancer (BC) patients, accounting for cerebrovascular risk factors.

Patients and methods
We studied the incidence of cerebrovascular disease (CVA; stroke and transient ischemic attack (TIA)) in 10-year survivors of early BC (n = 4414) treated from 1970 to 1986. Follow-up was 96% complete until January 2000. Treatment-specific incidence of CVA was evaluated by standardized incidence ratios (SIRs) based on comparison with general population rates and by Cox proportional hazards regression.

Results
After a median follow-up of 18 years, 164 strokes and 109 TIAs were observed, resulting in decreased SIRs of 0.8 (95% confidence interval (CI) 0.6-0.9) for stroke and 0.8 (95% CI 0.7-1.0) for TIA. Significantly increased risk of stroke was found in women who had received hormonal treatment (HT; tamoxifen), and in women who had hypertension or hypercholesterolemia, with hazard ratios (HRs) of 1.9, 2.1, and 1.6, respectively. Patients irradiated on the supraclavicular area and/or internal mammary chain (IMC) did not experience a higher risk of stroke (HR 1.0; 95% CI 0.7-1.6) or TIA (HR 1.4; 95% CI 0.9-2.5) compared with patients who did not receive radiotherapy or who were irradiated on fields other than supraclavicular area or IMC.

Conclusions
Long-term survivors of BC do not experience an increased risk of cerebrovascular events compared with the general population. HT is associated with an increased risk of stroke. Radiation fields including the carotid artery do not seem to increase the risk of stroke compared with other fields.

Introduction

The prognosis of patients with early breast cancer (BC) has significantly improved over the past decades as a result of earlier diagnosis and the use of multimodality treatment. Meta-analyses of randomized clinical trials by the Early Breast Cancer Trialists' Collaborative Group have shown an important reduction in local recurrence rate and in BC mortality as a result of the application of postoperative adjuvant radiotherapy (RT)[1-3] and adjuvant systemic therapy.[4] However, adjuvant RT has also been associated with increased risks of cardiovascular morbidity and second primary cancers.[5-7] Exposure to chemotherapy or hormonal therapy (HT) may even further increase the risk of cardiovascular disease.[8,9]

In BC patients treated with adjuvant RT, the coronary arteries, brachiocephalic trunk, subclavian artery, and common carotid arteries (CCAs) may be exposed, depending on the fields applied. As a result, BC patients are potentially at risk for late vascular sequelae of RT.[10-14] So far, nearly all studies on vascular sequelae after BC irradiation have focused on the risk of cardiac disease. RT-related stroke is mediated by accelerated atherosclerosis that can result in enhanced thromboembolism and stenosis of the area of the carotid artery within the RT portal.[15,16] Head and neck cancer patients and survivors of Hodgkin's lymphoma treated with local RT on the neck experience an increased risk of stroke during long-term follow-up.[17-19] In case of irradiation on the supraclavicular lymph nodes, the proximal part of the CCA is located within the RT portal. Therefore, we hypothesize that BC patients irradiated at the supraclavicular lymph nodes are subject to an increased risk of stroke.

Until now, no study has reported on the incidence of ischemic stroke in relation to specific radiation regimens for BC. Therefore, we examined the incidence of cerebrovascular accident (CVA) in the Dutch Late Effects Breast Cancer cohort. Unique features of this study include near-complete and long-term follow-up (median 18 years), the assessment of cerebrovascular risk according to radiation field, and the incorporation of cerebrovascular risk factors into the analysis.

Patients and methods

Data collection procedures

The Late Effects Breast Cancer cohort consists of 7425 1-year survivors, younger than 71 years of age at diagnosis, treated for stage I, II, or IIIA female BC in the period from 1970 to 1986 in the Netherlands Cancer Institute or the Erasmus MC, Daniel den Hoed Cancer Center. A detailed description of data collection procedures has been published previously.[20] In brief, all patients were identified through the hospital-based

cancer registries of the two centers. From the registries and the oncologic records, we collected the following information: date of BC diagnosis, tumor histology, axillary lymph node involvement, dates and treatment modalities of primary BC and of recurrent disease (i.e. type of surgery, radiation fields, cytostatic agents, and HT), dates of stroke and transient ischemic attack (TIA), cerebrovascular risk factors, date of most recent medical information or date of death and primary cause of death. Risk factors (such as smoking, hypertension, diabetes mellitus (DM), and hypercholesterolemia) were recorded both at the date of diagnosis of BC and at the end of follow-up. Smoking was scored positive when the patient was currently smoking or had stopped smoking less than 1 year before. Hypertension, hypercholesterolemia and DM were scored as positive when stated in the medical information or when treated.

We restricted this study to patients who survived BC for at least 10 years (n = 4414) because the increase in risk of vascular events associated with RT seems to emerge after 10 or more years.[2,5,15,16,18,20] For these patients, we updated information until at least January 1, 2000 on cerebrovascular diagnoses and risk factors by sending questionnaires to their general practitioners (GPs). In The Netherlands, nearly all residents have a GP who receives all medical correspondence from attending physicians. Forty-six patients were excluded from the cohort because their oncologic records did not contain information after 10 years since diagnosis and no additional information on vascular events could be obtained from their GPs. For the remaining 4368 patients, we collected cerebrovascular data for 83% of the patients from both the medical record and the GP, and for the other 17% of patients, we collected data from the oncologic records only. Complete follow-up information was eventually available for 4259 patients (96%). For patients who died from a stroke, without prior evidence of a cerebrovascular event, the date of death was recorded as date of diagnosis of stroke.

Treatment

During the 1970s, standard treatment for stage I, II, and IIIA BC was modified or radical mastectomy with or without RT. As of 1975, adjuvant systemic treatment was introduced for node-positive patients, including combination chemotherapy for premenopausal patients and, gradually from 1980 onwards, tamoxifen for postmenopausal patients. Standard adjuvant chemotherapy consisted of cyclophosphamide, methotrexate and fluorouracil during the whole study period. In 1980, breast-conserving therapy was introduced in both hospitals. The RT regimen depended on type of surgery and stage of disease. In both hospitals, irradiation of the ipsilateral internal mammary chain (IMC) field was common for patients with centrally or medially located tumors and/or axillary lymph node metastases. The dose in the IMC varied from 40 Gy in 15 fractions in 3 weeks to 50 Gy in 25 fractions, using either photon beams or a mixture of photons and

electrons. In case of extensive axillary nodal metastases, the axilla and supraclavicular nodes were irradiated as well (50 Gy in 25 fractions). In case of irradiation of the IMC including the medial supraclavicular nodes or of the supraclavicular nodes, the dose in the proximal part of the CCA was estimated between 80 and 100% of the total dose (equivalent of 40 to 50 Gy in fractions of 2 Gy, figures 1a and 1b).

Figure 1. Schematic representation of the radiotherapy portal of the internal mammary chain field and the McWhirter (= supraclavicular + axillary) field in case of a) left-sided breast cancer and b) right-sided breast cancer. The estimated radiation dose at both the left and right common carotid artery is 40-50 Gy.

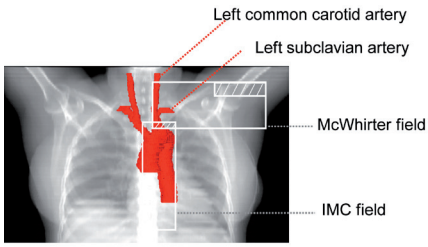

Figure 1a

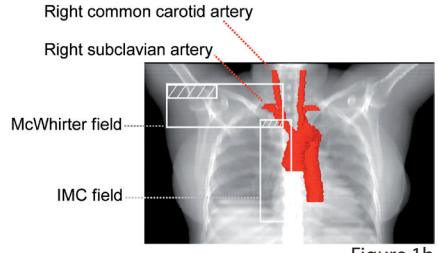

Figure 1b

Statistical analysis

We compared the incidence of stroke and TIA in the study population with the incidence in the Dutch female population, taking into account the person-years of observation in the cohort (by age, calendar period, and follow-up interval). Incidence data of the Continuous Morbidity Registration–Nijmegen, derived from several GP practices from representative regions in The Netherlands, were used as reference rates.[21] This registry has collected data on the incidence of vascular events (including TIA) for the period from 1972 to 2000, allowing for multiple separate diagnoses per person but recording only the first of a specific diagnosis per person. To assess treatment effects on stroke risk, we distinguished five mutually exclusive treatment categories based on all treatments received (table 1). Treatments administered in the last year of follow-up were excluded from the analysis because we did not want to take into account all salvage treatments received for recurrent disease during the last period in life. We also analyzed the effects of specific RT fields.

Follow-up time was defined as the period from the date of first treatment until the date of most recent medical information (including date of death). Because the study was restricted to 10-year survivors, time at risk began 10 years after the start of first treatment and ended at date of diagnosis of stroke or TIA, date of death, or date of most recent medical information, whichever came first. Observed numbers were based on all first events of stroke and TIA occurring during time at risk (i.e. after at least 10 years since first treatment); patients diagnosed with a cerebrovascular event before BC

diagnosis or within 10 years since first treatment were excluded from the analysis. The standardized incidence ratios (SIRs) of the observed and expected numbers of stroke and TIA in the study population were determined, and the confidence intervals of the SIRs were calculated using exact Poisson probabilities of observed numbers.[22] P-values for tests for trend were calculated according to standard methods. Absolute excess risk was calculated by subtracting the expected number of cerebrovascular events in our cohort from the number observed and dividing by person-years at risk (expressed per 10,000 person-years).

The Cox proportional hazards model was used to quantify the effects of different treatments on the risk of CVA, taking into account several covariates. To evaluate the independent effects of primary adjuvant treatment, we did a separate analysis where time at risk ended at date of treatment for recurrent disease. Cox models were fitted with the use of SPSS statistical software (SPSS Inc, Chicago, IL, USA).

Results

Patient characteristics

The median age at BC diagnosis in the study population was 49 years, and 32% of patients were younger than 45 years at diagnosis (table 1). Median follow-up time was 17.7 years, and 31% of the patients were followed for more than 20 years. Fifty-four percent of the patients were treated with a combination of RT and surgery, and 32% received RT and adjuvant chemotherapy and/or HT, the latter mostly for recurrent disease. Fifty-eight percent of patients received IMC RT, usually including the medial supraclavicular area, 50% were irradiated to the chest wall or breast region, and 24% were irradiated to the supraclavicular area.

Table 1. Characteristics of 10-year survivors in the Dutch Late Effects BC Study

Characteristic	No. of BC patients	%
No. of patients	4368	100
Hospital		
NKI	2045	46.8
DDHK	2323	53.2
Age at BC diagnosis (years)		
< 45	1379	31.6
45 - 54	1681	38.5
≥ 55	1308	29.9
Year of first treatment of BC		
1970 - 75	1075	24.6
1976 - 80	1059	24.2
1981 - 86	2234	51.1
Axillary node involvement (at diagnosis)		
Node negative	2557	58.5
Axillary node pos., subclav. neg.	1544	35.3
Subclav. pos.	164	3.8
Unknown	103	2.4
Laterality		
Left	2229	51.0
Right	2097	48.0
Bilateral	42	1.0
Treatment category, primary + follow-up treatment		
Surgery only	516	11.8
RT (+ surgery)	2362	54.1
RT + CT (+ surgery)	529	12.1
RT + HT (+ surgery)	438	10.0
RT + CT + HT (+ surgery)	448	10.3
Other/unknown	75	1.7
Radiation fields, primary + follow-up treatment*		
IMC	2538	58.1
Chest wall	880	20.1
Breast	1319	30.2
Supraclavicular	1061	24.3
Axilla	1356	31.0
Radiation fields, primary + follow-up treatment**		
IMC, no supraclavicular	1712	39.2
Supraclavicular, no IMC	227	5.2
IMC + supraclavicular	826	18.9
Other fields; but no IMC or supraclavicular	934	21.4
Unknown	60	1.4
Follow-up time (years)		
10 - 14	1081	24.7
15 - 19	1917	43.9
≥ 20	1370	31.4

Abbreviations: BC, breast cancer; NKI, Netherlands Cancer Institute; DDHK, Erasmus MC, Daniel den Hoed Cancer Center; RT, radiotherapy; CT, chemotherapy; HT, hormonal therapy.
*Allowing more than one field per patient.
** Mutually exclusive treatment groups.

Table 2 displays the information on cerebrovascular risk factors in the study population. We compared the distribution of hypertension, DM, and hypercholesterolemia by age categories in our study to the reference population from CMR–Nijmegen (table 3). Since this Registry had no data on smoking habits, we used figures from a nationwide survey held in 2000 for comparison.[23] At the end of follow-up, the distribution of risk factors was very similar in our study group compared with the control population, with the exception of patients aged more than 75years, who had a significantly higher prevalence of hypertension (44% versus 34%, respectively; $p < 0.001$)

Table 2. Risk factors for stroke or TIA in 10-year survivors of the Dutch Late Effects BC Study

	No. of patients	%
Smoking:		
Never	2136	48.9
Unknown at BC diagnosis, but not at end of follow-up	334	7.6
Smoking at BC diagnosis, but not anymore at end of follow-up	413	9.5
Smoking at BC diagnosis, unknown at end of follow-up	551	12.6
Smoking through the end of follow-up	426	9.8
Unknown	508	11.6
Hypertension:		
No	3039	69.5
Diagnosed prior to BC diagnosis	444	10.2
Developed during follow-up	716	16.4
Unknown	169	3.9
Diabetes Mellitus:		
No	3826	87.6
Yes	383	8.8
Unknown	159	3.6
Hypercholesterolemia:		
No	3739	85.6
Yes	441	10.1
Unknown	188	4.3
History* of stroke/TIA:		
No/ Unknown	4355	99.7
Yes	13	0.3

Abbreviations: BC, breast cancer; TIA, transient ischemic attack.

*Before BC diagnosis.

Table 3. Distribution of risk factors (in %) by age categories

Smoking:	Late effects BC study	Dutch population
Age in 2000:	%	%
35 - 49	36	37
50 - 64	28	28
>= 65	15	15
Hypertension:	**Late effects BC study**	**CMR Nijmegen**
Age in 2000:	%	%
< 45	2	2
45 – 64	17	13
65 – 74	34	31
>= 75	44	34
Diabetes mellitus:	**Late effects BC study**	**CMR Nijmegen**
Age in 2000:	%	%
< 45	0.7	0.4
45 – 64	4	4
65 – 74	11	11
>= 75	12	15
Hypercholesterolemia:	**Late effects BC study**	**CMR Nijmegen**
Age in 2000:	%	%
< 45	0.2	0.4
45 – 64	12	7
65 – 74	17	16
>= 75	10	9

Abbreviations: BC, breast cancer; CMR, continuous morbidity registration.

Risk of CVA by age, follow-up and treatment regimen

Overall, we observed 164 strokes and 109 TIAs (table 4), including 14 patients with both (TIA preceding stroke). In total, 51 patients died from a stroke. The median age at stroke diagnosis was 75.5 years after a median follow-up of 17.0 years; TIAs were diagnosed at a median age of 73.1 years after a median follow-up of 16.8 years.

With 217.6 strokes expected versus 164 seen, the risk of stroke was significantly decreased by 25% (SIR 0.75; 95% CI 0.64 - 0.88, table 4). Decreased risk of stroke was found for all age groups. For TIA, the risk was increased in patients younger than 45 years old at BC diagnosis, with SIRs showing a consistent decline with older ages at

diagnosis of BC (p for trend < 0.0001; table 4). There was no trend over follow-up time for risk of stroke or TIA.
Risks of stroke and TIA did not differ between patients who were treated with surgery alone and those who received RT in combination with surgery. However, among patients who were treated with RT plus HT, we observed an elevated risk of stroke (SIR 1.31; 95% CI 0.87-1.88) compared with the general population, whereas risk of TIA was significantly increased in patients treated with RT plus chemotherapy (SIR 2.90; 95% CI 1.4-5.19).

Risk of CVA by RT field: Cox model analysis
Patients irradiated on the supraclavicular and/or IMC fields did not experience a higher risk of stroke or TIA compared with patients irradiated on fields other than supraclavicular or IMC fields or patients treated without RT (table 5). Risk of stroke was most strongly associated with HT (HR 1.88), hypertension (HR 2.07), and hypercholesterolemia (HR 1.64). For smoking and DM, we found nonsignificantly increased HRs of 1.37 and 1.33. In the analysis by primary treatment, where time at risk ended at date of treatment for recurrent disease, risk of stroke remained increased for adjuvant HT (HR 2.14; 95% CI 0.62-7.32; table 5).

Discussion

This is the first long-term cohort study assessing the incidence of cerebrovascular events in early BC patients according to RT fields delivered. Overall, the risk of stroke was decreased by 25% in comparison with the general female population. Contrary to our expectation, risk of stroke was not increased in patients treated with adjuvant RT at the carotid arteries compared with non-irradiated patients. Of all treatment modalities, only HT was associated with an increased risk of stroke. Strongest risk factors were hypertension and hypercholesterolemia, but these factors did not modify the risk estimates for treatment.
Data on risk of stroke in BC patients are scarce. Recently, Jagsi et al. found a non-significantly elevated SIR of CVA (1.74; 95% CI 0.94-2.37) in patients with early BC after a median follow-up of 6.8 years.[24] In the EBCTCG meta-analysis on effects of RT, the gain in BC survival from RT was partly offset by an increase of vascular mortality.[2] A recent update[3] showed that this excess vascular mortality mainly involved heart disease, whereas risk of stroke was not increased in irradiated versus non-irradiated patients. In a large population-based study (median follow-up, 5.4 years), Nilsson et al. found that BC patients had an overall relative risk (RR) of stroke of 1.12 (95% CI 1.07-1.17) compared with the general population.[25]

Table 4. Overall risk of stroke and TIA, by age at start of treatment, treatment category and follow-up interval

	Stroke*					TIA				
	O	E	SIR	95% CI	AER#	O	E	SIR	95% CI	AER#
Overall	164	217.6	0.75	0.64 – 0.88	-15.2	109	133.3	0.82	0.67 – 0.99	-6.8
Age at start of treatment										
< 45 years	17	19.6	0.87	0.51 – 1.39	-2.3	12	6.80	1.76	0.91 – 3.08	4.5
45 – 54 years	52	56.9	0.91	0.68 – 1.20	-3.5	39	33.4	1.17	0.83 – 1.60	3.9
>= 55 years	95	141.0	0.67	0.55 – 0.82	-47.6	58	93.1	0.62	0.47 – 0.81	-35.9
			Ptrend = 0.1					Ptrend < .0001		
Treatment										
Surgery only	24	39.3	0.61	0.39 – 0.91	-31.0	11	24.6	0.45	0.22 – 0.80	-27.4
RT (± surgery)	90	134.4	0.67	0.54 – 0.82	-21.3	71	83.0	0.86	0.67 – 1.08	-5.7
RT+CT (± surgery)	10	10.7	0.94	0.45 – 1.72	-1.9	11	3.79	2.90	1.45 – 5.19	19.3
RT+HT (± surgery)	28	21.5	1.31	0.87 – 1.88	21.6	10	14.4	0.69	0.33 – 1.28	-14.5
RT+CT+HT (± surgery)	7	8.4	0.83	0.34 – 1.72	-6.0	4	5.2	0.77	0.21 – 1.97	-5.1
Follow-up interval										
10 – 14 years	51	84.8	0.60	0.45 – 0.79	-17.7	37	59.1	0.63	0.44 – 0.86	-11.5
15 – 19 years	70	75.6	0.93	0.72 – 1.17	-5.0	47	44.3	1.06	0.78 – 1.41	2.4
>= 20 years	43	57.2	0.75	0.54 – 1.01	-28.8	25	29.9	0.84	0.54 – 1.23	-9.9

Abbreviations: TIA, transient ischemic attack; O, observed number of events; E, expected number of events;
SIR, standardized incidence ratio; AER, absolute excess risk; RT, radiotherapy; CT, chemotherapy; HT, hormonal therapy.
* Type of stroke: 90% ischemic, 5% hemorrhagic, 5% unknown.
# Per 10,000 patients per year.

