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Radioiodine Therapy Does Not Change the Atherosclerotic Burden of the Carotid Arteries

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Background and aim: Atherosclerosis evolves or accelerates when arteries are exposed to ionizing radiation, both early and late after exposure. Radioiodine therapy of benign thyroid disease exposes the carotid arteries to 4–50 Gy, and may thereby increase the risk of atherosclerosis. Increased risk of cerebrovascular events has been reported after radioiodine therapy. This study aimed to examine whether atherosclerosis develops early or late after radioiodine therapy of benign thyroid disease.

Method: Patients treated for benign thyroid disorders (nontoxic goiter, adenoma, and hyperthyroidism) were examined with ultrasound for the main outcome, carotid intima media thickness (CIMT), and for plaque presence (plaque presence only in late damage). Signs of early damage from radioiodine were studied in 39 radioiodine-treated patients, who were examined before treatment and at 1, 3, 6, and 12 months after treatment. Late changes were studied in a cross-sectional case-control design, with radioiodine-treated patients as cases ($n = 193$) and patients treated with surgery as controls ($n = 95$). Data were analyzed with repeated measurement for longitudinal data, and with multivariate regression for cross-sectional data. Results were adjusted for age, sex, cholesterol, smoking status, known atherosclerotic disease, and body mass index.

Results: No changes in CIMT were found in the patients followed prospectively for one year after treatment with radioactive iodine for benign thyroid disease ($p = 0.58$). In the study on late effects, there was no difference in CIMT ($p = 0.25$) or presence of plaques ($p = 0.70$) between those treated with radioactive iodine and those treated with surgery (9.8 and 5.6 years since treatment, respectively). Furthermore, the level of thyrotropin (TSH) did not influence these atherosclerosis markers.

Conclusion: No early changes in CIMT were detected in patients treated with radioactive iodine for benign thyroid disease. No signs of late effects of radioactive iodine on CIMT or plaque presence were found after 10 years of follow-up. The radiation to the carotid arteries by radioactive iodine therapy for benign thyroid disease may therefore have no or low effect on atherosclerotic burden of the carotid arteries in general.

Introduction

Atherosclerosis is known to evolve and accelerate after ionizing radiation of arteries in a dose–response pattern, although the dose–effect correlation is complex (1). Increased risk of cardio- and cerebrovascular events after local radiotherapy of cancer has been described even within the first 0–4 years after exposure (2). Ionizing radiation has also been reported to increase carotid intima media thickness (CIMT) after low-dose exposure among catheterization laboratory workers (3). Therefore, all treatments that include radiation of arteries carry the potential to induce atherosclerosis.

Radioiodine therapy (RAI) with ^{131}I is frequently used for treating hyperthyroidism (overt as well as subclinical), symptomatic goiter, and after thyroidectomy in patients with

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thyroid cancer. During RAI of benign thyroid disease, the carotid arteries are exposed to a total committed absorbed dose of 4–50 Gy per GBq orally administered (4). This dose is of such a magnitude that RAI might potentially induce or accelerate development of pre-existing atherosclerosis. This possibility is supported by the observation that there seems to be an increased risk of cerebrovascular events after RAI in hyperthyroid (5–8) as well as euthyroid patients (8). Nevertheless, the pathophysiology behind this increase is debated, particularly whether the increased risk of cerebrovascular events is related to the thyroid disease or the RAI treatment.

Progression of atherosclerosis after RAI can be examined by measuring CIMT and the presence of plaques with ultrasound of the carotid arteries. These are used as valid surrogates for developing and existing atherosclerosis, respectively, and are both linked to increased risk of cardio- and cerebrovascular endpoints (9–11). Several studies have shown an increase in CIMT, plaque, and stroke in head and neck cancer patients treated with radiation therapy (12). Furthermore, a recent study showed increased CIMT three months after RAI treatment, indicating that these changes might be induced early on by radiation from RAI (13). However, this study included only hyperthyroid patients, and looked solely at the early effects of radiation (one year follow-up). There are no data on acute changes in CIMT after RAI in euthyroid patients or on long-term changes in CIMT after RAI.

