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Longitudinal atherosclerotic changes after radio(chemo)therapy of hypopharyngeal carcinoma

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Abstract

Background: Radiotherapy treatment of head and neck cancer affects local arteries and increases the risk of stroke. This study aimed at a closer characterization of this damage and its development in time with a longitudinal study set up.

Methods: Male patients treated between 2011 and 2016 for hypopharyngeal carcinoma were identified from the in-house clinical data base. They were included into the study if besides the planning CT at least one additional CT image was available from follow-up (13 patients) or at least two MRI scans (16 patients of which 2 were already included). All patients received radiotherapy, and chemotherapy was administered to 16 patients. The time from the beginning of radiotherapy to the last available image ranged from 2 months to 4.5 years.
For six segments of the carotid arteries, the number and volume of atherosclerotic plaques were determined from the CT scans, and the intima media thickness from the MRI scans. Information on comorbid cardiovascular disease, hypertension and diabetes mellitus was retrieved from medical records.

Results: Total plaque volume rose from 0.25 cm^3 before to 0.33 cm^3 after therapy but this was not significant ($p = 0.26$). The mean number of plaques increased from 5.7 to 8.1 ($p = 0.002$), and the intima media thickened from 1.17 mm to 1.35 mm ($p = 0.002$). However, the mean intima media thickness practically did not change in patients with comorbid diabetes mellitus (p-value for homogeneity: 0.03). For patients without diabetes mellitus, dynamics of both plaque number and intima media thickness, was consistent with an increase until about one year after therapy and no further progression thereafter.

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Conclusion: Our study confirmed the thickening of artery walls and the increase in the number of plaques. Results imply that definitive radiation damage to the artery walls can be determined not earlier than about one year after radiotherapy and there is no substantial deterioration thereafter. Reasons for the absence of an observable intima media thickening in patients with diabetes are unclear.

Keywords: Hypopharyngeal carcinoma, Radiotherapy, Atherosclerosis, Intima media thickness, Plaque, Diabetes mellitus

Introduction

Radiotherapy (RT) of the head and neck can lead to vasculopathy of medium- and large-diameter arteries and double the risk for ischemic strokes and transient ischemic attacks [1]. With progress in survival for head and neck cancer patients, side effects of the RT treatment become more important. Moreover, radiation vasculopathy might be relevant for all cancer patients with favorable prognosis, and was therefore investigated recently also in breast cancer patients [2].

Radiation vasculopathy can manifest itself in an increase in plaques, thickening of the intima media, and stenosis. These impairments have been primarily observed in ultrasound examinations [3–5] but can also be seen in CT [6–8], and MRI follow-ups [9, 10].

Carotid stenosis is an established side-effect after local cancer radiotherapy [11]. Only few studies, however, have monitored the atherosclerotic development longitudinally from the onset of RT and including several time points [8, 12]. Therefore, the exact dynamics of the arterial deterioration remains unknown. The aim of the present retrospective study was to investigate the time-dependent development of plaques and intima media thickness in patients treated with RT or a combined treatment with RT and chemotherapy for hypopharyngeal cancer.

Materials and methods

Patients

Male patients treated with RT for primary hypopharyngeal carcinoma between 2011 and 2016 were identified from the in-house clinical data base. In total, 28 patients were included, who besides a planning CT either had at least one additional CT from the follow-up (13 patients) or at least two MRIs (16 patients). For two patients, both criteria were fulfilled. In total, 30 CTs and 38 MRIs were used for data analysis. Treatment plans and comorbid conditions were collected from the medical records.

Imaging analysis

Data from CT and MRI performed during routine follow-ups were analyzed.

Data acquisition was performed on a 3 T MRI scanner (Magnetom Verio, Siemens Healthcare, Erlangen, Germany) with a 32-channel head coil array. T1- weighted 3D magnetization rapid- acquisition gradient echo (MP-RAGE) MRI scans in an axial orientation were included in the data set. MRI data was inspected for image quality.

Vessel thickness in the T1 (repetition time: 687; echo time: 12) was measured using a PACS workstation (Picture Archiving and Communication System, AGFA Healthcare Corp., Greenville, SC, USA) at 3 levels: In the internal carotid artery (ICA) at the most caudal image level also showing the cerebellum, 5 mm cranial to the carotid bifurcation and in the common carotid artery (CCA) at the level of the third cervical vertebrae.