Table 5. Multivariate Cox regression analyses of potential risk factors for stroke and TIA

	Analysis based on total treatment		Analysis based on primary treatment*
	Risk of stroke#	Risk of TIA#	Risk of stroke#
Risk Factor	HR (95% CI)	HR (95% CI)	HR (95% CI)
RT			
No RT/ fields not incl. carotid artery†	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
IMC only	1.04 (0.72 – 1.49)	1.39 (0.88 – 2.20)	1.00 (0.66 – 1.49)
Supraclavicular (± IMC)	1.04 (0.69 – 1.58)‡	1.45 (0.85 – 2.46)§	0.79 (0.47 – 1.33)
CT vs no CT	0.91 (0.53 – 1.57)	1.32 (0.71 – 2.47)	0.76 (0.33 – 1.76)
HT vs no HT	1.88 (1.28 – 2.75)	0.91 (0.52 – 1.59)	2.14 (0.62 – 7.32)
Smoking vs. never:			
Through the end of follow-up	1.37 (0.96 – 1.95)	1.33 (0.86 – 2.05)	1.24 (0.81 – 1.88)
Ex-smoker	1.00 (0.58 – 1.72)	0.74 (0.36 – 1.56)	0.89 (0.47 – 1.68)
Hypertension vs no/unknown	2.07 (1.49 – 2.87)	1.23 (0.81 – 1.86)	2.44 (1.65 – 3.60)
Diabetes Mellitus vs no/unknown	1.33 (0.88 – 2.00)	1.47 (0.86 – 2.49)	1.27 (0.78 – 2.05)
Hyperchol. vs no/unknown	1.64 (1.09 – 2.47)	1.69 (1.00 – 2.83)	1.89 (1.20 – 2.97)

Abbreviations: TIA, transient ischemic attack; HR, hazard ratio; RT, radiotherapy;
IMC, internal mammary chain; CT, chemotherapy; HT, hormonal therapy.
* In the analysis based on primary treatment, time at risk ended at the date of treatment for recurrent disease.
# Adjusted for age at diagnosis; furthermore, all listed variables were included in the model.
† Fields not including carotid artery: no IMC or supraclavicular field.
‡ Risk of stroke by laterality: HR for left supraclavicular field, 1.03 (0.61–1.71); for right supraclavicular field, 0.87 (0.49–1.54).
In the analysis by laterality, time at risk would end at date of a contralateral BC, but only if the contralateral side had received RT.
As a consequence, some events were excluded from the analysis and therefore the separate risk estimates for left- and right-sided tumors were somewhat lower than the risk estimate for RT in this region when laterality was not taken into account.
§ Risk of TIA by laterality: HR for left supraclavicular field, 2.00 (1.11- 3.59); for right supraclavicular field, 0.84 (0.38–1.85).

This increased risk was especially pronounced during the first year after diagnosis (RR 1.22; 95% CI 1.06-1.39). Possibly, the increase during the first year was caused by tumor-related coagulation disorders.[26,27] The effect of specific treatment regimens could not be examined because of lack of information. Retrospective studies of head and neck tumor patients and survivors of Hodgkin's lymphoma irradiated to the carotid region show a significantly increased risk of stroke. In BC patients, both left and right supraclavicular radiation portals include the ipsilateral CCA, with the left artery exposed over a slightly longer stretch than the right one. Therefore, we expected an increased risk of CVA, probably somewhat higher for RT on the left side. Overall, we found no increased risk of CVA. When analyzing by laterality, we observed an increased risk of TIA among women irradiated on the left supraclavicular region (HR 2.00; table 5, see footnote), whereas no such risk increase was found for the right side (HR 0.84). No left-right difference was observed for stroke, however. Although there were some differences in fractionation schedules used in our study population, all schedules had a more or less equivalent biological effective dose. Consequently, we did not expect any differences in risk between these fractionation regimens.

HT such as tamoxifen increases the risk of venous thromboembolism, and some recently published studies have investigated risk of stroke associated with tamoxifen.[28-30] Results from a meta-analysis by Bushnell and Goldstein[8] showed an elevated risk of ischemic stroke (RR 1.82; 95% CI 1.41 - 2.36). However, the International Breast Cancer Intervention Study-I prevention study[28] and the nested case-control study by Geiger et al.[30] did not demonstrate a significantly increased risk of stroke with tamoxifen. In our study, we observed a nearly two-fold elevated risk of stroke in patients treated with HT. However, tamoxifen is often prescribed for metastasized BC. Therefore, the association with tamoxifen may be confounded by the presence of active disease, which in itself may predispose to thrombosis[26] and thereby to ischemic stroke.[31] The separate effects of active disease and HT could not be disentangled in earlier studies.[28,30] Therefore, we assessed the influence of HT on the risk of stroke separately in patients without signs of relapse and again observed a (nonsignificantly) increased risk of stroke (HR 2.14).

Our recent study on cause-specific mortality in BC patients already showed a (non-significant) 16% decrease in overall mortality from stroke.[20] Importantly, this study showed no mortality increase from stroke during the first 10 years of follow-up, justifying our decision to focus on 10-year survivors of BC in the current study. There are several explanations for reduced risk of stroke in long-term BC survivors compared with the general population. First, the risk profile for BC (e.g., late menopause) may be protective against (cerebro-)vascular disease.[32] In addition, women may opt for a healthier lifestyle (e.g., more exercise, healthier diet) after BC diagnosis, which would reduce their risk profile for stroke even more.[33,34] Although we did not observe a more favorable risk profile in the study population compared with the general population,

our BC cohort may have been subject to more subtle changes in risk profile during follow-up (e.g., dietary changes, less smoking rather than cessation of smoking). Hypertension was even more frequently diagnosed in our BC population than in the general female population, probably as a result of surveillance bias. Paradoxically, this might explain the reduced risk of stroke. BC patients with known hypertension will receive treatment and thus reduce their risk of stroke, whereas a high proportion of the general population with hypertension may not be correctly diagnosed and thus will remain untreated. Finally, particularly in this cancer center-based study population, we may have studied BC patients with higher socioeconomic status, which has been reported to be associated with lower rates of vascular disease.[35,36]

Strengths of our study include the availability of data on all primary and follow-up treatments, including radiation fields, and on cerebrovascular risk factors. Follow-up was near complete and very long, with over 30% of patients followed for more than 20 years.

A potential weakness of our study concerns underreporting of CVA diagnoses. However, a study on cardiovascular risk in the same study population[37] rendered a significant 1.3–fold increased risk of cardiovascular disease, which was comparable to results from other studies.[2,5,38] In both studies on vascular events, we obtained information from GPs for the large majority of patients because a pilot study had shown that 20% of vascular events were not registered in oncologic records. Furthermore, since the GP was the source of information for both observed events and the reference rates used for comparison, any underreporting by GPs would not affect the validity of our results.

Although we had information on cardiac risk factors at baseline and also at follow-up, it was not always available at the time we were most interested in (i.e. at 10 years after first treatment). We used hypertension, DM, and hypercholesterolemia as fixed covariates in the analysis with a positive score obtained at any point in time. Although this approach may have introduced some misclassification, this would be expected to bias our risk estimates to unity. As for smoking, this problem was largely avoided by using separate categories for smokers who continued smoking until end of follow-up and for ex-smokers (those who stopped at the time of BC diagnosis).

In conclusion, no association between stroke risk and irradiation to the supraclavicular nodes was found in our BC population. Although adjuvant HT[1] clearly improves BC survival, physicians should be aware of the increased risk of stroke after HT in long-term BC survivors.

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Chapter 2.3

Increased risk of stroke and transient ischemic attack (TIA) in 5-year survivors of Hodgkin's lymphoma

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Abstract

Background
Information on clinically verified stroke and transient ischemic attack (TIA) following Hodgkin's lymphoma is scarce. We quantified the long-term risk of cerebrovascular disease associated with the use of radiotherapy and chemotherapy in survivors of Hodgkin's lymphoma, and explored potential pathogenic mechanisms.

Methods
We performed a retrospective cohort study among 2201 5-year survivors of Hodgkin's lymphoma treated before age 51 between 1965 and 1995. We compared incidence rates of clinically verified stroke and TIA with the general population. We used multivariable Cox-regression techniques to study treatment-related and other risk factors.

Results
After a median follow-up of 17.5 years, 96 patients developed cerebrovascular disease (55 stroke, 31 TIA, 10 TIA and stroke; median age 52 years). Most ischemic events were of large-artery atherosclerotic (36%) or cardioembolic subtype (24%). The standardized incidence ratio for stroke was 2.2 (95% confidence interval (CI) 1.7-2.8); and 3.1 for TIA (95% CI 2.2-4.2). The risks remained elevated after prolonged follow-up. The cumulative incidence of ischemic stroke or TIA 30 years after Hodgkin's lymphoma treatment was 7% (95% CI 5-8%). Radiation to the neck and mediastinum was an independent risk factor for ischemic cerebrovascular disease (Hazard ratio 2.5; 95% CI 1.1-5.6). Treatment with chemotherapy was not associated with an increased risk. Hypertension, diabetes mellitus and hypercholesterolemia were associated with the occurrence of ischemic cerebrovascular disease, whereas smoking and overweight were not.

Conclusion
Patients treated for Hodgkin's lymphoma experience a substantially increased risk of stroke and TIA, associated with radiation to the neck and mediastinum. Physicians should consider appropriate risk-reducing strategies.

Introduction

The prognosis of patients diagnosed with Hodgkin's lymphoma has significantly improved during the last decades; as a consequence many patients will become long-term survivors. During follow-up, therapy-related complications have become an important issue, especially in young adult survivors. The spectrum of late complications following curative therapy is diverse and includes impaired fertility, second malignancies and cardiovascular disease.[1-6] Presently, only few studies considered stroke and transient ischemic attack (TIA) as the outcome of interest.[7,8] In addition, none of these were able to compare the incidence of clinically verified stroke and TIA to the general population.

In Hodgkin's lymphoma patients, both the carotid arteries and the heart are exposed to radiotherapy in case of mantle field irradiation. These patients could experience an increased risk of cerebrovascular disease by accelerated atherosclerosis resulting in carotid stenosis. Stroke and TIA risk may be further increased by cardioembolisms following radiation-induced cardiac disease. Those Hodgkin's lymphoma patients who are treated with chemotherapy are at risk for chemotherapy-induced vascular toxicity, which may result in stroke. Especially acute occurring stroke, possibly due to a hypercoagulable state, is associated with antineoplastic agents such as L-asparaginase, 5-fluorouracil, cisplatin, methotrexate and cyclophosphamide.[9-11] These agents are not part of standard treatments for Hodgkin's lymphoma, and the long term effects are not yet defined. Furthermore, anthracycline-induced heart failure[12] or cardiomyopathy could result in an increased risk for stroke and TIA.

In females, premature menopause induced by gonadotoxic chemotherapy[5] may be a risk factor for late occurring cerebrovascular disease, as shorter lifespan of ovarian activity is associated with an increased risk for ischemic stroke.[13]

Until now, only few studies have reported on clinically verified stroke in long-term survivors of Hodgkin's lymphoma.[7,8] It has also not been analyzed which pathogenic mechanisms contribute to stroke incidence. We examined the incidence of both stroke and transient ischemic attack (TIA) in a large cohort of Hodgkin's lymphoma survivors in the Netherlands. We restricted this study to patients who survived more than 5 years because the risk of vascular events associated with radiotherapy seems to emerge after 5 years or more.[7,14,15] The acute effects of the first-line treatment, e.g. acute occurring stroke, are beyond the scope of our study.

Unique features of our study include the relatively young age of the cohort (< 51 years at diagnosis), clinically verified strokes and TIAs, near complete follow-up, the assessment of cerebrovascular disease according to radiation fields and type of chemotherapy, and the availability of cerebrovascular risk factors.

Methods

Data collection procedures

We performed a cohort study among patients who were treated at 4 cancer centers/ University hospitals in The Netherlands (the Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital (NKI/AVL) in Amsterdam, Erasmus MC - Daniel den Hoed Cancer Center (EMC/DdHK) in Rotterdam, Leiden University Medical Center (LUMC) in Leiden, the Emma Children's Hospital/Academic Medical Center (EKZ) in Amsterdam). Patients were younger than 51 years at treatment for Hodgkin's lymphoma (1965-1995) with either radiotherapy and/or chemotherapy. Patients were excluded if they had been treated with radiotherapy or chemotherapy before the diagnosis of Hodgkin's lymphoma. Patient selection and methods of data collection in NKI/AVL and EMC/DdHK have been described in detail previously[1,3,16,17]; in the other centers methods were comparable. Data were collected directly from the medical records. In case the information could not be obtained from the medical record, questionnaires were sent to general practitioners and attending physicians. Collection of follow-up data for the current study took place between December 2004 and June 2008. Medical follow-up was complete for 94% of the cohort (51 patients had moved abroad, 78 were discharged from the primary hospital and attending physicians elsewhere could not be reached). We collected the following information: date of Hodgkin's lymphoma diagnosis, treatment modalities of primary as well as salvage treatment for Hodgkin's lymphoma, (i.e., radiation fields, cytostatic agents, and number of cycles), dates of stroke, TIA and other cardiovascular diseases, cerebrovascular risk factors, age at menopause, date of diagnosis and treatment of second malignancies, date of most recent medical information or date of death and primary cause of death. Smoking, weight, height and overweight were recorded both at the date of diagnosis of Hodgkin's lymphoma and at the end of follow-up. Cerebrovascular risk factors were assessed according to clinical guidelines. Of the 2253 5-year survivors identified, 39 were excluded, because follow-up for cardiovascular diseases was less than 5 years following treatment for Hodgkin's lymphoma, 6 were excluded because they developed a second malignancy that was treated with radiotherapy or chemotherapy within the first 5 years following treatment, and another 7 individuals were excluded because they developed a stroke or TIA before or within the first 5 years after treatment of Hodgkin's lymphoma, leaving 2201 patients eligible for analyses.

Outcome definition

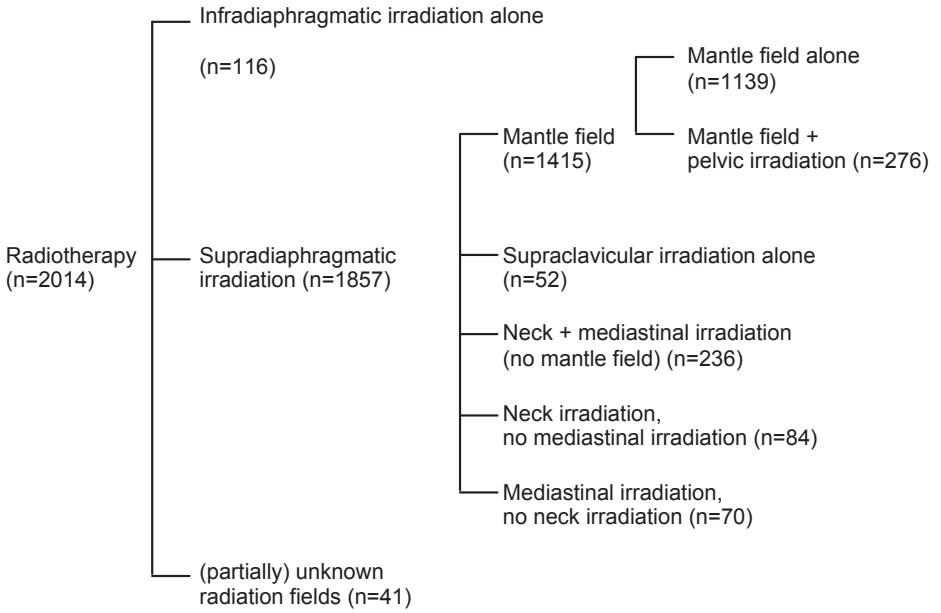
Cases were defined as cohort members who developed a stroke or TIA 5 years or more after first treatment for Hodgkin's lymphoma. Stroke or TIA diagnoses were verified by treating neurologists or general practitioners, who provided additional information

on type of stroke (ischemic/hemorrhagic), vascular territory (carotid or vertebrobasilar system), origin of stroke or TIA. Stroke etiology was further assigned using the TOAST criteria (large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology and stroke of undetermined etiology.[18] We also collected data on treatment and clinical outcome (on average) 3 months after the event according to the Modified Rankin Score (see table 1 for detailed description).[19] TIA was defined as any new neurological deficit (either ocular or cerebral) that resolved completely within 24 hours. Stroke was defined as any new neurological deficit (either ocular or cerebral) that persisted > 24 hours or ended in death within 30 days.