To address these knowledge gaps, this study aimed to examine both early and late effects of radiation from RAI treatment on atherosclerosis in a population of thyroid patients that consisted of both hyperthyroid and euthyroid (goiter) subjects.

Methods

Study design and participants

Early radiation effects. To examine the early effects of radiation, a longitudinal design was used. A cohort of 40 patients referred for RAI therapy at Herlev University Hospital from May 2012 to May 2013 was followed. Patients were treated with a fixed dose of 200, 400, or 600 MBq ^{131}I on the basis of the type of disease and size of the thyroid (14). Patients were examined five times: on the day of RAI therapy and again after 1, 3, 6, and 12 months.

Late radiation effects. To examine late effects of radiation, a cross-sectional case-control design was used. Cases were defined as patients treated with RAI, while the control group comprised patients treated with thyroidectomy (either hemi- or total thyroidectomy), both for benign thyroid disorders. Surgically treated patients were chosen as a control group, as they to some extent have the same kind of disease as those treated with RAI, but receive a different treatment. Patients were recruited from two different databases with information on former patients (for RAI HEH.afdO 750.86-7 and for surgically treated 2000-41-0010). The selected patients were invited by letter to participate in the study. When no response was received, a second letter was sent.

Inclusion and exclusion criteria. The inclusion criteria were age between 18 and 85 years and treated for benign thyroid disease. The exclusion criteria were pregnancy at time of RAI (contraindication), suspicion of or confirmed thyroid cancer, prior radiotherapy of any kind other than RAI, for example for breast cancer or thyroid-associated orbitopathy. Participants in the study on early effects who had had RAI or surgery before or during follow-up were excluded. In the study on late effects, surgery in the RAI group or RAI in the surgery group resulted in exclusion.

The study was approved by the Regional Scientific Ethical Committee (H-4-2012-007 and H-1-2012-120), and all participants signed a written consent form.

Examination

Blood samples were drawn for the measurement of thyrotropin (TSH), thyroxine (T4), total cholesterol, LDL, HDL, and triglycerides. All analyses were carried out in the authors' in-house department of biochemistry in the routine setting. Serum T4 and TSH concentrations were measured using Immulite 2000 (Siemens) RIA kits, and cholesterol and derivatives on Vitros (LDL with spectrophotometry, others with calorimetry).

Data on self-reported diabetes, prior vascular disease (i.e., stroke, myocardial infarction, transient ischemic attack, or amaurosis fugax), smoking status (never smoked or smoker, including former smokers), other medical history, and prescribed medication were collected by interview and verified from the patient's chart when possible. Body mass index (BMI), office blood pressure, and heart rate were measured. Information on indication for treatment (i.e., multinodular nontoxic goiter or hyperthyroidism), treatment modality, and date of treatment were retrieved from either the patient's chart or the database.

Ultrasound examination

All patients were scanned lying in a supine position by the same operator on a Phillips iU22 equipped with a L9-3 linear array transducer. Far wall CIMT and presence of plaques was assessed bilaterally by B-mode imaging (15). CIMT was measured in the common carotid artery in a plaque-free zone where the thyroid and carotid arteries had the closest anatomical relationship, and thus where the impact of the radiation from RAI was deemed to be largest (4). A clip of a complete heartbeat cycle was recorded and stored for offline determination of far wall CIMT. The clips were transferred to a semi-automatic edge detecting offline program (AMS) (16,17). The operator (J.L.C.) then annotated the region of interest, and the CIMT was determined automatically by the program, but with the possibility for manual adjustments. A mean CIMT per scan for each patient on each side was stored. Reproducibility was verified in 14 randomly selected patients scanned twice on each side (28 arteries in total), and the variation coefficient was estimated to be 7.4%. The presence of plaque (yes/no) on either of the two sides in the common and internal carotid arteries was defined as a focal thickening into the lumen on gray-scale imaging (15,18,19).

Statistics

All baseline data are presented as percentages for categorical data and for continuous as means ± standard deviation (*SD*) where data followed a normal distribution, or medians and interquartile range (IQR) where they did not.