For CT imaging, a kilovoltage CT scan (Somatom Emotion 16, Siemens, Erlangen, Germany or Brilliance 64, Philips Healthcare) was performed with an axial slice thickness of 1–3 mm (Iopromid, Bayer Healthcare, Leverkusen, Germany). Plaques were counted as descriped by Walker et al. [13]. Briefly, the attenuation values were measured by use of a circular or elliptical region of interest. All foci with Hounsfield units (HU) deviating more than > 50 compared to the surrounding tissure were considered and counted as plaque.

Statistical analysis

To investigate significant changes in the measured parameters before and after RT, Wilcoxon signed-rank tests were performed. If two images after RT were available, an average value was calculated. Potential differences between different subgroups were analyzed by Wilcoxon rank-sum tests. The course of changes was fitted by a constant, a categorical, and a continuous model linear in the time after radiotherapy. Goodness of fit was assessed by the sum of squared residuals χ^2, using the constant model as null hypothesis. P-values < 0.05 were assumed as statistically significant. All analyses were performed with MATLAB R2018b.

Results

Patient and treatment characteristics are summarized in Table 1. Mean duration from the beginning of RT to the last available CT was 414 days (range: 91 to 938 days), and to the last available MRI 544 days (range: 63 to 1667 days).

Table 1 Characteristics of patients and treatments

Treatment age [years]	Median: 60, range: 44–78
Radiotherapy intent	18 definitive
	6 adjuvant
	1 palliative
	1 additive
Prescribed dose	3 times 54/55 Gy
	7 times 64 Gy
	17 times 70 Gy
Chemotherapy	16 (13 Cisplatin, 1 Carboplatin, 1 Cis- and Carboplatin, 1 Carboplatin and Paclitaxel)
History of cardiovascular disease	6 (3 coronary artery disease, 3 peripheral artery occlusive disease, 1 atrial fibrillation, 1 aortic stenosis, 1 stroke)
History of hypertension	10
History of diabetes	5

In the planning CTs, preexisting plaques were observed for 77% of patients. In 23% of the patients plaques were observed in the ICA at the level of the cerebellum to the middle of the third cervical vertebra, in 77% in the ICA and CCA from the middle of the third cervical vertebra to the middle of the sixth, and in 15% in the CCA at the cervical vertebral level 6 to the pulmonary apex. The average number of plaques was 0.8 for the ICA at the level of the cerebellum, 4.5 for the bifurcation, and 0.3 for the CCA at the cervical vertebral level 6. The average sizes per plaque for the different sites were 27 mm^3, 48 mm^3, and 32 mm^3. Intima media thickness was determined from MRIs. In the 10 patients with MRI scans prior to RT, the mean intima media thickness before RT was 0.97 mm (interquartile range 0.85–1.1) in the ICA at the level of the cerebellum, 1.25 mm (IQR 1.1–1.35) at the bifurcation, and 1.28 mm (IQR 1.0–1.35) in the CCA at the cervical vertebral level 6.

On average, the number of plaques increased from 5.7 (IQR 1–10.5) before RT to 8.1 (IQR 2–13; p-value for difference 0.002). The increase of the average total plaque volume from 249 mm^3 (IQR 7–597) to 326 mm^3 (IQR 8–540) was, however, not significant ($p = 0.26$). The intima media thickness increased from 1.17 mm (IQR 0.97–1.28) to 1.35 mm (IQR 1.16–1.52; $p = 0.002$). Results before RT and the observed changes are listed in Table 2 for all patients included as well as several patient subgroups

No significant difference in the increase of plaque numbers was seen between subgroups but a trend for a higher absolute increase with a pre-existing condition (cardiovascular disease, hypertension, diabetes mellitus, or an above-average number of plaques) was observed. The change in intima media thickness (IMT) was significantly lower for patients with hypertension (10 patients) or diabetes mellitus. Here it has to be noted, that all 5 patients with diabetes mellitus also suffered from hypertension. When excluding patients with diabetes mellitus from the analysis, the increase in IMT for patients with vs. without hypertension was no longer significantly different ($p = 0.38$). Therefore, patients with diabetes mellitus were excluded for further analysis.