Treatment

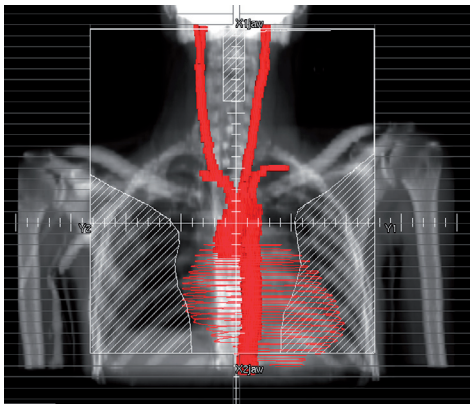
Dates of primary as well as first salvage treatment with radiotherapy and chemotherapy were recorded, as was detailed information on radiation fields, chemotherapeutic agents and number of cycles. Patients were usually treated in or according to EORTC (European Organization for Research and Treatment of Cancer) trials.[20] The distribution of radiation fields is given in figure 1, based on individual treatment data, for primary as well as salvage treatment. Radiotherapy techniques changed over the years. In the 1960s, patients were treated with cobalt-60 or orthovoltage therapy; from the 1970s onward, linear accelerators were used (usually 8 MV photons). Individual blocks were used to shield normal tissues as much as possible. Shielding of the distal part of the mediastinum was sometimes performed from the late 1980s onward in case there was no spread of disease below the aortic notch. The vast majority of cervically irradiated patients (82%) received a classical mantle field (at extended source skin distance involving the axillary, mediastinal and neck nodes), including the common carotid arteries, heart and thoracic aorta (figure 2). In addition, most patients were treated with 1 field per day only. The procedure of using 2 fields per day was gradually introduced in the late 1980s. Patients usually received 40 Gy (36-44 Gy) in fractions of 2.0 Gy. Historically, patients were treated to doses of 40 Gy and in the era that effective chemotherapy was not available they were sometimes re-irradiated for recurrences. In addition, compensation for dose inhomogeneity was not routinely performed in the first decades of the studied period and hotspots in the neck and axilla could be as high as 20-30% above the prescribed doses.[21] However, information on radiation techniques, radiation doses and fractionation schedules for individual patients was not collected.

Figure 1. Applied radiation-fields in study population (n=2201).



From the 1960s to the 1980s chemotherapy consisted mainly of MOPP (mechlorethamine, vincristine, procarbazine, prednisone). In the 1980s, anthracycline-containing regimens such as MOPP/ABV (mechlorethamine, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, vinblastine) and ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) were introduced as a part of the primary treatment.

Figure 2. Schematic representation of the radiotherapy of the mediastinum and neck including heart, aorta, carotid arteries (in red).



Statistical analyses

We compared the incidence of stroke and TIA in the study population with the incidence in the Dutch population, taking into account the person-years of observation in the cohort (by age, calendar period, and follow-up interval).[3] Incidence data of the Continuous Morbidity Registration-Nijmegen, derived from several general practices from representative regions in the Netherlands, were used as reference rates.[22] This registry has collected data on the incidence of TIA and stroke for the period from 1972 to 2000, allowing for multiple separate diagnoses per person but recording only the first of a specific diagnosis per person. There is no distinction between ischemic and hemorrhagic strokes in this registry. Follow-up started 5 years after the first treatment for Hodgkin's lymphoma and ended at date of diagnosis of stroke or TIA, date of diagnosis of a second malignancy treated with radiotherapy or chemotherapy, date of most recent medical information, or date of death, whichever came first. Observed numbers were based on all first events of stroke and TIA occurring during time at risk. Strokes or TIAs that occurred after treatment of a second malignancy were therefore not included in the analysis. Hodgkin lymphoma survivors may die (from other causes) before they can develop cerebrovascular disease, especially with prolonged follow-up. Therefore, we calculated the cumulative incidences of stroke, TIA and ischemic stroke/TIA with adjustment for competing risks of death due to any cause using S-plus statistical software (Insightful, Seattle, WA), including user-written functions.[23]

The standardized incidence ratios (SIRs) of the observed and expected numbers of stroke and TIA in the study population were determined, and the confidence intervals (CIs) of the SIRs were calculated using exact Poisson probabilities of observed numbers.[24] P- values for tests for trend were two-sided and were calculated using chi-square test statistics. Absolute excess risk was calculated by subtracting the expected number of strokes or TIAs in our cohort from the number observed and dividing by person-years at risk (expressed per 10,000 person-years).

To study the effects of different treatments taking into account several covariates, we performed multivariate Cox-regression analyses. As the proposed mechanisms for treatment-induced stroke and TIA are thought to cause ischemic events, we excluded hemorrhagic strokes and strokes of unknown type in these analyses. In case of multiple events, time at risk ended at date of the first stroke or TIA. All treatment-related exposure variables were analyzed time-dependent. We calculated hazard ratios (HR) as a measure of relative risk and 95% CIs to describe the precision of our estimates. We evaluated the proportional hazards assumption by assessing log minus log curve {ln [-ln (S)]} and by fitting interaction terms between treatment categories as well as covariates and the logarithm of follow-up time. No violations of the proportional hazards assumption were observed. Models were fitted with the use of SPSS statistical software (SPSS Inc, Chicago, IL).

Results

During follow-up (median 17.5 years) 96 patients developed a stroke or TIA (55 strokes, 31 TIAs and 10 patients with both a TIA and a stroke). Of the 65 strokes, 57 were ischemic, 7 were hemorrhagic (incl. 2 subarachnoid hemorrhages), and in 1 case the type could not be verified. Median time to first stroke or TIA was 17.4 years (range 5.1 to 37.6 years). In total 88 individuals developed at least 1 ischemic stroke or TIA (47 ischemic strokes, 31 TIAs and 10 both ischemic stroke and TIA). Thirty-five of the ischemic strokes and TIAs occurred before age 51, and can be defined as 'young strokes'. Most ischemic events were of large-artery atherosclerotic or cardioembolic subtype (table 1). Duplex ultrasonography revealed in 17% a significant (>50%) stenosis of the carotid artery. The majority of ischemic strokes and TIAs were pharmacologically treated. Twenty-two percent of the patients suffering from ischemic stroke had a poor clinical outcome (table 1).

The cumulative incidence of ischemic stroke or TIA accounting for death as a competing risk 30 years after first treatment was 7% (95% CI 5-8%), the separate cumulative incidences of stroke and TIA were 5% (95% CI 4-6%) and 3% (95% CI 2-4%) at that time, respectively (figure 3).

Figure 3. The cumulative incidence of ischemic stroke and TIA following Hodgkin's lymphoma treatment.

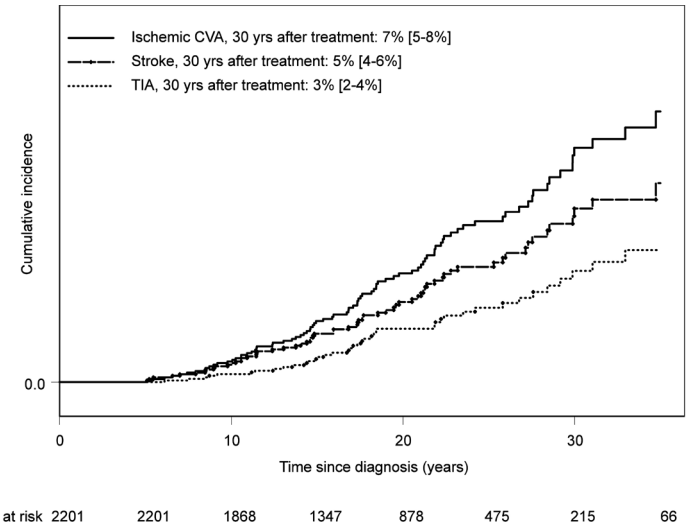


Table 1. Clinical characteristics of first ischemic strokes and TIAs.

	Ischemic stroke*		TIA*	
	n=49	(%)	n=39	(%)
Age at ischemic stroke/TIA				
Median age (min-max)	51.4	(27.4-79.9)	54.4	(32.7-80.6)
< 50 years	22	(45%)	13	(33%)
≥ 50 years	27	(55%)	26	(67%)
Hemisphere				
Right	19	(39%)	7	(18%)
Left	20	(41%)	20	(51%)
Both	6	(12%)	5	(13%)
Unknown	4	(8%)	7	(18%)
Vascular territory				
Carotid	39	(76%)	30	(77%)
Vertebrobasilar	9	(18%)	4	(10%)
Both	2	(4%)	5	(13%)
Unknown	1	(2%)	0	-
Etiology ischemic event				
Large-artery atherosclerosis	21	(43%)	11	(28%)
Cardioembolism	9	(18%)	12	(31%)
Small vessel occlusion	3	(6%)	0	-
Other determined etiology	1	(2%)	1	(3%)
Undetermined etiology	7	(14%)	5	(13%)
Unknown	8	(16%)	10	(26%)
Duplex ultrasonography				
Carotid artery				
- No stenosis	20	(41%)	16	(41%)
- 30-50% stenosis	2	(4%)	3	(8%)
- > 50% stenosis	10	(20%)	5	(13%)
Vertebrobasilar stenosis	2	(4%)	0	-
Not performed	13	(27%)	11	(28%)
Unknown	2	(4%)	4	(10%)
Treatment				
Antiplatelets/anticoagulants	40	(82%)	34	(87%)
Carotid endarterectomy	2	(4%)	2	(5%)
No treatment	7	(14%)	2	(5%)
Unknown	0	-	1	(3%)
Clinical outcome †				
No symptoms (MRS 0)	9	(18%)	39	(100%)
Mild symptoms (MRS 1-3)	29	(59%)	0	-
Severe symptoms (MRS 4-5)	2	(4%)	0	-
Dead (MRS 6)	9	(18%)	0	-

* Not including 8 ischemic strokes that occurred after a TIA, 7 hemorrhagic strokes, 1 stroke of unknown type, and 2 TIAs that occurred after an ischemic stroke. † Modified Rankin Score (MRS): 0: No symptoms at all; 1: No significant disability despite symptoms; able to carry out all usual duties and activities; 2: Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance; 3: Moderate disability; requiring some help, but able to walk without assistance; 4: Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance; 5: Severe disability; bedridden, incontinent and requiring constant nursing care and attention; 6: Dead

Compared to the general population, patients experienced an about 2-fold increased risk for stroke (SIR 2.2; 95% CI 1.7-2.8) and a 3-fold increased risk for TIA (SIR 3.1; 95% CI 2.2-4.2), resulting in 12 excess cases of stroke and 9 excess cases of TIA per 10,000 persons per year. There were significant trends of increasing SIRs with younger age at first treatment (p=0.004 for stroke and p=0.01 for TIA), but no increasing or decreasing trends with longer follow-up time or treatment period. There were no clear differences between men and women, and SIRs were only increased among those treated with radiotherapy alone, or combined modality treatment (table 2).

The multivariate Cox-regression analysis showed that patients treated with neck irradiation together with mediastinal irradiation experienced a significantly increased risk for ischemic stroke or TIA, compared to those treated with chemotherapy or infradiaphragmatic irradiation alone (HR 2.5; 95% CI 1.1-5.6) (table 3). Most of these patients (86%) received mantle field irradiation (figure 1). Neither anthracycline-containing chemotherapy, nor other chemotherapy was associated with an increased risk for ischemic cerebrovascular disease. Hypertension was an independent risk factor for ischemic stroke or TIA, hypercholesterolemia and diabetes mellitus were positively but non-significantly associated with ischemic cerebrovascular disease. Smoking and overweight were not associated with ischemic stroke or TIA (table 3). We did not find any evidence that premature menopause or gonadotoxic chemotherapy (related to cumulative procarbazine exposure)[5] was associated with an increased risk for ischemic stroke and TIA among females (table 4).

Of the 1651 patients treated with mediastinal and neck irradiation, 21% (n=348) developed cardiac disease (heart failure, myocardial infarction, arrhythmias, or valvular disease) before the occurrence of ischemic stroke, TIA or end of follow-up. This proportion was substantially lower among those treated with other radiation fields or without radiotherapy (56/509 = 11%). However, the risk to develop ischemic stroke or TIA in the period between first treatment for Hodgkin's lymphoma and end of follow-up among patients treated with mediastinal and neck irradiation did not differ from the risk in the same period among those who did not develop cardiac disease before end of follow-up (adjusted HR 0.6; 95% CI 0.4-1.1). On the other hand, when patient-time after the occurrence of cardiac disease was compared to patient-time before cardiac disease in a time-dependent analysis, we found that among patients treated with mediastinal and neck irradiation the risk for ischemic stroke or TIA was 2-fold increased after cardiac disease compared to before (adjusted HR 2.1; 95% CI 1.2-3.7).

Table 2. Standardized incidence ratios and absolute excess risks of stroke and TIA, according to sex, age at first treatment for Hodgkin's lymphoma, follow-up period, attained age during follow-up and treatment category.

		Stroke*						TIA*					
	Patients	O	E	SIR	(95% CI)	AER	(95% CI)	O	E	SIR	(95% CI)	AER	(95% CI)
Total cohort	2201	65	29.7	2.2	(1.7 - 2.8)	12	(7 - 18)	41	13.1	3.1	(2.2 - 4.2)	9	(6 - 14)
Sex													
Male	1233	34	17.0	2.0	(1.4 - 2.8)	10	(4 - 19)	21	7.8	2.7	(1.7 - 4.1)	8	(3 - 15)
Female	968	31	12.7	2.4	(1.7 - 3.5)	14	(6 - 23)	20	5.3	3.8	(2.3 - 5.8)	11	(5 - 19)
Age at treatment (years)				p-trend=0.004						p-trend = 0.01			
≤20	547	8	2.1	3.8	(1.6 - 7.4)	7	(1 - 17)	5	0.7	7.6	(2.4 - 17)	5	(1 - 14)
21-30	815	23	7.5	3.1	(1.9 - 4.6)	14	(6 - 24)	11	2.6	4.2	(2.1 - 7.5)	7	(3 - 15)
31-40	559	21	10.4	2.0	(1.2 - 3.1)	15	(4 - 30)	14	4.5	3.1	(1.7 - 5.2)	13	(4 - 27)
41-50	280	13	9.6	1.4	(0.7 - 2.3)	11	(-9 - 40)	11	5.4	2.1	(1.0 - 3.7)	18	(0 - 46)
Follow-up period (years)				p-trend = 0.64						p-trend = 0.92			
5-9	334	10	4.8	2.1	(1.0 - 3.8)	5	(0 - 13)	5	2.1	2.3	(0.8 - 5.5)	3	(0 - 9)
10-14	521	14	6.0	2.3	(1.3 - 3.9)	10	(2 - 22)	9	2.7	3.3	(1.5 - 6.3)	8	(2 - 18)
15-19	469	16	6.1	2.6	(1.5 - 4.3)	18	(6 - 36)	12	2.8	4.4	(2.3 - 7.6)	17	(6 - 33)
20-24	402	11	5.3	2.1	(1.0 - 3.7)	17	(1 - 43)	6	2.4	2.5	(0.9 - 5.5)	11	(-1 - 32)
≥25	475	14	7.5	1.9	(1.0 - 3.7)	26	(1 - 64)	9	3.2	2.8	(1.3 - 5.4)	23	(4 - 55)
Attained age (years) †													
<51	2201	29	11.7	2.5	(1.7 - 3.6)	7	(3 - 13)	14	4.4	3.2	(1.8 - 5.4)	4	(1 - 8)
≥51	821	36	18.0	2.0	(1.4 - 2.8)	29	(12 - 52)	27	8.8	3.1	(2.0 - 4.5)	30	(15 - 50)
Treatment													
Radiotherapy alone	609	21	10.5	2.0	(1.2 - 3.1)	11	(3 - 23)	16	4.7	3.4	(1.9 - 5.5)	12	(5 - 22)
Chemotherapy alone	187	1	2.7	0.4	(0.0 - 2.1)	-6	(-10 - 11)	0	1.1	-		-	
Radio/chemotherapy	1405	43	16.5	2.6	(1.9 - 3.5)	15	(8 - 24)	25	7.3	3.4	(2.2 - 5.1)	10	(5 - 17)
Treatment period ‡				p-trend = 0.80						p-trend = 0.44			
1965-1975	706	30	13.9	2.2	(1.5 - 3.1)	13	(5 - 24)	20	7.1	2.8	(1.7 - 4.4)	11	(4 - 20)
1976-1985	785	26	10.6	2.4	(1.6 - 3.6)	13	(6 - 24)	13	4.0	3.3	(1.7 - 5.6)	8	(3 - 16)
1986-1995	710	9	5.1	1.8	(0.8 - 3.4)	6	(-2 - 19)	8	2.1	3.9	(1.7 - 7.7)	10	(2 - 22)

TIA: transient ischemic attack, O: observed number of cases, E: expected number of cases, SIR: standardized incidence ratio, AER: absolute excess risk, CI: confidence interval.

* Including 8 ischemic strokes that occurred after a TIA, 7 hemorrhagic strokes, 1 stroke of unknown type, and 2 TIAs that occurred after an ischemic stroke.

† Attained age was defined as the age of patients at diagnosis of a given cerebrovascular event or at the end of follow-up and was calculated to assess at what ages patients experienced increased risk compared with their peers in the general population. Each patient contributed person-years to each consecutive attained-age category that the patient passed through during follow-up.

‡ Year in which patient was first treated for Hodgkin's lymphoma.

Table 3. Cox regression analyses of potential risk factors for ischemic stroke or TIA following treatment for Hodgkin's lymphoma.

Risk factor	Patients n=2201	Cases n=88	HR (95% CI) Univariate		HR (95% CI) Multivariate*	
Female sex (vs male)	968	40	1.0	(0.6 - 1.5)	0.8	(0.5 - 1.3)
Radiotherapy						
No supradiaphragmatic irradiation	303	7	1	(Ref)	1	(Ref)
Supraclavicular/neck irradiation	136	5	2.2	(0.7 - 7.0)	2.3	(0.7 - 7.6)
Mediastinal irradiation	70	1	1.0	(0.1 - 8.5)	1.2	(0.1 - 9.8)
Mediastinal + neck irradiation	1651	75	2.2	(1.0 - 4.7)	2.5	(1.1 - 5.6)
Partially unknown radiation fields	41	0	-		-	
Chemotherapy						
No chemotherapy	609	32	1	(Ref)	1	(Ref)
Anthracyclines	690	17	1.1	(0.6 - 2.1)	1.3	(0.7 - 2.5)
Other chemotherapy	902	39	0.8	(0.5 - 1.2)	1.0	(0.6 - 1.7)
Cerebrovascular risk factors						
High cholesterol (vs no/unknown)	203	25	2.6	(1.6 - 4.2)	1.6	(1.0 - 2.6)
Hypertension (vs no/unknown)	282	36	3.3	(2.1 - 5.0)	2.1	(1.3 - 3.3)
Diabetes mellitus (vs no/unknown)	120	13	2.7	(1.5 - 4.9)	1.5	(0.8 - 2.7)
Smoking (vs never/unknown)						
- Past	634	23	0.9	(0.5 - 1.4)	0.9	(0.5 - 1.4)
- Current	373	14	1.0	(0.6 - 1.8)	1.2	(0.7 - 2.3)
BMI >30 kg/m2 (vs ≤30 kg/m2)	199	12	1.6	(0.8 - 2.9)	1.2	(0.6 - 2.2)

HR: Hazard ratio, CI: confidence interval, BMI: body mass index.