Early radiation effects were analyzed with mixed models using multivariate repeated measurements statistics allowed by the longitudinal design. This permitted individual changes in CIMT to be used, rather than group means. REML estimation was used, which is recommended for small sample sizes (20). A backwards selection of variables was made. In the first analysis, the mentioned recorded variables were entered. Then variables with a p-value of <0.2 were selected for further analysis, including tests for interaction between all variables. Sex, age, and smoking status were retained in the model at all times. Furthermore, interaction between all variables was tested for in both overall and between-visit measures in the repeated-measurements analysis. The model for early changes ended up as: age, sex, side (left or right), total cholesterol, smoking status (never vs. former, or active), and BMI (>25 or <25). In this model, the individual and the individual's side were connected, as the individual CIMT differed from left to right.

The cross-sectional data baseline characteristics were tested for difference between the groups (RAI or surgery) with a t-test for continuous variables that followed a normal distribution and a non-parametric Mann–Whitney U-test for data that did not. For categorical variables, Pearson's chi-square test was used. When analyzing CIMT in the cross-sectional data on late effects of RAI, multivariate regression was used to test for differences between the two groups. Logistic multivariate regression was used when presence of plaques (binary outcome) was examined. The approach was the same as with the prospective data. First, all variables were entered. Next, a backwards selection for inclusion with variables with a p-value of >0.2 were left in the model. However, age, smoking status, and sex were retained at all times. The final model comprised age at participation in the current study, sex, TSH, smoking status (never vs. former, or active), BMI, office systolic blood pressure, known diabetes, known hypothyroidism, and total cholesterol for CIMT, and the same for plaque, except LDL instead of total cholesterol, and an interaction term between BMI and sex.

Sub-analyses tested whether the following variables affected CIMT, both early and late, and plaque in late effects: thyroid status at time of treatment (hyperthyroid [TSH <0.01 IU/mL and elevated T4] and subclinical hyperthyroid [TSH <0.01 and normal T4] vs. euthyroid], type of disease (adenoma, goiter, diffuse), and for early effects whether there were changes due to TSH and T4 at the different visits.

Power calculation

With a two-sided alpha of 5% and a beta of 80% and a normal range of CIMT covering 0.2 mm, it would be possible to detect a 0.1 mm increase in CIMT in this longitudinal study with the inclusion of 34 patients.

Results

Early radiation effects

Forty patients were included. Of these, 39 completed follow-up; one had surgery after nine months due to persistent goiter symptoms. The characteristics of the included patients are shown in Table 1.

There were no significant changes in CIMT after RAI over time. Mean CIMT at visit 1 was 0.73 mm [confidence interval (CI) 0.51–1.04], and at visit 5, it was 0.73 mm ([CI 0.51–1.05]; $p = 0.58$ for changes between visits; Fig. 1). Only two variables influenced the individual's baseline CIMT values: side measured (left thicker than right, $p < 0.001$) and age (increased CIMT with age, $p < 0.001$). None of the other characteristics in the model influenced changes in or baseline CIMT values (data not shown). Furthermore, the sensitivity analysis on influence on changes in CIMT of thyroid status at treatment, changes in thyroid status during follow-up, or the type of scintigraphic/ultrasound disease (diffuse, adenoma, or multinodular goiter,) showed that this did not influence the outcome ($p = 0.73$, $p = 0.41$, and $p = 0.87$, respectively). None of the patients experienced a cerebrovascular event during follow-up.

Table 1. Baseline Characteristics of the 39 Subjects Included in the Study of Early Radiation Effects

	Total n = *39*
$M_{age} \pm SD$, years	55.7 ± 12.2
Sex (female), *n* (%)	36 (92%)
Hyper- or subclinical hyperthyroidism as indication, *n* (%)	25 (64%)
BMI >25 kg/m^2, *n* (%)	16 (41%)
Smoking status (active or former), *n* (%)	6 (15%)
Total cholesterol, mmol/L, $M \pm SD$	5.4 ± 1.6
Systolic blood pressure, mmHg, $M \pm SD$	136 ± 19
Type of thyroid disease	
Adenoma	9 (23%)
Diffuse	8 (21%)
Multinodular	22 (56%)
Oral dose of ^{131}I, ordered for the individual	
200 MBq	8 (21%)
400 MBq	23 (59%)
600 MBq	8 (21%)

SD, standard deviation; BMI, body mass index.