The time course of the increase in the number of plaques and the thickening of the intima media were fitted by a categorical model and the results are shown in Fig. 1. For the number of plaques, the categorical model showed a superior goodness of fit but the improvement was not significantly better than the constant model based on a likelihood ratio test ($p = 0.13$). On the other hand, for intima media thickness the categorical model fitted significantly better ($p = 0.02$), implying that thickening takes some time after radiotherapy. To investigate whether a continuous increase would better describe the data, we fitted also a model linear in the time after radiotherapy. However, goodness of fit was markedly worse for both, number of plaques and intima media thickening.

Discussion

The deleterious effect of radio(chemo)therapy on the carotid arteries is well known [11, 14–16]. Progressive carotid stenosis was observed over several years after radiotherapy [5, 10, 17], with the same observation being made for the general plaque burden [18, 19]. With regards to IMT, long-term progression was seen in some but not all studies [19–22]. Most of these results, however, are based on cross-sectional studies. Few longitudinal studies include measurements before RT and those have a maximal follow-up of 2 years [8, 12]. While a continuous progression was observed in one study [12], no change could be observed in another one [8]. The present analysis with a maximal follow-up of 4.5 years supports an initial increase in intima media thickness, though no major development could be observed after about one year (Fig. 1 (b)).

Whether RT causes the formation of new plaques or accelerates existing atherosclerosis is important for developing a risk assessment for different patients and potentially employing countermeasures. The present study confirmed the formation of new plaques, which has already been observed immediately after RT [23]. Our results do not show any further increase in the number of plaques about one year after RT (Fig. 1 (a)).

In patients with diabetes mellitus, RT induced thickening of intima media was observed to be less pronounced than in other patients. However, this might have been caused by issues with the retrospective study set-up, and in particular with the small study size. Another weakness

Table 2 Increase in plaque number, plaque volume and intima media thickness for all patients included and for different subgroups. Tests for heterogeneity were applied to examine whether increase during follow-up was identical for two alternative subgroups

		Plaque number			Plaque volume [mm^3]			Intima media thickness (IMT) [mm]		
		Before RT	Increase during follow-up	Test for significance	Before RT	Increase during follow-up	Test for significance	Before RT	Increase during follow-up	Test for significance
All patients		5.7	2.4	**p = 0.002**	249	77	p = 0.26	1.17	0.19	**p = 0.002**
Prescribed dose < 70 Gy	yes	6.8	2.3	*p* = 0.06	308	−16	*p* > 0.5	1.23	0.16	*p* = 0.5
	no	4.7	2.4	p = 0.06	198	157	p = 0.13	1.15	0.20	***p* = 0.008**
Test for heterogeneity			p > 0.5			*p* = 0.46			p > 0.5	
Chemotherapy	yes	2.7	1.5	*p* = 0.25	108	81	p = 0.13	1.18	0.20	**p = 0.02**
	no	8.3	3.1	**p = 0.02**	370	73	p > 0.5	1.14	0.16	p = 0.25
Test for heterogeneity			*p* = 0.21			*p* = 0.41			p > 0.5	
Cardiovascular disease	yes	13.7	5.0	p = 0.25	709	194	p > 0.5	1.27	0.14	p = 0.5
	no	3.3	1.6	**p = 0.02**	111	47	*p* = 0.19	1.14	0.20	**p = 0.008**
Test for heterogeneity			*p* = 0.20			p > 0.5			p > 0.5	
Hypertension	yes	8.3	3.2	p = 0.25	466	−9	p > 0.5	1.26	0.10	p = 0.06
	no	4.9	2.2	**p = 0.02**	184	103	p = 0.19	1.07	0.27	p = 0.06
Test for heterogeneity			*p* = 0.27			p > 0.5			***p* = 0.03**	
Diabetes mellitus	yes	8.0	4.3	p = 0.5	392	−49	p > 0.5	1.31	0.06	p = 0.25
	no	5.3	2.0	**p = 0.008**	223	100	p = 0.13	1.11	0.24	**p = 0.02**
Test for heterogeneity			*p* = 0.10			p > 0.5			**p = 0.03**	
> 5 plaques before RT	yes	12.6	3.9	p = 0.06	633	116	p > 0.5			
	no	1.4	1.4	p = 0.06	9	52	p = 0.13			
Test for heterogeneity			*p* = 0.14			p > 0.5				
IMT > 1.2 mm before RT	yes							1.28	0.18	**p = 0.03**
	no							0.99	0.21	p = 0.13
Test for heterogeneity									p > 0.5	