* Adjusted for age at first treatment for Hodgkin's lymphoma, pelvic irradiation, and each other

Table 4. The influence of premature menopause and gonadotoxic chemotherapy on risk of ischemic stroke or TIA following treatment for Hodgkin's lymphoma.

	Patients n=2201	Cases n=88	HR (95% CI) Multivariate	
Premature menopause (model 1*)				
Male	1233	48	1.3	(0.7 - 2.2)
Female				
Menopause at age 41 or later	298	18	1	(Ref)
Menopause before age 41	213	8	1.0	(0.4 - 2.4)
Age ≤ 41 and premenopausal at end of study	191	2	1.7	(0.4 - 8.1)
Age at menopause unknown	266	12	1.0	(0.5 - 2.1)
Gonadotoxic therapy				
Overall (model 2†)				
No CT/ CT without procarbazine ‡	883	47	1	(Ref)
Alkylating CT, ≤8.4g/m2 procarbazine	733	28	1.3	(0.6 - 2.8)
Alkylating CT, >8.4g/m2 procarbazine	308	9	1.8	(0.7 - 4.6)
No pelvic irradiation	1742	67	1	(Ref)
Pelvic irradiation	459	21	1.3	(0.7 - 2.2)
Males (model 3†)				
No CT/ CT without procarbazine ‡	467	26	1	(Ref)
Alkylating CT, ≤8.4g/m2 procarbazine	427	15	1.2	(0.4 - 3.9)
Alkylating CT, >8.4g/m2 procarbazine	187	6	1.7	(0.4 - 6.5)
No pelvic irradiation	928	35	1	(Ref)
Pelvic irradiation	305	13	1.3	(0.7 - 2.6)
Females (model 4†)				
No CT/ CT without procarbazine ‡	416	21	1	(Ref)
Alkylating CT, ≤8.4g/m2 procarbazine	346	13	1.2	(0.4 - 3.7)
Alkylating CT, >8.4g/m2 procarbazine	121	3	2.1	(0.5 - 9.2)
No pelvic irradiation	814	32	1	(Ref)
Pelvic irradiation	154	8	1.4	(0.6 - 3.2)

HR: Hazard ratio, CI: confidence interval, CT: chemotherapy.
* Adjusted for age at first treatment for Hodgkin's lymphoma, supradiaphragmatic radiation field, chemotherapy, cerebrovascular risk factors (smoking, BMI>30 kg/m2, diabetes mellitus, hypertension, hypercholesterolemia) and each other.
† Adjusted for sex, age at first treatment for Hodgkin's lymphoma, supradiaphragmatic radiation field, other chemotherapy, cerebrovascular risk factors (smoking, BMI>30 kg/m2, diabetes mellitus, hypertension, hypercholesterolemia) and each other.
‡ Unknown CT/ unknown procarbazine dose was modeled as a separate category.

Discussion

To the best of our knowledge, this is the first long-term cohort study assessing the incidence of clinically verified stroke and TIA in survivors of Hodgkin's lymphoma, taking into account cerebrovascular risk factors as well as radiation fields, that compared the incidence to the general population. Overall, stroke and TIA risks are increased compared to the age- and sex-matched control population. Risks were especially elevated among patients treated at a young age (< 21 years), and remained increased for at least 25 years. The excess burden of stroke and TIA are 10 and 9 cases per 10,000 patients per year, respectively, implying 1 excess case of stroke and TIA each among 100 5-year survivors followed for 10 years. Radiation on the neck and mediastinum proved a significant risk factor for the occurrence of ischemic stroke and TIA. Other significant risk factors were age at treatment and hypertension.

Recently, the Childhood Cancer Survivor Study (CCSS) reported on self-reported incidence and risk factors for stroke in childhood Hodgkin's survivors.[7] Twenty-four late occurring strokes were observed in a cohort of 1926 survivors of childhood Hodgkin's lymphoma (relative risk (RR) 4.32; 95% CI 2.01-9.29). Patients irradiated with mantle fields even experienced a higher RR for stroke (5.62; 95% CI 2.59-12.25). Our results are in line with the CCSS, although the RRs we found are lower than those calculated by the CCSS. A probable explanation is that the CCSS population is younger, and in our data younger age at first treatment was associated with a greater risk increase of stroke. However, in the youngest group of our cohort, the risk is still lower than reported by CCSS. It is possible that self-report of stroke can lead to overestimation of the true incidence of the disease. For patients it is difficult to distinguish a stroke from other focal neurological disorders like epileptic seizures and e.g. collapses.

The most important risk factor for ischemic stroke and TIA in our study was irradiation to the neck and mediastinum. Studies in survivors of head and neck cancer showed that high-dose radiotherapy (60-66 Gy) to the neck is associated with a significantly increased risk of stroke.[14,15,25] The time interval from radiotherapy until stroke diagnosis was shorter in head and neck cancer patients (median time interval 10.9 years, range 1.3 to 21.0) than in the Hodgkin's lymphoma-survivors (median time interval 17.4 years, range 5.1 to 37.6). We hypothesize that in relatively young Hodgkin's lymphoma-survivors (median age at first treatment 27.1, range 3.1 to 50.9) with naïve atherosclerotic arteries, radiotherapy induces atherosclerosis. In contrast, in the older head and neck patients radiotherapy accelerates the already existing atherosclerotic lesions. Because radiation effects are presumed to be dose-related, mantle field irradiation (with a tumor dose of 30-40 Gy) may contribute to a longer time interval than the higher dose radiotherapy-schedules in head and neck patients.

In concordance with Hull et al.,[8] who studied risk factors for carotid and subclavian

disease among Hodgkin's lymphoma patients, we found that hypertension was an independent risk factor for ischemic stroke and TIA. In contrast, we were not able to confirm the high risk associated with diabetes mellitus. This could be due to coincidence or to the fact that Hull et al. studied a slightly different end-point, including not only stroke and TIA, but also subclinical carotid and subclavian stenosis.

Besides large-artery arthrosclerosis, another mechanism for ischemic stroke and TIA in these patients includes cardioembolisms. Hodgkin's lymphoma survivors have an increased risk of radiotherapy-related cardiovascular disease like myocardial infarction and valvular dysfunction.[3,8] We found that 24% of the ischemic strokes and TIAs had a cardioembolic etiology (table 1). We also found that after a patient had developed cardiac disease; the risk of subsequent ischemic stroke or TIA was 2-fold increased. Epidemiologic study of intermediate factors in the etiologic pathway of exposure and disease requires advanced statistical techniques.[26] Unfortunately, in our study population numbers were too small to successfully apply these techniques.

Overall, stroke and TIA were diagnosed at a relatively young age (median 52 years, range 24 to 80 years). The impact of stroke and TIA on quality of life of Hodgkin's lymphoma-survivors is high. In general, stroke is judged the sixth most common cause of reduced disability-adjusted life-years (DALY= sum of life years lost as a result of premature death and years live with disability adjusted for severity).[27] In our cohort 13% of the patients with ischemic stroke had a poor clinical outcome (Modified Rankin Score ≥4). Among young strokes (age <51 at diagnosis) the proportion of patients with a poor clinical outcome was much lower than among patients who suffered from ischemic stroke at older ages (14% vs. 29%). Long-term prognosis of ischemic stroke in young adults (range 15 to 45 years) is generally limited, especially in terms of work activity: only 53% of young ischemic stroke patients return to work again.[28] Functional independence is more favorable and is seen in 90%, which is comparable with our cohort (functional independence (Modified Rankin Score ≤3) in 86% (age <51)).

Primary prevention for cardio- and cerebrovascular disease after radiotherapy has not yet been established. As cardiovascular risk factors, like hypertension, contribute to the elevated risk of ischemic stroke and TIA after radiotherapy,[8,14] intervention in these risk factors after radiotherapy is important. Secondary preventive strategies after ischemic stroke and TIA in Hodgkin's lymphoma-survivors are not different than in classic atherosclerosis and consist of antiplatelet and anticoagulant treatment according to the origin of stroke (non-cardiogenic versus cardiogenic). Special attention is needed for screening of the carotid arteries and for cardioembolisms in case of symptomatic long-term survivors of Hodgkin's lymphoma. We do not advocate screening for carotid stenosis in asymptomatic patients because of the relatively low excess cases of stroke and TIA: about one excess case of stroke and TIA among 100 5-year survivors followed for 10 years.The best treatment for both asymptomatic and symptomatic carotid

artery stenosis is a matter of debate and should be patient-tailored. Both carotid endarterectomy and carotid artery stenting could be considered.[29]

Strong features of our study are near complete follow-up and the validation and outcome of stroke and TIA by information from the neurologist. We found that the proportion of strokes of the ischemic subtype (87%) was slightly higher compared to other population based series of strokes (54-88%).[30-33] Another interesting finding was the distribution of large-vessel atherosclerosis versus cardioembolic etiology between ischemic strokes (43% vs. 18%) and TIAs (28% vs. 31%). In addition, significant carotid stenosis was, at least, present in 20% of the patients who suffered from ischemic stroke, and 13% of the patients who experienced a TIA (table 1). These proportions might be underestimated because ultrasonoghraphy was performed in only 73% of all stroke patients and in 72% of all TIA patients.

Unfortunately, precise information on administered radiation dose was lacking in our study. In the study by Hull et al.,[34] the median low cervical radiation doses for patients who did and did not develop subclavian stenosis were 44Gy and 36Gy, respectively (p=0.002). However, the RRs of stroke were significantly elevated in patients treated between 1965-1985, while the RR was not significantly increased in patients treated between 1986-1995. This is suggestive of a dose effect, although it may also be due to fewer person-years with long-term follow-up, and associated lower power, among patients from the more recent era. The RRs of TIA, however, were similarly elevated throughout the calendar period of 1965-1995. Since then there have been substantial changes in radiation treatment for Hodgkin's lymphoma with the use of lower doses, smaller treatment fields and more conformal techniques to limit dose inhomogeneity. It would be interesting to further examine radiation dose-response relationships in future studies covering patients treated after 1995, when both applied radiation doses and volume were reduced.

Another limitation of our study is the proportion of missing data regarding the etiology of the ischemic strokes and TIAs (20% unknown). In some very disabled patients (Modified Rankin Score ≥4, 13%) no further research was performed by the treating neurologists for identification of the underlying cause. In the remaining patients we could not retrieve these data.

In summary, patients with Hodgkin's lymphoma experience a 2- to 3-fold increased risk of stroke and TIA for a prolonged period after treatment. Radiation to the neck and mediastinum importantly contribute to cerebrovascular late effects. Especially young survivors of Hodgkin's lymphoma are at increased risk of stroke and TIA, physicians should consider appropriate risk-reducing strategies such as treatment of hypertension, and lifestyle advice such as refraining from smoking.

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Chapter 3

Pathogenetic mechanism in radiation induced vascular disease

Chapter 3.1

Increased carotid wall thickening after radiotherapy on the neck

Published as:

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Abstract

Patients treated for head and neck tumors with local radiotherapy (RT) on the neck harbor 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 tumor 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 RT patients with a favorable prognosis.

Introduction

Patients treated for head and neck tumors with local radiotherapy (RT) harbor 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 significant 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 tumors 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 patient's contra-lateral carotid artery to serve as an internal control.

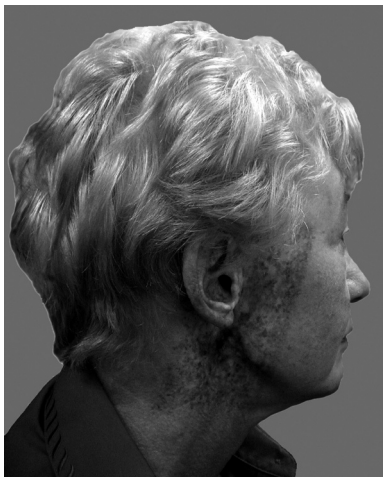
Patients and methods

Patients
We studied forty-two 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: (1) patients with parotid carcinoma and (2) patients with pleomorphic adenoma in whom massive uncontrolled tumor 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.

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 (figure 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 calculated at this level as well. The mean difference in IMT at both locations was used for this group of patients.

Figure 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.



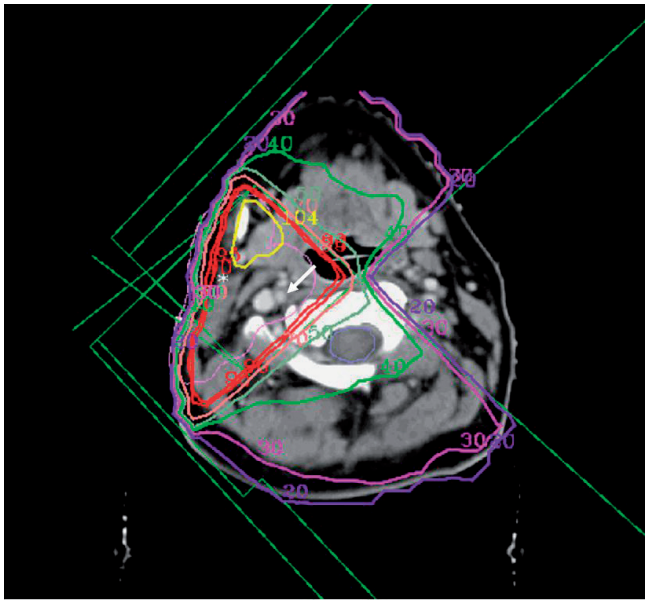
Radiation therapy

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 (figure 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).

Measurements of other covariates

All patients completed a standardized questionnaire to assess patients' and family history of cerebrovascular disease. Blood pressure was measured twice on the right arm in sitting position using a mercury sphygmomanometer. Hypertension was defined when systolic blood pressure ≥ 160 mm Hg and/or a diastolic blood pressure ≥ 95 mm Hg in both measurements; and/or the use of blood pressure-lowering medication. Diabetes mellitus was considered present if the patient was taking oral anti-diabetics or insulin. Hypercholesterolemia 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.

Figure 2. Contrast-enhanced 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).



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.

Results

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 pleomorphic adenoma. The median age at RT was 47.4 years (range 23 to 77 years). The median post-RT interval was 9.8 years (range 3.4 to 27.2 years).

The total therapeutic radiation dose ranged from 40 to 66 Gy and was delivered in fractions of 2.0 Gy. Patient characteristics and an outline of other covariates are summarized in table 1.

Table 1. Characteristics of study population

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

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 relation between the IMT difference and the duration of the post-RT interval (unstandardized ß (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 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		Δ IMT (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
≥ 10 years	1.35	0.68	+ 0.67	0.007

RT:radiotherapy

Occurrence of cerebrovascular accidents

Five patients had sustained a vascular ischemic event (3 TIA, 2 cerebral infarction) at a median of 11 years (range 5.9 to 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).

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 contra- lateral 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 the study was the cross-sectional design. Selection of patients with favorable oncology and a good vascular prognosis could 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 in 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 thrombo-embolic 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 percent 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 favors this hypothesis.

Our study group consisted of relatively young patients (median age of 47 years at the time of RT) with a favorable prognosis. The vascular changes become increasingly prominent during the time span after RT. In general, these patients develop cerebrovascular ischemic complications at an earlier age than indicated by the incidence rates of cerebrovacular disease in non-irradiated patients.[1,12] Both carotid endarterectomy[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 and colleagues could not detect a dose dependent relationship when they compared high dose RT (≥ 65 Gy) with lower dose RT (< 60 Gy) and the severity of the post RT carotid changes on MRI angiography.[17] 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, which further increase the risk of stroke in these irradiated patients.[1] Longitudinal prospective studies are needed to analyze the IMT-changes over a longer time period and, to investigate whether treatment with thrombo-modulating agents, like statins or ACE-inhibitors, can prevent or diminish these changes following RT.

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Chapter 4

Treatment of radiation induced carotid artery stenosis

Chapter 4.1

Outcome of carotid artery stenting for radiation induced stenosis

Submitted for publication:

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Abstract

Purpose
Patients who have been irradiated at the neck have an increased risk of symptomatic stenosis of the carotid artery during follow-up. Carotid Angioplasty and Stenting (CAS) can be a preferable alternative treatment to carotid endarterectomy which is associated with increased operative risk in these patients.

Patients and methods
We performed a prospective cohort study of 24 previously irradiated patients who underwent CAS for symptomatic carotid stenosis. We assessed periprocedural and non-procedural events composed of TIA, non-disabling stroke, disabling stoke and death. Patency rates were evaluated on duplex ultrasound scans. Restenosis was defined as a stenosis of > 50% at the stent location.

Results
Periprocedural TIA-rate was 8% and periprocedural stroke (non-disabling) occurred in 4% of patients. After a mean follow-up of 3.3 years (range 0.3 to 11.0 years) only one ipsilateral incident event (TIA) had occurred (4%). In 12% of patients a contralateral incident event was present: one TIA (4%) and 2 strokes (12%, 2 disabling strokes). Restenosis was apparent in 17%, 33% and 42% at respectively 3, 12 and 24 months, although none of the patients with restenosed vessels became symptomatic. The length of the irradiation to CAS interval proved the only significant risk factor for restenosis.

Conclusion
The results of CAS for radiation induced carotid stenosis are favorable in terms of recurrence of cerebrovascular events at the CAS-side.

Introduction

External neck irradiation is a risk factor for transient ischemic attack (TIA) and stroke, probably mediated by the development of carotid artery stenosis.[1-4] The occurrence of clinical symptoms may be long (range 1 to > 20 years) after radiotherapy (RT).[5] With the therapeutic advancement of primary head and neck malignancies and the attendant increased long-term survival after RT, these patients are at high risk for the development of RT induced carotid artery stenosis; hence the need for evaluating its treatment.