Late radiation effects

Of 728 patients contacted by letter, 431 responded (59%), and 288 were eligible (40% of those invited). Reasons for exclusion were: 67 did not wish to participate, 20 had had other radiation therapies, 40 in the RAI group underwent surgery before RAI, four in the surgery group were treated with RAI before surgery, and 13 were excluded for other reasons (e.g., failure to show up). In total, 193 RAI-treated and 95 surgically treated patients were included. The characteristics are shown in Table 2.

The t-test of difference in mean CIMT and the presence of plaques between the two groups was significant ($p < 0.05$). However, in the multivariate analyses, the difference was no longer significant ($p = 0.25$ for CIMT; $p = 0.70$ for plaque presence). Further, the multivariate analyses showed that CIMT depended on age ($p < 0.001$), smoking status ($p = 0.02$), and whether patients were known to be hypothyroid (and on levothyroxine) at the time of examination ($p = 0.01$). The presence of plaque depended on age ($p < 0.001$), smoking status ($p < 0.001$), LDL ($p = 0.003$), systolic blood pressure ($p = 0.008$), known diabetes ($p < 0.001$), sex ($p = 0.001$), and BMI ($p = 0.02$), and an interaction between sex and BMI

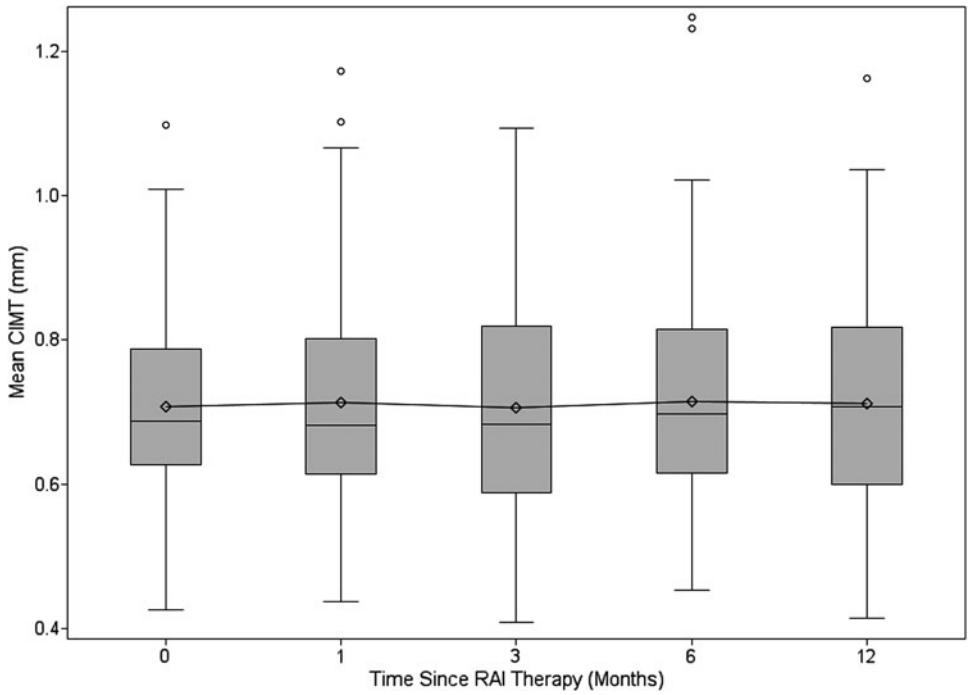

FIG. 1. Changes in mean carotid intima media thickness from visit to visit.

($p = 0.004$). Neither time since treatment nor TSH had any influence on CIMT or plaque status (data not shown).