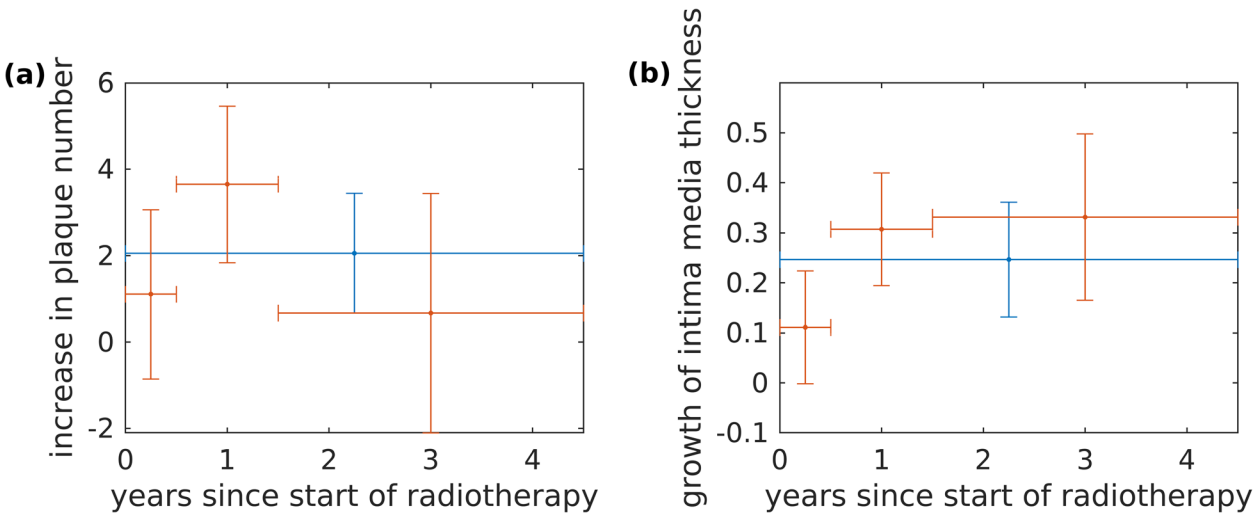

Fig. 1 **a** Average (blue) and time-dependent (red) increase of the number of plaques (**a**) and intima media thickness (**b**). Bars represent 90% confidence intervals

of the study design is that imaging was performed for tumor follow-up. As a result, only a fraction of patients with hypopharyngeal carcinoma could be included. Due to the limited resolution of the CT scans, small plaques might have been overlooked and respective volume measurements remain difficult. Although these limitations decrease the statistical power of the results, they are unlikely to yield a bias: scans were performed in a standardized way and image analysis was conducted blindly for patient and treatment characteristics. While being conceptually interesting, the number of plaques is problematic for long-term studies as not only new plaques may form, but established plaques may merge. This might have contributed to the apparent decrease in the number of plaques after 1.5 years in Fig. 1 (a), which, however, was not statistically significant, anyway. Finally, it should be noted that a normal progression of atherosclerosis could safely be neglected in this study as typical thickening of the intima media amounts to about 0.01 mm per year [24].

Conclusion

Radiotherapy of hypopharyngeal carcinoma leads to a persistent thickening of the intima media and formation of new plaques in the carotids. One year after radiotherapy these processes were largely completed, although longer term follow up is warranted. Larger study groups, however, are necessary to confirm this result.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13014-020-01541-3.

Additional file 1. Data analysed.

Abbreviations

CCA: Common carotid artery; CT: Computed tomography; ICA: Internal carotid artery; IQR: Interquartile range; MRI: Magnetic resonance imaging; RT: Radiotherapy

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Authors' contributions

MM, CS, CK, SEC have made substantial contributions to the conception, and MM, CS, TA, KB, SP to the design of the work. TA, MM, KB have made substantial contributions to the acquisition, CS, PK to the analysis, and CS, MM, TA, KB, SP, SEC to the interpretation of data. CS, MM and SEC have drafted the work or substantially revised it. All authors of the manuscript have read and agreed to its content and are accountable for all aspects of the accuracy and integrity of the manuscript.

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Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Ethics approval and consent to participate

The ethics committee of Klinikum rechts der Isar, TU München has approved this study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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