Although RT-induced carotid stenosis can surgically be treated by carotid endarterectomy (CEA)[6], this technique is challenging due to diminished healing capacities, scar tissue due to former radical neck dissection and /or the irradiation itself, compared with stenosis based on atherosclerosis. In addition, the surgical access is considered more difficult because of a often, more proximally located stenosis in the common carotid artery.[7] Therefore, the American Stroke Association guidelines state that Carotid Angioplasty and Stenting (CAS) can be considered for patients under specific conditions such as radiation induced stenosis.[8] Although theoretically CAS could possibly overcome some of these limitations that exist for CEA, reliable empirical data on incident stroke and patency rates of CAS after RT induced carotid artery stenosis are sparse.[9,10]

We therefore performed a prospective study to investigate incident cerebrovascular events and the occurrence of restenosis among 24 patients who were treated with CAS after RT.

Subjects and Methods

Subjects and possible risk factors

We assembled a cohort of patients who underwent CAS for symptomatic RT induced carotid stenosis between the years 1998 and 2006 at the Neurointerventional Radiology department of two institutes (St Antonius Hospital, Nieuwegein and the University Medical Center Utrecht). Inclusion criteria were prior RT of the neck before CAS, complete periprocedural data of CAS and complete clinical follow-up.

By medical record review, we collected baseline data including age, sex, neurological symptoms prior to stenting, vascular risk factors according to clinical guidelines hypertension (defined as either treatment for high blood pressure or a blood pressure that exceeded twice the limit of 95 mm Hg), diabetes mellitus, dyslipidemia/statin treatment, smoking (current, former and never), cardiovascular morbidity and previous CEA. We also took tumor type and oncological treatment regimen into account

including: RT-dose, RT–CAS interval and previous neck surgery (radical neck dissection and/or laryngectomy). Symptomatic carotid disease prior to stenting was diagnosed if the patient had experienced a TIA or stroke referable to the carotid lesion.

Procedure

Diagnosis of carotid stenosis was made by duplex ultrasound (DUS), in combination with either computed tomographic (CT) angiography or magnetic resonance (MR) angiography. Pre-stent stenosis of the carotid artery was further graded on digital subtraction angiography according to the NASCET criteria.[11] All patients were treated with CAS for symptomatic stenosis of their carotid artery, at either the common carotid artery (CCA), the internal carotid artery (ICA) or both, depending on the location of the stenosis. In all patients, CAS was performed in accordance with our previously described protocol.[12,13] All procedures were performed under local anesthesia, from a groin approach. Procedures were performed by an experienced interventionalist. Technical failure was defined as residual stenosis of 30% graded on the digital subtraction angiography after the procedure.

Follow-up

The whole cohort was followed for the occurrence of the following primary end points; TIA and (non) disabling stroke (either ipsilateral or contralateral of the CAS procedure) and death. TIA was classified as any neurological deficit (either ocular or cerebral) that resolved completely within 24 hours, non-disabling stroke if the modified Rankin score was ≤ 2 (on a scale of 0-5, with higher score indicating more disability), a disabling stroke if the modified Rankin score was 3 points of more.[14] Death was categorized as death from stroke, death from vascular cause or death from other cause.

Follow-up evaluations were performed by an independent stroke neurologist. In addition DUS were performed at 48 hr, 30 days, 3 and 12 months post-CAS and thereafter annually. If patients were not followed anymore in our tertiary centers, information on outcome events was collected by the general practitioner. Peri-procedural complications were classified as events that occurred within 30 days after CAS. Non-procedural events were collected from 30 days after the procedure until the end of follow-up, i.e. the last surveillance by the neurologist or the general practitioner.

DUS was performed by an independent rater and consisted of the ipsi-and contralateral CCA (proximal and distal), ICA (proximal, middle and distal) and external carotid artery (ECA). The DUS criteria used in our vascular laboratory are based on the Strandness criteria.[15] In terms of classification of the degree of ICA or CCA stenosis, we used the same velocity criteria in the post-stenting as for the pre-stenting situation. We measured the highest peak systolic (PSV) and enddiastolic velocities (EDV) in the stented artery

for grading the restenosis. Restenosis was defined as a stenosis of > 50%. Contralateral stenosis was graded as 50% or more.

Endpoints

The primary endpoint was the occurrence of non-procedural incident cerebrovascular events (TIA, non-disabling, disabling stroke) and death during follow-up.
The secondary endpoint was the occurrence of restenosis of the stented carotid artery during follow-up. Restenosis was defined as a stenosis of > 50% at the CCA or ICA at the treated side.

Statistics

Statistical analyses were performed using the statistical software package SPSS 14.0 (SPSS, Inc., Chicago, Il). Actuarial survival analysis was performed by Kaplan Meier life tables in order to analyze the occurrence of incident cerebrovascular events.
Multivariate Cox proportional hazard models were used to assess the risk of the primary end points, adjusted for possible confounding factors including hypertension, diabetes mellitus, smoking, oncologic treatment (time interval between RT-CAS) and procedure related factors (previous neck operation, contralateral carotid disease).
The relationship between restenosis at specific time points and potential risk factors (hypertension, diabetes mellitus, smoking, contralateral stenosis, previous neck operation and time-interval between RT and CAS) was assessed by means of sex and age adjusted logistic regression analysis.

Results

Patient characteristics

We identified 24 patients who underwent CAS for symptomatic radiation induced carotid stenosis. The demographic characteristics, tumor en RT-status are presented in table 1. The mean time elapsed between RT and CAS was 13.1 years (SD 8.1). The contralateral carotid artery was occluded in 6 patients (25%), while 8 patients (33%) had a contralateral ACI stenosis of > 50%. In 12 patients (50%) a stenosis of more than 50% was observed at the ipsilateral external carotid artery (ECA).

Table 1. Demographics of 24 patients undergoing CAS for radiation induced carotid stenosis.

Characteristics	n= 24 (%)
Age (years) (mean, SD)	68 (8.1)
Male	18 (75)
Tumor type	
Larynxcarcinoma	11 (46)
Oropharynxcarcinoma	6 (25)
Lymphoma	2 (8)
Other	5 (21)
Radiotherapy	
< 40 Gy	2 (8)
40-60 Gy	5 (21)
> 60 Gy	17 (71)
Time elapsed between RT-CAS (years, SD)	13.1 (8.1)
Previous operation	
Lymph node dissection or laryngectomy	13 (54)
Carotid endarterectomy (ipsilateral)	2 (8)
Concomitant vascular risk factors	
Hypertension	13 (54)
Smoking (current)	5 (21)
Diabetes mellitus	3 (13)
Hypercholesterolemia/ Statin treatment	11 (46)
Cardiovascular disease	5 (21)
Qualifying symptoms	
TIA	14 (59)
Ischemic Stroke	10 (42)
Preprocedural stenosis	
50-69%	1 (4)
70-89%	8 (33)
90-99%	15 (63)
Lesion location of stenosis	
Common carotid artery	4 (17)
Internal carotid artery	18 (75)
Both internal and common carotid artery	2 (8)
Contralateral carotid patency	
Stenosis (50-99%)	8 (33)
Occlusion	6 (25)

Outcomes

Technical and perprocedural angiographical success (i.e. a residual stenosis of less than 30%) was achieved in 100 % of patients. Within 30 days, 2 patients (8%) had a TIA and one patient suffered (4%) a non-disabling stroke that resolved completely within 2 days. The 30-day-all-cause-mortality was 0%. The mean clinical follow-up time after CAS was 3.3 years (SD 2.3; range 0.3 to 11.0 years). Non-procedural cerebrovascular events occurred in four patients: one patient had a ipsilateral TIA (4%) and in 3 patients a contralateral event (12%) occurred (table 2). The proportion without any cerebrovascular events during follow-up is shown in figure 1. Multivariate Cox-proportional hazard analysis showed no risk factor for ipsi -and contralateral incident cerebrovascular events.

Rates and degrees of restenosis are presented in table 3. No in-stent occlusion occurred. None of the restenosed vessels were symptomatic. In only one patient a restenting procedure was performed because of a rapid occurring instent restenosis of 90-99% with good post-procedural results (free from rerestenosis after 2 years).

The length of the RT-CAS interval proved to be the most significant risk factor for restenosis at 3 months (RR 1.14; 95 % CI 1.0-1.3), meaning that each year elapsed since RT, the risk of restenosis increases with 14%.

Table 2. Clinical outcome of CAS for radiation induced stenosis.

Clinical outcomes	n= 24 (%)
Technical failure	0
Any periprocedural TIA, stroke or death (up to 30 days)	
TIA	2 (8)
Non-disabling Stroke	1 (4)
Death	0
Any non-procedural TIA & strokes (disabling and non-disabling)	4 (16%)
Ipsilateral	
TIA	1 (4)
Contralateral	
TIA	1 (4)
Disabling stroke	2 (8)
Any non-procedural deaths	7 (29)
Contralateral stroke*	1 (4)
Other vascular death **	2 (8)
Non-vascular death †	4 (16)

* One patient died after the disabling stroke.

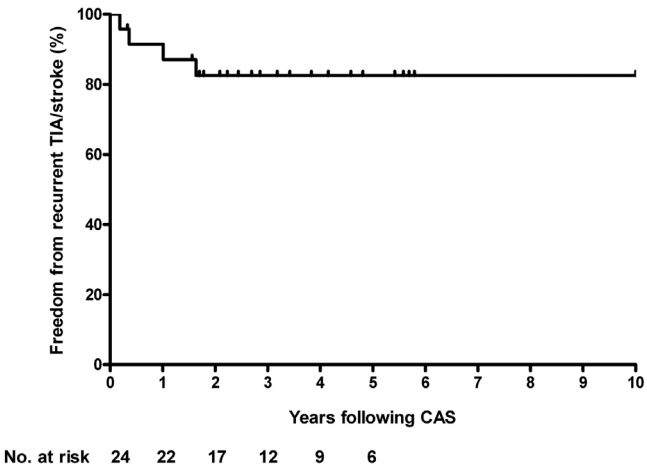
** Other vascular dead consisted of myocardial infarction and heart failure.

† Other causes of non-vascular dead consisted of breast cancer, pneumonia, car accident and 1 unspecified cause of dead.

Table 3. Stent patency measured by duplex ultrasound at 3 months, 1 and 2 years follow-up.

Stent patency	n (%)
Restenosis 3 months (n= 23)	
0-49%	19 (83)
50-69%	4 (17)
70-89%	0
90-99%	0
Occlusion	0
Restenosis 1 year (n=21)	
0-49%	14 (67)
50-69%	3 (14)
70-89%	3 (14)
90-99%	1 (5)
Occlusion	0
Restenosis 2 year (n= 17)	
0-49%	10 (59)
50-69%	4 (24)
70-89%	1 (6)
90-99%	2 (12)
Occlusion	0

Figure 1. Kaplan-Meier analysis showing the cumulative freedom from cerebrovascular events (TIA and stroke) at the ispilateral and contralateral side of CAS.



Discussion

We report the long term outcome for patients with Carotid Angioplasty and Stenting (CAS) for symptomatic carotid stenosis after RT on the neck. These patients are at increased operative risk during carotid endarterectomy (CEA) and are excluded by large randomized intervention trials. In this high risk population we found that periprocedural CAS risks appear to be comparable to CAS in non-irradiated patients.[16] Disabling stroke or death within 30 days was 0%. Overall, the non-procedural proportion of ipsilateral incident cerebrovascular events in our study was low (4%) and only transient (one patient with TIA). The actuarial risk of any incident TIA and stroke was 16% after a median follow-up of 3.3 years. At 3 years follow-up this is comparable to other high risk surgical patients (those with coexisting conditions, such cardiac morbidity and a destructed neck anatomy). The recently completed SAPPHIRE study reported an overall stroke occurrence in 9% of patients at 3 years which is comparable to the 8% stroke occurrence in our cohort.[17] The observed incident cerebrovascular events cannot be attributed to failure of the CAS procedure, since 3 out of 4 events occurred at the non-CAS side. The occurrence of new cerebrovascular events is most likely a reflection of high incidence of bilateral carotid disease after RT rather than a result of restenosis: almost 60% of our patients had a contralateral stenosis or occlusion of the carotid artery.

Restenosis was apparent in 17%, 33% and 42% of patients at 3 months, 1 and 2 years following CAS. None of these patients became symptomatic. These results are comparable to two cohort studies of CAS after irradiation: both studies show high restenosis rates of respectively 21% and 43% after a mean follow-up of 28 months (n=16 patients) and 14.4 months (n=23 patients).[18,19] This high percentage of restenosis can be a result of overrating.[20] DUS velocity criteria, e.g. PSV, correlate with angiographic percentages of stenosis in non-stented carotids. In CAS patients, DUS velocity criteria are not yet well established. One recent cohort study proposed new criteria for grading percentage of stenosis after CAS by ultrasound after comparison with the gold standard: angiography.[21] In this study it was found that compliance and flow characteristics are much different when compared to non-stented arteries. New thresholds of velocity criteria for different degrees of intrastent stenosis were found much higher. It is conceivable that in our patient cohort, with fibrous and scarred necks, duplex application is even more difficult than in non-irradiated patient. Also, a contralateral occlusion (present in 25% of our patients) is known to overrate the degree of ipsilateral stenosis.[22] We therefore advise to perform (CT- or MR-) angiography to confirm restenosis in case of symptomatic disease. In case of restenosis without symptoms it is warranted to carefully survey these patients by frequent DUS at intervals of 3 months to detect any progression of restenosis.

The study has limitations. First, we performed an observational study. Ideally comparison of CAS versus CEA is warranted to define the best treatment; however, such randomized trial is not feasible for this specific, relatively small cohort of patients. Second, DUS follow-up is not complete. This is due to the fact that our centers serve as tertiary referral hospitals and most patients will be followed by their referral physician.

Despite of this, we consider strong elements of our study being a double-center, cohort study with 100% response rate and complete clinical follow-up.

The final decision how to treat a patient with radiation induced carotid stenosis should be individualized and based on several factors, including e.g. former neck operation and cardiovascular risk factors. Also the time elapsed between RT and the primary cerebrovascular symptoms should be weighted, as in our study a longer time interval since RT proved to be negatively correlated with patency rates. Although we found a high rate of restenosis on DUS only 2 patients (8%) progressed to high grade (90-99%) stenosis. The long-term clinical follow-up results in our cohort are favorable i.e. no new strokes occurred at the ipsilateral stented carotid artery. Close surveillance of patency is necessary also for detection of contralateral stenosis that remains a risk factor for new cerebrovascular events.

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Chapter 5

Prevention of radiation induced carotid artery stenosis

Chapter 5.1

Design of a randomized study: "the effect of a statin on the intima-media thickness induced by radiotherapy"

In preparation:

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Background and introduction

Successful curative treatment for malignancies is increasingly available; additional attention must therefore be paid to prevent complications. One of these complications is radiation induced vascular side effects. These vascular side effects have been reported as early as 1899. Thereafter several studies reported the histopathological findings of radiation induced vascular disease.[1,2] Endothelial swelling and proliferation, in combination with ischemia of the medial and adventitial layer due to damage of the vasa vasorum, leads to obliteration of the irradiated vessel and can cause thromboembolism.[3] The latter plays an important role in the neurological sequelae in patients irradiated for head and neck malignancies.

The radiation induced vessel changes observed in patients and duplicated in animal models are similar to accelerated age-related atherosclerosis although restricted to the radiation portal. The vasculopathy is both time and dose dependent; however, Chung et al. did not find a specific relation between dosage and luminal narrowing at pre- and postradiation MR scans in patients irradiated for head and neck malignancies. In this study the minimum radiation dose inducing vessel narrowing was 40 Gy.[4] The radiation-related vessel changes increase in time and appear to have a significant clinical effect i.e. transient ischemic attack or cerebral infarction in case of radiotherapy (RT) on the neck. In a retrospective study on the relative risk (RR) of stroke in patients younger than 60 years irradiated for head and neck malignancies we found a RR of 5.6 of occurrence of stroke after RT on the neck.[5] The incidence rates of cerebral infarctions in the normal population according to the Oxfordshire community stroke project are shown in table 1.[6]

Recently, Muzaffar et al. demonstrated that duplex ultrasonography of the intima-media thickness (IMT) of the irradiated carotid artery showed progressive thickening of the IMT during the first 12 months after RT. Furthermore, they found this process to be continuing during the second year.[7] In this study they estimated the acceleration of the normal process of atherosclerosis to be 21 fold greater than normal per year.

IMT of the carotid artery is a reliable and independent predictor of cerebrovascular disease.[8,9] In a large prospective, multicenter study, O'Leary et al. demonstrated that the RR of stroke is increased with the IMT ($p<0.001$). Moreover, in this study an increase of one standard deviation (0.20 mm) of IMT causes an increase of the risk of stroke of 27% (adjusted for age, sex and other risk factors).

The use of HMG-coA reductase inhibitors ("statins") or ACE-inhibitors can influence the mode of acceleration of atherosclerotic plaques.[10,11] HMG-coA reductase inhibitors lower the LDL, VLDL-cholesterol and triglycerides concentration. Next to that, they increase the level of HDL-cholesterol. They diminish the acceleration of the atherosclerotic process by reducing the foamed macrophagic cells in the

atherosclerotic plaques. Furthermore, statins have a pleiotropic effect.[12] Their action would be plaque stabilization by direct biological effects on the endothelial function, arterial wall and the biological promoters of plaque stabilization, meaning avoiding rupture or ulceration.[13] The LIPID study group showed a significant declination in the mean arterial wall thickness in a group of cerebrovascular risk patients with normal cholesterol levels treated with pravastatin compared to a placebo in 4 years of follow up.[10] Side effects of statin treatment occur only infrequent and are usually mild.[14,15]
In this study we want to investigate the efficacy of the HMG-coA reductase inhibitor, atorvastatin 20 mg in reducing the progression of radiation induced IMT-thickening. The effect will be studied in an open label multicenter clinical trial. The study group will be treated with atorvastatin 20 mg. The control group will not receive medication. The primary end-point is the difference in IMT before, 0.5 and 2 years after RT on the neck. The IMT of the carotid artery will be measured by duplex ultrasonography. This is a safe and non-invasive technique. The Spearman correlation between readers varies between 0.75 tot 0.86 in the literature which indicates a high interobservers agreement.[8,9] IMT-measuring of the carotid artery is a reliable indicator of atherosclerosis and truly reflects the anatomical intima and media layer.[16] Therefore this technique can be applied to document the process of atherosclerosis in time and measure intervention on atherosclerosis.[17]
Furthermore, we will investigate whether inflammatory markers, which are known to increase during age-related athrosclerosis[18,19], are upregulated during RT and whether they are influenced by treatment with an HMG-coA reductase inhibitor. The pattern of expression of these markers will provide more insight in the process of atherosclerosis after RT.