Discussion

RAI therapy is frequently used for benign thyroid diseases, with a rough estimate of about 140,000 treatments a year in the European Union (21). It is known that ionizing radiation has vascular side effects (21), and this could be an unrecognized side effect of RAI. Early and late atherosclerosis development was studied in patients treated with RAI from 0 to a median of 10 years earlier, and no evidence was found of any influence of ionizing radiation from RAI on CIMT or plaque status in either hyperthyroid or euthyroid patients after RAI therapy.

A priori, such an effect had been anticipated, since it has previously been shown that the carotid arteries are exposed to about 4–55 Gy per GBq ^{131}I orally administrated during RAI (4), and patients treated with RAI have an increased risk of

Table 2. Characteristics of the 288 Subjects Included in the Cross-Sectional Study on Late Radiation Effects

Treatment modality	*Surgery,* n = *95*	*Radioactive iodine,* n = *193*
$M_{age} \pm SD$ at participation, years	56.2 ± 12.1	62.5 ± 9.4**
Sex (female), *n* (%)	79 (83%)	160 (83%)
Years since treatment, median (IQR)	5.6 (4.3– 7.7)	9.8 (7.3–13.2)**
BMI, kg/m^2, $M \pm SD$	28 ± 5	28 ± 5
Thyroid status at treatment (hyperthyroid), *n* (%)	45 (47%)	31 (16%)**
Smoking status (active or former), *n* (%)	52 (55%)	99 (51%)
Total cholesterol, mmol/L, $M \pm SD$	4.9 ± 1.1	5.2 ± 1.1*
LDL, mmol/L, $M \pm SD$	3.0 ± 1.0	3.2 ± 1
HDL, mmol/L, $M \pm SD$	1.3 ± 0.5	1.4 ± 0.4
Triglyceride, mmol/L, median (IQR)	1.1 (0.8–1.6)	1.1 (0.9–1.8)
Current TSH, IU/mL, median (IQR)	1.4 (0.3–3.8)	2.6 (1.3–4.3)**
Hypothyroid, *n* (%)	84 (88%)	81 (42%)**
Diabetes, *n* (%)	8 (8%)	16 (8%)
Hba1c, mmol/mol, $M \pm SD$	38 ± 7	37 ± 7
Prior ischemic vascular event, *n* (%)	9 (10%)	18 (9%)
Hypertension, *n* (%)	29 (30%)	79 (41%)
Accumulated MBq ^{131}I dose, median (IQR)		592 (400–600)
Total thyroidectomy, *n* (%)	80 (84%)	
Mean CIMT, mm ($2 \times SD$)	0.67 (0.46–0.98)	0.73 (0.50–1.07)**
Plaque present (yes), *n* (%)	37 (39%)	103 (53%)*

*$p < 0.05$; **$p < 0.001$, using a *t*-test for continuous variables following normal distribution, Mann–Whitney *U*-test for continuous data that did not, and Pearson's chi-square test for categorical variables.

IQR, interquartile range; TSH, thyrotropin; CIMT, carotid intima media thickness.

cerebrovascular events (8). Therefore, a theoretical risk of atherosclerosis induction exists, as this radiation dose far exceeds the 2 Gy shown to induce an inflammatory response in mice (22,23).

Thyroid status at time of treatment did not influence CIMT. This is in line with a similar excess risk of cerebrovascular events after RAI among hyperthyroid and euthyroid patients (8), but in contrast to what others have found in population-based studies of healthy subjects (24). Further, findings from other studies were reproduced, namely that CIMT and presence of plaque depended on age (25,26), smoking status (27), whether patients were rendered hypothyroid by treatment (28), and whether CIMT differed from left to right (left > right) (3).

The main results of no change in CIMT are in contrast to those of Surucu *et al.* (13), who followed 38 hyperthyroid RAI-treated patients for one year and found an increased CIMT (approximately 0.05 mm) after just three months. This difference may be explained by several factors. The current study used a semi-automatic determination of CIMT in one video clip covering a whole cardiac cycle, whereas Surucu *et al.* (13) used a static image and manually positioned electronic calipers, thus introducing a risk of bias (29). Additionally, this study scanned most of the patients in an area of laminar flow in the carotid artery, while Surucu *et al.* (13) measured CIMT near the carotid bulb, an area more prone to atherosclerotic changes due to high flow and turbulence (30,31).

Even though a relationship between CIMT and atherosclerotic events is documented in many studies (15), it is not as strong as the presence of plaques. Further, CIMT and plaque are only surrogate markers for atherosclerotic events, and there are several possible pitfalls when measuring CIMT (11). In addition, changes in CIMT over time at the level of the individual have yet to be properly validated (32). Therefore, one has to be cautious when making claims that changes in CIMT lead to hard outcomes (33).

There is a discrepancy between the negative findings in the current study and the increased risk of stroke after RAI that has been demonstrated in epidemiological studies. One possibility is of course that the increased risk of stroke is due to hyperthyroidism rather than radiation-induced atherosclerosis after RAI, as proposed by others (5–7,34). However, a recent epidemiological study shows that the risk is similar among both hyperthyroid and euthyroid patients (8). This would not be anticipated if hyperthyroidism was the only factor responsible. Depending on the timing of the atherosclerotic process, radiation might yield different results—exposure early in the disease process may even be protective (35). Furthermore, radiation of pre-existing plaques might render the plaque more prone to rupture, explaining why increased risk is already seen within the first few years (22,35). It might be that patients with pre-existing mild to severe atherosclerosis are the only ones at risk of later radiation-induced cerebrovascular events, as they perhaps are more radiosensitive. However, this study was not set up to investigate this hypothesis, and perhaps a larger study in which patients are screened for plaques before and after RAI should be conducted.

Strengths and limitations of the study

The limitations of the study are mostly related to the method and measurement of CIMT by ultrasound, as discussed briefly in the Discussion section. However, one of the strengths of CIMT is that it is non-invasive and can be measured relatively quickly, allowing a greater number of patients in the trial.

Accurate dosimetry might have increased the strength of the study by allowing the calculation of a dose–response relationship. However, in the study by Surucu *et al.* (13), there was no correlation between iodine uptake at 4 and 24 hours and changes in CIMT (13). Furthermore, individual radiosensitivity of the arteries as well as the thyroid may exist but cannot yet be predicted. Therefore, a dose–response may exist in the individual, but remains difficult to demonstrate at a group level.

This study has a possible lack of power. The power calculation was made on the assumption that the normal distribution of CIMT had a spread of 0.2 mm, and the spread in this study was approximately 0.5 mm. This means that this study is underpowered for the detection of a 0.1 mm change, and therefore a 0.05 mm change may be overlooked, as shown by Surucu *et al.* (13). In the study of late effects, an attempt was made to create two groups so they were alike in terms of age, equal time since treatment, and similar thyroid disease in order to lower the risk of bias from these confounders. However, due to bias by indication, the surgically treated patients were younger and more often hyperthyroid at the time of surgery.

The strengths of the study are that a single ultrasound operator was used and the same high-end ultrasound machine was used, thus minimizing the risk of scanner bias. Furthermore, the risk of reading bias was minimized by using a semi-automatic program for CIMT determination, achieving an acceptable coefficient of variation of 7.4%. Finally, this is the first study on late radiation effects of RAI on CIMT and plaques.

Conclusion

No acute or long-term changes in CIMT or plaques after RAI therapy were detected, even though it is established that atherosclerosis can be induced when arteries are exposed to ionizing radiation. The study thus indicates that the atherosclerotic effects of radiation from RAI on the carotid arteries are low or non-existing.

The possibility that a longer follow up, with a more precise method, done on a larger cohort may reveal a difference cannot be excluded, since many types of radiation-induced damaged evolve >10 years after exposure and are minimal in the individual but significant on a group level.

The present findings offer no explanation as to why epidemiological data indicate an increased risk of cerebrovascular events after RAI therapy. Further studies may thus be needed to clarify whether radiation-induced atherosclerosis is part of the mechanism.

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Author Disclosure Statement

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