Table 1. Adapted from Bamford et al.[6] Rates / 1000 population/year

Age	Male	Female	Total (rate)
< 45	7	11	18 (0.1)
45-54	11	6	17 (0.4)
55-64	54	33	87 (2.3)
65-74	93	74	167 (5.9)
75-84	89	100	189 (11.9)
85+	19	48	67 (15.0)
Total	273	272	545 (1.3)

Objectives of the trial

Primary objectives

1. To investigate the effect of an HMG-coA reductase inhibitor, atorvastatin 20 mg, on the progression of IMT of the carotid artery after RT in patients treated for head and neck tumors.
2. To determine the change in IMT of the irradiated carotid artery in comparison with the unirradiated femoral artery and to document the impact of an HMG-coA reductase inhibitor on both arteries.
3. To document any difference in the IMT of the bilateral carotid arteries in patients receiving an HMG-coA reductase inhibitor following unilateral irradiation to the neck.
4. To document any changes in the pattern of inflammatory markers, i.e. c-reactive protein (CRP), intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM-1) during RT and the following 2 years and to see whether this is influenced by an HMG-coA reductase inhibitor; atorvastatin 20 mg.

Secondary objectives

To quantify the occurrence of cerebrovascular events (transient ischemic attack, amaurosis fugax and stroke) in patients irradiated on the neck after treatment with an HMG-coA reductase inhibitor in comparison to those receiving no further treatment.

End-points

1. The primary end-point will be the mean change in IMT between the treated and non-treated group after 2 years of treatment.
2. The second end-point will be the change in IMT between the irradiated carotid artery compared to the unirradiated femoral artery after treatment with an HMG-coA reductase inhibitor
3. The third end-point will be the rate of ischemic cerebral vascular accidents in both groups.

Patient selection criteria

Inclusion criteria

- Patients older than 18 years with T1, T2 laryngeal carcinoma (N0-2, M0) are included. They will all be treated by RT with a curative option.
- Or patients with parotid carcinoma T1, T2 (N0-2, M0) are included if they will receive RT after conservative parotidectomy as post-operative treatment.

- Or patients with pleomorphic adenoma are included when they will be treated with RT in the postoperative course in case of tumor spill or incomplete resection.
- Or patients with oropharynx carcinomas T1, T2 (N0-2, M0) or hypopharynx carcinoma T1, T2 (N0-2, M0) are included. They will receive RT with a curative option.
- Or patients with non-Hodgkin lymphoma or M. Hodgkin are included when they will be treated with RT on the neck.
- Written informed consent.

Exclusion criteria
- Patients with a history of cerebrovascular disease.
- Patients who are pregnant or breast-feeding.
- Patients who are receiving ongoing treatment with an HMG-coA reductase inhibitor.
- Life expectancy < 2 years.
- Patients who are not able to give informed consent because of receptive language difficulties, intellectual decline or psychiatric illness.
- Patients taking inhibitors of cytochroom P450 i.e. ciclosporine, fibrates, macrolidic antibiotics, azol micotica, nicotinic acid and verapamil.
- Patients with active liver disease or high levels of serum transaminases (>3 times the upper limit)
- Patients with 5 times normal level of creatine phosphokinase.
- Patients with hypercholesterolemia i.e. serum cholesterol > 7.0 mmol/l. Patients will be referred to their general practitioner in order to start treatment.

Number of patients
A power analysis (see sample size) revealed that a minimum number of 151 patients is needed for both groups. Per year, at the Netherlands Cancer Institute, approximately 166 patients are irradiated in case of laryngeal carcinoma, parotid tumor, oropharynx and hypopharynx carcinoma. At the Radboud University Nijmegen Medical Center around 150 patients are irradiated for these indications per year. In total an expected number of 316 patients will be eligible for the study. Taking into account a refusal or ineligibility percentage of 50%, annually 158 patients could be included. Therefore an inclusion period of 2 years is determined.

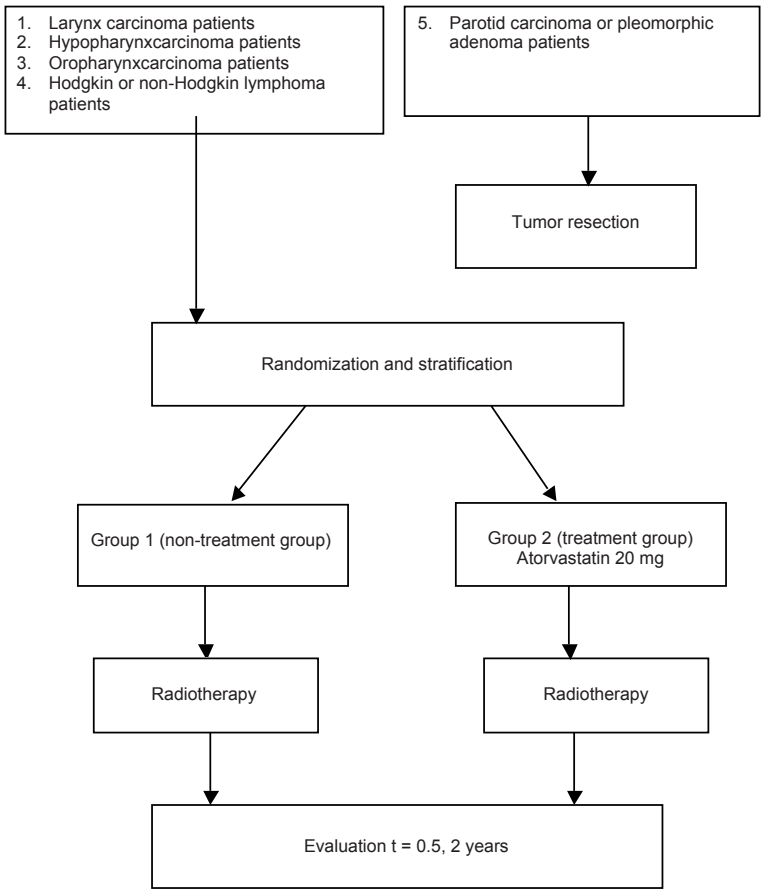
Trial Design

- The trial will be conducted as an open-label, multicenter clinical trial.
- The trial will be conducted in three centers i.e. the Radboud University Nijmegen

Medical Center, Nijmegen and the Netherlands Cancer Institute/ Antoni van Leeuwenhoek Hospital, Amsterdam and the University Medical Center Maastricht, Maastricht.

- Patients will be equally randomized in two groups. The study group will receive oral daily administration of an HMG-coA reductase inhibitor i.e. atorvastatin 20 mg. The control-group does not receive any medication.
- Stratification will be done according to tumor type, age, chemotherapy, and cerebrovascular risk factors i.e. hypertension, smoking, atrial fibrillation and diabetes mellitus.
- Before RT patients are stratified and randomized in equal groups and enrolled to the study.
- Before RT is given baseline measurements will be performed.

Figure 1. Randomization and treatment protocol



Therapeutic regimens, expected toxicity, dose modifications

Study medication
An HMG-coA reductase inhibitor atorvastatin; (3R,5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid, is used as study-medication. The tablet is film coated. HMG-coA reductase inhibitors are prescribed in case of hypercholesterolemia. They reduce the total- and LDL cholesterol level and increase the HDL-cholesterol. They are know to reduce the incidence of cardiovascular morbidity and therefore prescribed as secondary prevention in case of high risk patients.
In case of swallowing difficulties the tablet can be crushed.

Treatment design
Eligible patients will be screened according to the specifications described in paragraph "Patient selection criteria". Patients are equally randomized in each group (treatment versus non-treatment). Two weeks before RT is started the study group will start treatment with atorvastatin 20 mg.

Group 1 (non-treatment group)
These patients will not receive medication. They will be reviewed for follow-up at the same time-schedule (see "during treatment t=5 and t=6") as the treatment-group. Clinical and laboratory studies will be performed during RT (5 weeks after the start of the study, i.e. 3 weeks after the start of RT) and at the same time of ultrasonography measurements i.e. baseline, 0.5 and 2 years after treatment (see "during treatment t=5 and t=6").

Group 2 (treatment group)
The treatment group will receive 20 mg of atorvastatin daily. The patients will start with the study medication two weeks before RT starts. Clinical and laboratory studies will be performed at the same time as the ultrasonography measurements i.e. baseline, 0.5 and 2 years after treatment and during RT (see "during treatment t=5 and t=6").

Toxicity
Side effects are usually mild and temporally. Side effects described in literature which occur frequently (> 1%- < 10 %) are dyspepsia, nausea, abdominal pain, insomnia, and headache. Rare (> 0.1%- < 1%) reported side effects consist of myalgia, myopathy, rash and urticaria. Very rare (< 0.1%) occurring side effects are hepatitis, myositis, rhabdomyolysis, edema of the face, angioedema, vasculitis, and lupes-like reactions.
In few patients (< 2%) liver-transaminases were elevated more than 3 times the upper

limit. Seldom, elevated levels of creatine phosphokinase were reported. Atorvastatin can interact with cytochroom P450 (cyp3A4) inhibitors like claritromycine, delavirdine, diltiazem, verapamil, erytromycin, itraconazol, ketaconazol, nefazodon and protease inhibitors. Patients who are receiving ongoing treatment with digoxine should be frequently evaluated.

Off trial
Patients who will receive cytochroom P450 inhibitors. They will be withdrawn from the study. Patients with recurrent disease who will need further treatment in the head and neck region will be censored from further analysis. Patients who are lost to follow-up or die will also be censored from further analysis.
Patients who suffer from a cerebrovascular event (i.e. a transient ischemic attack, amaurosis fugax or stroke) during the study will be censored from further analysis also and they will be referred to a neurologist for further management.

Clinical evaluation, laboratory tests and follow-up

General
At baseline (i.e. before RT starts), at 0.5 and 2 years after RT patients will be evaluated by duplex ultrasonography. At the same time as duplex ultrasonography is performed and 5 weeks after the start of the study (i.e. 3 weeks after the start of RT) physical examination and laboratory test will be repeated.

Before treatment (time(t)=1)
Patients are enrolled in the study with the diagnosis T1-2, N0-2, M0 laryngeal carcinoma, pleiomorphic adenoma, T1-2, N0-2, M0 parotid carcinoma and T1-2, N0-2, M0 oropharynx and hypopharynx carcinomoma. Patients with laryngeal carcinoma, oropharynx and hypopharynx carcinoma will will receive baseline measurements before RT starts. Patients with a parotid tumor (i.e. pleomorphic adenoma or parotid carcinoma) will receive baseline measurements after performing superficial parotidectomy.

Baseline measurements performed before radiotherapy are:
1. Physical examination
2. Screening for cerebrovascular risk factors
3. Laboratory testing; baseline blood test and inflammatory markers
4. Duplex ultrasonography

1. Physical examination and medical history

- Routine physical examination (including weight, length)
- Performance status
- Systolic and diastolic blood pressure. The blood pressure is measured at the right arm with the patient in sitting position.
- Evaluation of medication

2. Screening cerebrovascular risk factors

- Diabetes Mellitus (see also laboratory test)
- Hypertension (RR> 160/95).
- Smoking;
  - Never smoked,
  - Former smoker (those who stopped smoking before participation in the study for at least 3 years).
  - Current smoker (those who continued smoking) or stopped smoking less than 3 years ago.
- History of cardiovascular disease
- Family history of cardiovascular disease

3. Laboratory test

- Baseline blood test: Hemoglobin, white blood cells, neutrophils, platelets, renal and hepatic function, lipid profile and homocystein after overnight fast (cholesterol, HDL-cholesterol, LDL-cholesterol, triglicerides, lipoproteins), creatine phosphokinase, glucose, thyroid stimulating hormone and thyroxine.
- Inflammatory markers: CRP, intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM-1). The CRP will be measured according to a standard laboratory procedure in both the Netherlands Cancer Institute and the Raboud University Nijmgen Medical Center. The ICAM and VCAM-1 will be measured by L. Dorresteijn at the Laboratory of the department of Neurology at the Radboud University Nijmegen Medical Center. This will be performed by commercial available ELISA-methods.

4. Duplex ultrasonography

- Patients with laryngeal carcinoma and hypopharynx carcinoma:
  Duplex ultrasonography of both carotid arteries is performed with a 7.5 MHz Linear array transducer using a duplex scanner as described by Pignoli et al..[20] In supine position, at a marked point (the isocenter, i.e. a part of the carotid artery which receives > 95% of the irradiated doses, defined in cm distance from the mandibular angle) and 1 cm above and below the isocenter the far wall of the

common or internal carotid artery is assessed. Also the far wall of the femoral artery is assessed by the same technique. Images are freezed on video by the reader who is blinded for clinical information. The IMT is defined as the distance between the intima and media double line pattern and expressed in millimeters. From the videotape, the frozen images are digitized and displayed on the screen of a personal computer using additional dedicated software.[21] Computer software calculates the mean values as well as the maximum values for IMT. This procedure is obtained for both sides.

- Patients with parotid tumors and oropharynx carcinomas:
  The same technique as described above is used i.e. both irradiated as well as not-irradiated carotid artery is measured. The measuring point is the isocenter and 1 cm above and below the isocenter.

Randomization and stratification (t=2)
All eligible patients are equally randomized in two groups. Randomization will be centrally performed according to the Netherlands Cancer Institute procedures (see statistical considerations). Patients who enter the study are stratified by using a minimization technique (see stratification criteria).

Treatment (t=3)
Patients who are randomized in group 2 will receive daily administration of an HMG-coA reductase inhibitor, atorvastatin 20 mg two weeks before starting RT. The treatment will continue during the study period i.e. 2 years.

Radiotherapy (t=4)
- All patients who are enrolled in the study will receive RT according to the standard treatment protocol. Patients with laryngeal carcinoma and hypopharynx carcinoma receive RT with opposed lateral fields. Both carotid arteries are within the RT-portal.
- Patients with pleomorphic adenoma, parotid carcinoma and oropharynx carinoma receive radiotherapy unilaterally with a wedge pair technique as post-operative treatment.
- Before and during RT the radiation status is screened
  - Dose of RT
  - Fractionation
  - Side of RT (bilateral or unilateral)
  - Length of the carotid artery within the RT-portal.
  - Percentage of dose to the carotid artery at the marked points (i.e. isocenter and 1 cm above and below). This is calculated by CT simulation at the time of radiotherapy planning

- During RT (t=4) patients will be screened for baseline blood test, inflammatory markers and performance status at 3 weeks after the start of RT.

During treatment (t=5 and t=6)
Patients will be evaluated at 0.5 and 2 years after start of treatment with an HMG-coA reductase inhibitor by

- Physical examination
- Tumor status
- Laboratory testing
- Ultrasonography

After completion of the study
After completion of the study the results will be evaluated. However, the medical supervision will continue in order to document cerebrovascular events in both groups. Until the results are available patients who are on medication are advised to continue this. Patients will be monitored once a year, and after a follow-up period of 5 years IMT-measurement is repeated.

Summary table

	t=1 Screening Pre-study	t=2 Randomization & Stratification	t=3 Start Treatment	t=4 Radiotherapy	t=5 0.5 year	t=6 2.0 years
Medical history	x					
Performance state	x		x	x	x	x
Tumor status	x				x	x
Medication	x					
Cerebrovascular risk factors	x					
Physical examination	x		x	x	x	x
Baseline blood test	x			x	x	x
Inflammatory markers	x			x	x	x
Ultrasonography	x				x	x

Criteria of evaluation

End-points

Intima-media thickness

- The IMT will be measured at a three marked points for both left and right carotid artery. In patients with laryngeal and hypopharynx carcinoma measurements will be performed at the isocenter, 1 cm above and below the isocenter.
- In patients with parotid tumors and oropharynx carcinomas the IMT will be measured at the isocenter, 1 cm above and below the isocenter and repeated for both sides.
- The primary endpoint is the mean change (of the three measurements) of the IMT. This is calculated by the difference of IMT at a given time point (t=5, t=6) compared to the baseline measurement. The mean change of the IMT is expressed in millimetres. Furthermore the difference between the change in IMT of the carotid artery and the femoral artery is calculated.

Cerebrovascular accidents

- In case of an ischemic cerebrovascular accident patients are evaluated by a independent neurologist. The type of the cerebrovascular accident is assessed as well as the vascular territory and the affected cerebral hemisphere.
- The amount of ischemic cerebrovascular accidents is assessed.

Stratification criteria

Patients are stratified before enrolling into the study. Stratification criteria are type of tumor i.e. laryngeal carcinoma, parotid tumor, oropharynx, hypopharynx carcinoma, Hodgkin and non-Hodgkin lymphoma. Stratification is also performed according to age, chemotherapy and cerebrovascular risk factors, which are known to have an impact on the IMT as smoking versus non-smoking, hypertension versus non-hypertension and diabetes mellitus versus non-diabetes mellitus. Also stratification is performed for patients with atrial fibrillation. Treatment assignment will be made using a minimization technique.

Statistical considerations

Sample size

From previous studies the increase of IMT in four years is estimated to be around 0.05 mm in non-irradiated patients. In irradiated patients this increase is accelerated 15-20 times. We expect to detect a difference of -0.150 mm after 2 years of treatment. A sample size of 151 patients in each group will have a power of 90% to detect a

difference in means of -0.150 (the difference between a group 1 mean, μ_1, of 0,150 and a group 2 mean, μ_2, of 0.000) assuming that the common standard deviation is 0.400 mm[22] using a two group t-test with a 0.05 two-sided significance level.

Randomization and stratifications
Patients will be centrally randomized. A minimization technique will be used for random treatment allocation by the Netherlands Cancer Institute (Dept. of biostatistics, O. Dalesio).

Adverse Event
Adverse event (AE) – definition: Any untoward medical occurrence in a subject participating in this study. An AE does not necessarily have causal relationship with the study drug or RT. For this study all AEs will be reported to the study coordinators. AEs will be collected from the time the subject signs the informed consent. They include any change from the subject's pretreatment (screening) condition as symptoms or physical findings. An abnormal laboratory value may be considered an AE if the identified abnormality leads to any type of intervention, e.g. withdrawal of the study treatment, withholding treatment pending additional investigations.
AE criteria will be graded on a 3-point scale (mild – moderate – severe).
Mild - discomfort noticed, no disruption normal daily activity
Moderate - discomfort sufficient to reduce or affect daily activity
Severe - incapacitating, with inability to work or perform daily activity
Patients who stop the study medication because of intolerance will go off the study.

Serious adverse events

Serious Adverse Events (SAE) are defined as follows according GCP-rules:

- results in death
- life threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect

All SAEs, irrespective of relationship to the study treatment must be reported to the trial office at the NCI/AvL as soon as possible, but no later than one working day. The SAE report should include the investigator's assessment of causality. If follow-up information changes the investigator's assessment of causality, this should be noted on the follow-up SAE form. SAEs occurring within 30 days after discontinuation of the study treatment should be reported.

Ethical considerations

Patient protection
The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong and Somerset West amendments) or the laws and regulations of the country, whichever provides the greatest protection of the patient.
The protocol will by approved by the Local, Regional or National Ethics Committees.

Subject identification
The name of the patient will not be asked nor recorded at the Data Center. A sequential identification number will be automatically attributed to each patient registered in the trial. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, patients initials (maximum of 4 letters), date of birth and local chart number (if available) will also be reported on the case report forms.

Informed consent
All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician. It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered or randomized at the Netherlands Cancer Institute Data Center. This must be done in accordance with the national and local regulatory requirements.

Administrative responsibilities

The study coordinator
The study coordinator (in cooperation with the Data Center) will be responsible for writing the protocol, reviewing all case report forms and documenting his/her review on evaluation forms, discussing the contents of the reports with the Data Manager and the Statistician, and for publishing the study results. He will also generally be responsible for answering all clinical questions concerning eligibility, treatment, and the evaluation of the patients.

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The Netherlands Cancer Institute Data Center
The Data Center will be responsible for reviewing the protocol, collecting case report forms, controlling the quality of the reported data, and generating reports and analyses in cooperation with the study coordinator.

Publication and authorships

All information generated by this study is full property of the investigators as mentioned in the writing committee. Original subject records are audited and reviewed by the study coordinators to verify the accuracy of data and protocol adherence. None of this information may be used for publication or presentation without the written approval of the study coordinator.

Trial Insurance

For this study with a low-risk profile the Netherlands Cancer Institute is insured by Medirisk.

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Chapter 6

Summary and General Discussion

Summary

Cancer affects one-third of the male and a quarter of the female population in the Netherlands. With increasing survival rates due to better treatment, cancer is becoming a chronic disease. In view of this increased survival, it has become exceedingly important to focus on long-term treatment-related complications. Knowledge of late complications may not only be of importance for modifying cancer treatment regimens but also to consider possible preventive strategies for these late complications at the time of cancer diagnosis and treatment. Late complications consist e.g. of second malignancies and cardiovascular disease. Among the latter, stroke is a major cause of long term disability that affects patients' cognitive and functional outcome.[1,2]

Aims of the studies described in this thesis are to assess incidence and risk factors for radiation induced cerebrovascular disease, and to study outcome and prevention of radiation induced carotid disease.

In **chapter 2.1** we present the incidence of ischemic stroke in patients irradiated on the neck for head and neck tumors: laryngeal carcinoma (n=162), pleomorphic adenoma (n=114) and parotid carcinoma (n= 91). Patients were treated with local radiotherapy (RT) on the neck at age below 60 years and followed for a median of 7.7 years (3011 person years). Follow-up information was gathered by medical record review at the Netherlands Cancer Institute (NKI/AVL). If follow-up information was incomplete, we collected data on stroke and cerebrovascular risk factors from the patient's general practitioner.
In our population we found an increased risk of ischemic stroke of 5.6 (95% confidence interval (CI) 3.1-9.4) when compared to the general population, and adjusted for age and sex. Each patient group exhibited an increased risk of ischemic stroke: patient with laryngeal carcinoma had a relative risk (RR) of 5.1 (95% CI 2.2-10.1), patients with pleomorphic adenoma had a RR of 5.7 (95% CI 1.5-14.5) and parotid tumor patients a RR of 8.5 (95% CI 1.0-30.6). Analysis of other risk factors for stroke showed that hypertension and diabetes mellitus caused a further increase of the RR after RT. Stroke risk continued to increase with progression of time: after 10-years of follow up the RR increased to 10.1. The 15-year cumulative risk of stroke was 12%.

In **chapter 2.2** we describe treatment specific risk and stroke of cerebrovascular events (stoke and transient ischemic attack (TIA)) in all 10-year survivors (n=4414) of the Late Effect Breast Cancer Study. The Late Effect Breast Cancer Study is a retrospective cohort study consisting of 7425 1-year survivors of breast cancer, treated from the 1970s through the 1980s in the two major cancer centers in the Netherlands (i.e. NKI/AVL and

DDHK). Overall we found that the risk of stroke was decreased by 25% in comparison with the general female population. Patients irradiated at the supraclavicular area (encompassing the common carotid artery) and/or the internal mammary chain (encompassing the aortic notch) did not experience a higher risk of stroke (hazard ratio (HR) 1.0; 95% CI 0.7-1.6) or TIA (HR 1.4; 95% CI 0.9-2.5) in comparison with patients who did not receive RT or were irradiated on fields other than supraclavicular or internal mammary chain. Significant increased risks of stroke were found in women who had received hormonal treatment (tamoxifen), and in women who had hypertension or hypercholesterolemia, with HR of 1.9, 2.1, and 1.6, respectively. From these data we may conclude that long-term survivors of breast-cancer experience no increased risk of cerebrovascular disease compared with the general population. Hormonal treatment is associated with an increased risk of stroke, while radiation fields including the proximal part of the common carotid artery do not increase the risk of stroke compared to other fields.

In **chapter 2.3** we studied the clinically verified incidence of stroke and TIA in a cohort of 5-year Hodgkin's lymphoma survivors treated at age < 51 years (n=2201). After a median follow-up period of 17.5 years, 96 patients developed cerebrovascular disease: 55 a stroke, 31 a TIA, and 10 patients both a TIA and a stroke. Of the 65 strokes, 57 were ischemic, 7 were hemorrhagic (incl. 2 subarachnoid hemorrhages), and in 1 case the type could not be verified. Most ischemic events were of large-artery atherosclerotic (36%) or cardio-embolic (24%) subtype.
When compared to a sex and age-matched population, we found that Hodgkin's lymphoma survivors have a 2.2-fold (95% CI 1.7-2.8) increased risk of stroke and a 3-fold (95% CI 2.2-4.2) increased risk of TIA. The overall cumulative incidence of TIA and stroke was 7% at 30-years of follow up. There was a significant trend of increasing risk with younger age at first treatment. Irradiation on the neck and mediastinum appeared to be an independent risk factor for the occurrence of ischemic cerebrovascular disease. Furthermore, we found that concurrent cardiac disease increased the subsequent risk of stroke and TIA by 2-fold.

In **chapter 3.1** we address the question whether the increased incidence of stroke in patients irradiated on the neck for head and neck tumor is related to life style habits of smoking and drinking in these particular patients, or to irradiation to the carotid area. In case of unilateral irradiation, the contralateral unirradiated carotid artery can serve as an internal control. 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. We included 42 consecutive patients who were treated with unilateral irradiation for parotid tumors (n= 18 parotid carcinoma, n=24 pleomorphic adenoma). Intima-media thickness (IMT)

was assessed by duplex ultrasonography. The median age at tumor diagnosis and radiation treatment was 47.4 years. The median interval between irradiation and IMT-measurement was 9.8 years (range 3.4 to 27.2 years).
Overall, the irradiated side exhibited a significantly increased IMT of 1.13 mm compared to the unirradiated side (IMT=0.83). The mean difference in IMT was 0.30 mm (95% CI 0.03-0.57, p= 0.031). Stratification for the time interval from irradiation and IMT-measurement showed that patients treated less than 10 years ago did not show a significant IMT-difference, whereas the mean IMT difference was 0.67 mm (p=0.007) if the post-irradiation time interval exceeded 10 years. A linear relation was apparent between the IMT-difference and the duration of the post-irradiation time interval.
We concluded that irradiation on the neck was a significant risk factor for increase in IMT.

In **chapter 4.1** we present the outcome of patients who underwent Carotid Angioplasty and Stenting (CAS) for radiation-induced stenosis of the carotid artery. CAS might be a preferable treatment modality for symptomatic carotid stenosis as it bypasses carotid endarterectomy that is associated with increased operative risks in former irradiated and operated neck patients. We followed a cohort of 24 patients who underwent CAS for symptomatic carotid stenosis after irradiation on the neck (mean time interval between RT and CAS 13 years). After a mean follow-up of 3.3 years (range 0.3-11.0 years), 1 patient developed a TIA (4%) at the ipsilateral CAS-side. In 3 patients (12%) a new cerebrovascular event occurred at the contralateral side (1 TIA and 2 ischemic strokes). Restenosis, assessed by duplex ultrasonography, was apparent in 17%, 32% and 42% at respectively 3 months, 1 and 2 years although none of the patients with restenosed vessels became symptomatic. We concluded that CAS is a safe treatment modality and is effective in the prevention of new cerebrovasular events.

In **chapter 5.1** we describe the design of a currently ongoing multicenter, randomized, controlled trial on the effect of a statin on the progression of the IMT induced by radiotherapy. The radiation-related vessel changes increase in time and appear to have a significant clinical effect i.e. TIA or ischemic stroke in case of irradiation on the neck. It is now beyond question that irradiation causes increase of the IMT. This is already apparent within the first 12 months after irradiation and seems to progress measurably during the second year.
The aim of the study is to investigate the efficacy of the HMG-coA reductase inhibitor, atorvastatin 20 mg, in reducing the progression of radiation induced IMT-thickening.
The study is an open label multicenter clinical trial with a treatment group and control group. The treatment group receives atorvastatin 20 mg, at the start of RT whereas the control group does not receive medication. The primary end point is the mean

change in IMT between the treatment and control groups after 2 years of treatment. The secondary objective is to compare the occurrence of cerebrovascular events (TIA, amaurosis fugax and ischemic stroke) between the two study groups. In addition, in both study groups vascular inflammatory factors are assessed.
Patients, older that 18 years, are included before undergoing irradiation to the neck with curative intention for a larynxgeal carcinoma (T1 and T2), a parotid tumor (pleomorphic adenoma or carcinoma), a oropharynx carcinoma (T1, T2), a hypopharynx carcinoma (T1, T2) or a lymphoma in case of Hodgkin's lymphoma. The IMT of the carotid artery is measured by duplex ultrasonography before irradiation, at 6 months and 2 years after irradiation. A power calculation determined that a minimum number of 151 patients is required per group (total of 302 patients) for the trial to reveal a significant difference of 0.150 millimeters in IMT after 2 years of treatment. The study was approved by the ethics committees of the three Dutch medical institutions (NKI/AVL, UMCN, and UMCM). The number of patients included from March 2003 to October 2008 was 106 patients.

General discussion

Radiation induced stroke

We studied three different cohorts of tumor survivors in order to evaluate the impact of local irradiation on the carotid artery and the occurrence of stroke. The first study, which is described in **chapter 2.1**, showed that head and neck cancer patients (laryngeal carcinoma, parotid carcinoma and pleomorphic adenoma) harbor a strongly increased risk of (ischemic) stroke. This finding is in line with other studies reporting on the incidence and risk of stroke in head and neck cancer patients (table 1).[3,4]

Table 1. Comparison of different studies on the risk of stroke in head and neck cancer patients

	Dorresteijn et al.	Hayes et al.[3]	Smith et al.[4]
Year of publication	2002	2002	2008
No. of patients	367	413	6,862
Relative risk or Hazard ratio	5.6 (95% CI 3.1-9.4)	2.1	4.4
Actuarial incidence	12% (at 15 years)	12% (at 5 years)	19% (at 5 years)
Mean/median age	49	< 80 (not further defined)	76 (+/- 7) Younger patients (<65) excluded
Median age at stroke	63	NR*	NR
Median follow up (years)	7.8	NR	2.4

*NR: not reported

With respect to the relative risk (RR) of stroke, our patient group carries the highest RR. This might be due to the fact that we included a young cohort of head and neck tumor patients (median age at diagnosis 49 years) with corresponding low expected stroke rates (observed 14, expected 2.5; RR 5.6, **chapter 2.1**) The difference in age at RT (i.e. median age 49 years within our cohort vs. < 80 years and 76 years, respectively, in the two other cohorts) is likely responsible for the observed difference in actuarial stroke incidence (12% at 15 years, and respectively 12% and 19% at 5 years, table 1), indicating that stroke risk increases with age.

The same trend for increased risk of stroke was observed within the cohort of Hodgkin's lymphoma survivors **(chapter 2.3)**. Overall, we found an increased risk of stroke of 2.2. This finding is corroborated by the Childhood Cancer Survivor Study (CCSS) that presented self-reported incidence and risk factors for stroke in childhood Hodgkin's survivors (RR 4.32, 95% CI 2.01-9.29).[5] The main explanation why the CCSS

reported higher stroke risk is probably reflected by the difference in data acquisition: the CCSS gathered information by questionnaires to the patients themselves, whereas we collected the stroke information from the treating neurologist. In addition, the age at treatment in the CCSS cohort was younger than in our study population (<21 years vs. <51 years). Also in Hodgkin's lymphoma survivors, radiation to the neck and mediastinum proved an independent risk factor for ischemic stroke.

In both our cohort studies **(chapter 2.1 and chapter 2.3)**, young age at tumor diagnosis was found to be a detrimental factor: head and neck cancer patients treated with RT at age before 50 years harbor a RR of stroke of 9.8 (95% CI 3.2-22.9). Survivors of Hodgkin's lymphoma who were treated at young age (≤ 20 years) have a RR of 3.8 (95% CI 1.6-7.4).

Contradictory results

Contrary to what we expected, in the third study **(chapter 2.2)**, we found an overall decreased risk of stroke in 10-year survivors of breast cancer (RR 0.8; 95% CI 0.6 - 0.9). We had anticipated finding, in line with our other observations, an elevated stroke risk as radiation treatment encompasses the supraclavicular lymph nodes, and thereby also the proximal part of the common carotid artery (chapter 2.2 figure 1). We attributed this lower risk to several factors. First, breast cancer patients may modulate their cerebrovascular risk factors from the time of breast cancer diagnosis: e.g. they may opt for more exercise or a healthier diet and thereby reducing overweight.[6,7] Even if the latter was also the case in our study within head and neck cancer patients **(chapter 2.1)**, with a much shorter follow-up time in this group, risk modulation was not apparent (median follow up time 7.8 years versus 17.7 years within the breast cancer survivors). Second, the risk profile for breast cancer (i.e. late menopause) could be protective against (cerebro-)vascular disease.[8,9] Finally, the supraclavicular radiation field encompasses significantly smaller parts of the carotid artery than irradiation fields for head and neck patients and Hodgkin's lymphoma patients (chapter 2.3 figure 1 vs. chapter 2.2 figure 1).

On the other hand, hormonal treatment in breast cancer patients did increase stroke risk (HR 1.88; 95% CI 1.28 – 2.75). This finding is corroborated by others: Bushnell and Goldstein showed an elevated risk of ischemic stroke (RR 1.82; 95% CI 1.41 - 2.36).[10]

Stroke risk after breast cancer has also been investigated by others who, in contrast to our finding, reported elevated stroke rates. Recently, Jagsi et al. found a non-significantly elevated risk of stroke (RR 1.74; 95% CI 0.94 - 2.37) in patients with early breast cancer after a median follow-up of 6.8 years.[11] And in a large population-based study (median follow-up 5.4 years), Nilsson et al. found that breast cancer patients had an overall RR of stroke of 1.12 (95% CI 1.07 - 1.17) compared with the general population,[12] but

increased risk was especially found during the first year after diagnosis (RR 1.22; 95% CI 1.06 - 1.39). Possibly, the increase rate during the first year was caused by tumor-related coagulation disorders.[13,14] As we studied only those patients who survived more than 10 years, acute or early occurring strokes (i.e. those strokes that occur within the first time interval after cancer diagnosis and during treatment) were beyond the scope of our study.

Mechanisms underlying late occurring radiation induced stroke

The pathogenesis of radiation induced stroke has been studied during the last two decades. From animal models we have learned that already in the acute phase endothelial damage appears after irradiation on large arteries.[15] Endothelial cell activation and damage probably leads to a cascade of inflammatory reactions[16,17] that can result in the proliferation of the endothelial (i.e. intima) layer, fibrosis of the media layer, and obliteration of the vasa vasorum in the adventitia layer.[18] There is also evidence that radiation induces prothrombotic effects which increase platelet adherence and thrombus formation in irradiated capillaries and arteries.[19,20] The combination of these changes will eventually lead to plaque formation and narrowing of the arterial lumen. We hypothesize **(chapter 5.1)** that the first hit, i.e. the endothelial damage, may be prevented or at least be diminished by statin treatment. The presumed action of statins in normal age-related atherosclerosis is plaque stabilization by direct biological effects on the endothelial function and a slowing-down of the acceleration of the atherosclerotic process by reducing the foamed macrophagic cells in the atherosclerotic plaques.[21,22]

Intima and media thickness (IMT), the inner arterial wall, can be reliably studied by duplex ultrasonography.[23-25] We and others have shown that unilateral irradiation causes significant increase of the IMT compared to the non-irradiated side **(chapter 3.1)**.[26] The incidence of significant carotid stenosis on the irradiated side of the neck is also higher than on the contralateral side. The risk of IMT enhancement and carotid artery stenosis increases both with a longer time interval after RT.[26,27] We hypothesize that the increased risk of stroke is associated with the enhanced IMT and the consequent carotid artery stenosis. In general, carotid artery stenosis is one of the main causes of stroke.[28]

Another possible mechanism of stroke after irradiation is by cardio-embolism. To our best knowledge, we were the first to report on stroke risk in relation to cardiac disease after mantle field irradiation: in patients with RT-induced cardiac disease, the subsequent risk of stroke and TIA was increased by 2-fold during follow up **(chapter 2.3)**. Hodgkin's lymphoma survivors have an increased risk of radiotherapy-related

cardiovascular disease like myocardial infarction and valvular dysfunction.[29-31] It is possible that the increased risk of cardiac disease and the subsequent risk of cardio-embolisms also explains why in our population stroke rates are increased whereas IMT-increase of the carotid artery and stenosis rates after mantle field irradiation are not as prominent as those observed within head and neck patients. Martin and others showed that 14 lymphoma patients irradiated on one side of the neck with relatively low dose (30-35 Gy/10 fractions) did not exhibit a significant increase of IMT (compared to the non-irradiated side),[26] whereas 26 head and neck cancer patients, treated with high dose irradiation (50-60 Gy/ 20-25 fractions) showed a significant increase of IMT compared to the non-irradiated side.[26]

Limitations of the presented studies on radiation induced stroke

Strong elements of the three presented studies on stroke risk are the long-term and the relatively complete follow-up. However, a potential weakness of our studies concerns under-reporting of stroke diagnoses by chart- and retrospective review. Another matter, which actually concerns all studies on late effects, is that results of retrospective studies evaluating late adverse effect of treatment regimens from the past, do not per se hold true for current clinical practice with newer radiation techniques (e.g. involved field for Hodgkin's lymphoma) and other radiation schedules. Finally, from our studies it was not possible to resolve whether the combination of irradiation and chemotherapy augments the risk of stroke.

Clinical implications

On the basis of our studies it is clear that subgroups of cancer survivors are at risk for late treatment-related effects. Especially those patients in whom longer lengths of the carotid artery were irradiated (head and neck patients and Hodgkin lymphoma survivors) carry an increased risk of stroke. This is even more pronounced when patients are treated with RT at a young age and in the presence of other cerebrovascular risk factors (i.e. hypertension, diabetes mellitus) **(chapter 2.1 and 2.3)**.

Instead of advocating a change in current treatment regimens, we merely would like to make physicians aware of these already long-time under-estimated complications. In addition, the fact that other risk factors for cerebrovascular disease augment the risk for stroke implies that physicians should screen intensively for these risks and advise on cerebrovascular risk factor modulation by e.g. more exercise, stop smoking and/or healthier diet. The latter may have played an important role in the observed decreased risk of stroke among our breast cancer survivors **(chapter 2.2)**.

When survivors of cancer, who have been treated with mantle or neck irradiation, display symptomatic carotid disease (TIA and stroke), we advise to screen the carotid arteries for stenosis and to explore the heart for sources of cardio-embolisms. When a

symptomatic carotid stenosis of more than 50% is detected, our advice is to evaluate surgical risks. When patients have a low risk profile (e.g. no cardiac disease, no neck operation), a carotid endarterectomy can safely be performed.[32] In case of high surgical risk (e.g. former neck operation, fibrosis of the neck after radiotherapy, a long delay between irradiation and symptomatic disease), we would suggest carotid angioplasty and stenting (CAS). This technique may prevent new cerebrovascular events from occurring **(chapter 4.1)**. During follow up, regular screening (e.g. every 6 months) of the stented or operated carotid artery and contralateral carotid artery is necessary. This as, firstly, after irradiation there is an increased risk of restenosis with the presently applied duplex criteria, and secondly, the contralateral carotid artery may also become symptomatic **(chapter 4.1)**. However, physicians should be cautious when the duplex outcome is "restenosis" since the present duplex criteria are yet not validated for stented carotids. One should therefore always confirm the duplex using other imaging techniques like CT-angio, MR-angio or conventional angiography. A recent study comparing present duplex criteria, with confirmation by conventional angiography showed that duplex velocities are much higher in stented arteries than in non-stented ones.[33] New follow-up studies with validated duplex criteria should become available within the coming years. For stented carotid arteries after irradiation, the follow up results on restenosis should then be reassessed.

Recommendations for further research

"Ignoti nulla cupido" is definitely true for late treatment related effects: in other words these complications have longtime been neglected due to unawareness. Further insight and attention for late complications has increased during the last two decades.

Especially childhood survivors have been studied intensively in large cohorts studies during the last years. The results have led to a broad insight in complications and quality of life for these survivors.[34-36] We would strongly support such a systematic screening for adult long-term survivors in order to gain more insight and knowledge on late complications and quality of life. Patients should ideally be screened and, if possible, treated by professionals within the field of late complications e.g. a radiation oncologist and other organ specific specialists, like cardiologists and neurologists, in case of specific complications.

Further research on preventive measurements is warranted. With the launch of the open-label trial on statin treatment in the reduction of IMT-progression **(chapter 5.1)**, we are the first to clinically explore the possibilities of reducing late occurring vascular complications after irradiation. If statins are effective in IMT-reduction for neck irradiation, this preventive treatment could be offered to other groups of cancer patients with expected long term survival and who received irradiation to large arteries

and to the heart. Since randomized clinical trials often require to include large numbers of patients, it is important to be able to explore new preventive treatments in animal models. At the present, animal models are available for studying radiation induced arterial- and cardiovascular disease. Studies in hypercholesterolemic rabbits and mice have found that irradiating large arteries accelerates the formation of atherosclerotic plaque.[37-39] New research initiatives could focus on other treatment options that have shown to diminish atherosclerosis by improving endothelial function such as ACE-inhibitors, new anti-inflammatory drugs or endothelial progenitor cells. [40,41]

Finally, in the future more insight in the DNA-profile will help us to study and define subgroups of patients who are at possible risk for specific late effects. We know that patients vary considerably in their responses to radiation and it is the tolerance of the more sensitive subjects that limits the dose that can be given to the patient population as a whole. This may limit the chance of tumor cure in some cases. At least some of this variation is genetically determined, which therefore stimulates research into identifying those patients who are more susceptible for radiation damage.[42,43]

I hope that this thesis will challenge us all in recognizing and preventing late-treatment related effects, improving cancer treatment and thereby ameliorate the long-term well being of cancer patients!

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Chapter 7

Samenvatting Bestralingsvasculopathie en cerebrale ischemie

Kanker treft één derde van alle mannen en één kwart van alle vrouwen in de Nederlandse populatie. Met de steeds verbeterende behandelingsmogelijkheden is de prognose van kankerpatiënten de afgelopen decennia aanzienlijk verbeterd; kanker kan hiermee in sommige gevallen een chronische ziekte worden. Door de verbeterende overleving is er meer aandacht gekomen voor late therapiegerelateerde complicaties. Late therapiegerelateerde complicaties betreffen o.a. het optreden van tweede tumoren, fertiliteitstoornissen maar ook (cardio-) vasculaire complicaties. Een belangrijke late cardiovasculaire complicatie is het herseninfarct.
Deze late therapiegerelateerde complicaties hebben vaak een belangrijke impact op het dagelijks functioneren en de kwaliteit van leven van patiënten nadat zij curatief behandeld zijn voor hun primaire maligniteit. Kennis over de late therapiegerelateerde complicaties is dan ook van essentieel belang in het kader van eventuele behandelingsmodificaties maar ook om uit te zoeken of deze complicaties voorkomen kunnen worden door preventieve maatregelen. Ten slotte is het van belang patiënten vóór aanvang van de behandeling een goede voorlichting te geven over de eventuele late therapiegerelateerde complicaties.

De belangrijkste vragen die in dit proefschrift worden onderzocht zijn: (I) welke risicofactoren bestaan er voor bestralingsgeïndiceerde vasculopathiëen en het hieraan gerelateerde herseninfarct en wat is de incidentie hiervan, (II) hoe kan bestralingsgeïnduceerde carotisstenose behandeld worden en (III) bestaat er een preventieve behandeling om bestralingsgeïnduceerde vasculopathiëen te voorkomen?

In **hoofdstuk 2.1** wordt een klinische studie beschreven over de incidentie van herseninfarcten bij patiënten die bestraald zijn op het halsgebied vanwege een larynxcarcinoom (n=162), een pleiomorfadenoom (n=114) of een parotiscarcinoom (n=91). De patiënten werden bestraald vóór de leeftijd van 60 jaar en werden gemiddeld 7,7 jaar gevolgd (3011 persoonsjaren). Gegevens over het optreden van een herseninfarct werden verzameld door statusonderzoek of door het opvragen van informatie bij de huisarts. In deze patiëntengroep werd een bijna zes keer verhoogd risico op een herseninfarct gevonden (Relative Risk (RR) 5.6; 95% confidence interval (CI) 3.1-9.4) ten opzichte van een voor leeftijd- en geslacht gecorrigeerde groep uit de algemene populatie. Voor elke afzonderlijke patiëntengroep bleek een verhoogd risico op het ontwikkelen van een herseninfarct te bestaan: patiënten met een larynxcarcinoom hadden een relatief risico (RR) van 5.1 (95% CI 2.2-10.1), bij patiënten met een pleiomorfadenoom werd een RR van 5.7 (95% CI 1.5-14.5) gevonden en bij parotiscarcinoom patiënten vonden we een RR van 8.5 (95% CI 1.0-30.6). De aanwezigheid van de bijkomende risicofactoren diabetes mellitus en hypertensie

resulteerden in een verdere toename van het risico op een herseninfarct. Gedurende de jaren na de bestraling nam het risico op een herseninfarct cumulatief toe: na 15 jaar was dit gestegen tot 12%.

In **hoofdstuk 2.2** beschrijven we het behandelingspecifieke risico op cerebrovasculaire aandoeningen (CVA; herseninfarct, hersenbloeding en transient ischaemic attack (TIA)) in 4414 patiënten uit de "Late Effects Breast Cancer Study" die langer dan 10 jaar overleefden. Over het geheel genomen was het risico op een CVA in de studiepopulatie 25% lager dan in de algemene bevolking. Voor patiënten bestraald op het supraclaviculaire en/of het parasternale gebied was het risico op een CVA niet verhoogd (Hazard Ratio (HR) 1.0; 95% CI 0.7-1.6) ten opzichte van patiënten die niet met radiotherapie werden behandeld of die werden bestraald op velden gelegen buiten de supraclaviculaire of parasternale regio. Een toegenomen risico op een CVA werd gevonden bij vrouwen die met hormonale therapie (tamoxifen) waren behandeld, en bij vrouwen met hypertensie of hypercholesterolemie. De gevonden HR in deze groepen bedroeg respectievelijk 1.9, 2.2 en 1.6.
Uit deze resultaten blijkt dat lange termijn overlevenden van een mammacarcinoom geen verhoogd risico hebben op een CVA in vergelijking met de algemene bevolking. Hormonale behandeling is wel geassocieerd met een verhoogd risico op een CVA. Bestralingsvelden waarin de arteria carotis is gelegen tonen geen verhoogd risico op een CVA ten opzichte van andere bestralingsvelden.

In **hoofdstuk 2.3** wordt het risico op een CVA in een groep van 2201 overlevenden van een Hodgkin lymfoom beschreven. Deze patiënten werden behandeld voor het Hodgkin lymfoom vóór hun 51e levensjaar en werden gevolgd vanaf 5 jaar na de behandeling. Na een mediane follow-up van 17,5 jaar hadden 96 patiënten een CVA of TIA doorgemaakt: 55 patiënten maakten een CVA door, 31 patiënten een TIA en 10 patiënten zowel een TIA als een CVA. Van de 65 patiënten die een CVA doormaakten betrof het in 57 gevallen een herseninfarct en in 7 gevallen een hersenbloeding (1 incident ongedefinieerd). Bij de meeste herseninfarcten (36%) was de oorzaak gelegen in de grote vaten (large-atherosclerotic subtype) en in 24% bleek er sprake van een cardiale emboliebron.
Hodgkin lymfoom patiënten bleken een ruim twee keer zo hoog risico te hebben op het ontwikkelen van een herseninfarct (HR 2.2; 95% CI 1.7-2.8) en een drie keer verhoogd risico op een TIA (HR 3.1; 95% CI 2.2-4.2) ten opzichte van de algemene bevolking. In de jaren na de behandeling neemt het cumulatieve risico op een herseninfarct en/of TIA verder toe (7% na 30 jaar follow-up). Bij behandeling van patiënten op jonge leeftijd (< 21 jaar) bleek het risico op een herseninfarct en/of TIA extra verhoogd. Bestraling op de hals en het mediastinum (de zogenaamde mantelveld bestraling) was een

onafhankelijke risicofactor voor het ontwikkelen van een herseninfarct en/of TIA. Ten slotte, bleek dat patiënten die een cardiale aandoening (hartfalen, ritmestoornissen, myocardinfarct, kleplijden) ontwikkelden, hierna een twee keer zo hoog risico op het optreden van een herseninfarct en/of TIA hadden.
Samenvattend blijken Hodgkin lymfoom patiënten een verhoogd risico te hebben op een herseninfarct en een TIA; dit verhoogde risico is met name aanwezig bij patiënten die een mantelveldbestraling ondergaan (waarbij het hart en de carotiden in het bestralingsveld gelegen zijn), en wanneer behandeling plaatsvindt op jonge leeftijd (< 21 jaar).

In **hoofdstuk 3.1** is onderzocht of het verhoogde risico op een herseninfarct te wijten is aan de levensstijl van patiënten met een maligniteit in het hoofd/hals-gebied (verhoogd rookgedrag en alcoholconsumptie) of dat dit gerelateerd is aan bestraling op het halsgebied. Patiënten die unilateraal werden bestraald voor een hoofd-hals tumor ondergingen een duplex meting van de arteria carotis communis (ACC) of van de arteria carotis interna (ACI), afhankelijk van het bestralingsveld. Door de bestraalde arteria carotis te vergelijken met de niet bestraalde, contralaterale arteria carotis werd een interne controle bewerkstelligd en werd voor andere risicofactoren gecorrigeerd. Van 42 opeenvolgende patiënten werd de binnenste vaatwand dikte (intima-media; IMT) door middel van duplex onderzoek bestudeerd. De mediane leeftijd ten tijde van de diagnose en behandeling was 47,4 jaar. Patiënten werden na een mediane follow-up van 9,8 jaar geanalyseerd. Aan de bestraalde zijde werd een significante toename van de IMT waargenomen ten opzichte van de niet-bestraalde zijde (1,13 mm versus 0,83 mm, gemiddelde verschil 0,30 mm, 95% CI 0.03-0,57). Het verschil in IMT bleek veder toe te nemen bij een follow-up duur van meer dan 10 jaar en er bleek een lineaire relatie te bestaan tussen de follow-up duur en de toename van de IMT. Uit deze studie blijkt duidelijk dat bestraling een toename van vaatwanddikte geeft.

In **hoofdstuk 4.1** wordt bij 24 patiënten de behandeling middels carotis angioplastiek en stentplaatsing voor een symptomatische carotis stenose na bestraling bestudeerd. Carotis stenting kan mogelijk een goed behandelalternatief zijn voor bestraalde patiënten, aangezien het halsgebied van bestraalde patiënten vaak ernstig beschadigd is door eerdere operaties (radicale halsdissectie, tracheostomie) en door de bestraling zelf (huidfibrose, veranderde anatomie). Deze patiënten hebben theoretisch een verhoogd operatierisico als zij een carotisdesobstructie, de standaard behandeling, ondergaan. Gemiddeld ontwikkelden de patiënten 13 jaar na de halsbestraling neurologische symptomen en ondergingen daarvoor een endovasculaire behandeling middels stentplaatsing in de aangedane arteria carotis. Na een mediane follow-up van 3,3 jaar ontwikkelde 1 patiënt (4%) een TIA aan de ipsilaterale zijde en trad

er bij 3 patiënten (12%) een TIA of herseninfarct aan de contralaterale zijde van de stent op. Na 3 maanden, 1 en 2 jaar had respectievelijk 17%, 24% en 42% een re-stenose ontwikkeld (gedefinieerd als een stenose van ≥ 50%). Overigens ontwikkelde geen van de patiënten met een re-stenose een nieuwe TIA of herseninfarct. We concluderen uit deze studie dat endovasculaire behandeling middels stenting voor een bestralingsgeïnduceerde carotisstenose veilig lijkt met een laag risico op het ontwikkelen van nieuwe symptomen aan de stent-zijde.

In **hoofdstuk 5.1** wordt het design van een gerandomiseerde, gecontroleerde, multicenter studie gepresenteerd. In deze studie wordt de hypothese getoetst of atorvastatine (een cholesterolverlagend medicijn) de progressie van IMT na bestraling kan tegengaan. De studie heeft een open label opzet waarbij de patiënten in de therapiegroep met dagelijks 20 mg atorvastatine worden behandeld. Patiënten, ouder dan 18 jaar, die bestraald gaan worden op het halsgebied vanwege een larynxcarcinoom, een parotistumor, een hypopharynxcarcinoom of een oropharynxcarcinoom worden geïncludeerd, gerandomiseerd en gedurende 2 jaar gevolgd. Vóór de bestraling, en 6 en 24 maanden na de bestraling wordt de IMT gemeten. De primaire uitkomstmaat is het verschil in IMT tussen de behandelde en de niet behandelde groep. Secundaire uitkomstmaten zijn het optreden van TIA's en herseninfarcten gedurende de follow-up. Tevens worden inflammatoire markers, die mogelijk verhoogd zijn, tijdens bestraling en een verklaring kunnen geven voor het onderliggende pathogenetische mechanisme, bepaald. Een power-berekening toonde aan dat beide groepen minimaal uit 151 patiënten moeten bestaan om een significant verschil van 0,150 mm in IMT na 2 jaar behandeling te kunnen vaststellen. De studie is goedgekeurd in 3 centra: het Nederlands Kanker Instituut/Antoni van Leeuwenhoekhuis, het Universitair Medisch Centrum St Radboud en het Universitair Medisch Centrum Maastricht.

Hoofdstuk 6 bevat een Engelse samenvatting en een algemene discussie over de resultaten van de onderzoeken beschreven in dit proefschrift en plaatst deze in een breder perspectief.

Samenvattend tonen de studies in dit proefschrift het volgende: (I) patiënten die bestraald worden op het halsgebied vanwege een hoofdhals tumor en een Hodgkin lymfoom hebben een verhoogd risico op een herseninfarct (II) bestraling lijdt tot een toegenomen vaatwanddikte en is een onafhankelijke risicofactor voor bestralingsgeïnduceerd vaatlijden (III) carotis stenting lijkt een goede behandeling voor patiënten met een symptomatische carotisstenose na bestraling (IV) ten slotte zal de toekomst moeten uitwijzen of bestralingsvasculopathieën voorkomen kunnen worden met een cholesterolverlagend geneesmiddel, zoals atorvastatine.

Chapter 8

Dankwoord

Dankwoord

De resultaten beschreven in dit proefschrift zijn de opbrengst van een vruchtbare multidisciplinaire samenwerking. Op deze bladzijden wil ik van harte alle mensen bedanken die mij geholpen hebben bij de totstandkoming van dit proefschrift. In het bijzonder wil ik de patiënten bedanken die hebben deelgenomen aan de verschillende studies.

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