

Risk of Subclinical Hypothyroidism in Breast Cancer Patients Treated With CT-Guided Radiation Therapy: A Prospective Observational Study

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Purpose: The thyroid gland is an organ at risk in breast cancer survivors who receive radiation therapy to the supraclavicular lymph nodes. We investigated the effect of radiation dose to the thyroid gland on the incidence of hypothyroidism in early-stage breast cancer patients treated with CT-guided radiation therapy.

Patients and Methods: We recruited women aged ≤ 75 years diagnosed with breast cancer from March 2016 through August 2017 at Odense University Hospital, Denmark. Thyroid function was measured in blood samples drawn at baseline, 6, 12, and 18 months. We delineated the thyroid gland using CT scans to estimate thyroid volume and radiation dose to the thyroid. Subclinical hypothyroidism was defined as a thyroid-stimulating hormone (TSH) level of >4 milli-international units per liter (mIU/l) in the presence of normal free thyroxine. We also conducted a subanalysis with a threshold resulting in approximately 20% events within the cohort. We used mixed logistic regression to estimate associations between radiation dose to the thyroid and subclinical hypothyroidism.

Results: Among 102 patients, four developed subclinical hypothyroidism. There was no association between increasing radiation dose to the thyroid and incidence of subclinical hypothyroidism. However, a trend was observed suggesting that higher mean radiation dose to the thyroid was associated with elevated risk of subclinical hypothyroidism at a TSH threshold of >2.5 mIU/l.

Conclusion: Using current reference levels, increasing radiation dose to the thyroid was not associated with subclinical hypothyroidism, but at lower TSH thresholds, radiation therapy may predispose to hypothyroidism.

Keywords: breast neoplasms, radiotherapy, hypothyroidism, thyroid gland

Introduction

Increasing survival after breast cancer highlights a need to focus on the adverse effects of cancer treatment, such as hypothyroidism. Hypothyroidism is associated with substantial morbidity, but there is no convincing evidence that it increases mortality if treated properly.^{1,2} Hypothyroidism has a prevalence of about 3% in European populations, is more frequent in women, and the risk increases with age.³ Subclinical hypothyroidism, characterized biochemically by elevated serum thyroid-stimulating hormone (TSH) above the upper limit of the reference range of 0.40–4.0 milli-international units per liter (mIU/l) in the presence of normal free thyroxine (fT4), affects up to 20% of women over 60 years of age.^{4–6}

Hypothyroidism is a well-known side effect of radiation therapy to the head and neck, as the thyroid gland is located close to or within the radiation field.^{7–10} Radiation-induced hypothyroidism develops gradually within the first year after treatment and follows a dose-dependent pattern.⁸ Our previous research in a historical registry-based cohort in Denmark

showed an increased risk of hypothyroidism in breast cancer survivors compared with women from the general population without breast cancer. The risk was particularly elevated in breast cancer survivors receiving radiation therapy to the lymph nodes, especially among those who also received chemotherapy.¹¹ The elevated risk persisted for up to 12 years after primary diagnosis. Yet, we were unable to evaluate the risk of subclinical hypothyroidism as thyroid function tests are not routinely assessed before and after radiation therapy in breast cancer patients in Denmark. Furthermore, we were unable to evaluate the radiation dose to the thyroid gland since the thyroid has not typically been considered an organ at risk and thus not delineated during treatment planning.¹² In addition, we had no information on thyroid volume, which may affect the risk of radiation-induced hypothyroidism.^{13,14}

We therefore investigated the potential dose-dependent effect of radiation therapy on the incidence of hypothyroidism in a contemporary cohort of early-stage breast cancer patients in Denmark treated with Computed Tomography (CT)-guided radiation therapy. We incorporated information on radiation dose, thyroid volume, and thyroid function tests during follow-up.

Materials and Methods

Study Population

This prospective study included women ≤ 75 years of age diagnosed with early-stage operable breast cancer without distant metastases who presented for treatment at the Oncology Department, Odense University Hospital, between March 1st 2016 and August 31st 2017. We aimed to recruit (i) 50 patients with lymph node-negative disease who received adjuvant chemotherapy and breast irradiation without prescribed lymph node irradiation; and (ii) 100 patients with lymph node-positive disease, who were assigned to breast and lymph node irradiation, with or without chemotherapy and endocrine therapy. Patients with a history of thyroid disease, benign or malignant breast disease or cancer who received radiation therapy at any anatomic site above the waist were not eligible for inclusion. Informed consent was obtained from all individual participants included in the study.

Radiation Therapy and Thyroid Dose

All patients received CT-based field-in-field conformal radiotherapy according to the DBCG guidelines. Target volumes were delineated according to the DBCG guidelines.^{15,16} The lymph nodes near the thyroid gland were treated using an anterior field typically angled 15° towards the healthy side. We retrospectively delineated the thyroid gland on the planning CT scans (ie, those used to guide radiation therapy) of all included patients and used these to measure thyroid volume and dose.

Covariates

Based on prior knowledge and to reduce the risk of confounding, we included the following covariates from patient medical records—adjuvant chemotherapy (yes or no), body mass index (BMI) at breast cancer diagnosis in kg/m² derived from height and weight measurements, patient age (years), Charlson Comorbidity Index score (0 or ≥ 1), tumour size (mm), number of lymph nodes removed, intended adjuvant endocrine therapy (yes or no), type of endocrine therapy (Tamoxifen or Letrozole), malignancy grade (grade I, II, or III), type of primary surgery (lumpectomy or mastectomy), HER-2 status (positive or negative), Ki67 (mean), and estrogen receptor (ER) status (%). We also included baseline TSH levels to account for any intra-personal variation in thyroid function.

Blood Samples and Subclinical Hypothyroidism

Upon agreeing to participate, all patients gave a baseline blood sample before adjuvant therapy. All blood samples were collected before 9 a.m. as thyroid hormones fluctuate during the day.^{17–19} Follow-up blood samples were collected after completion of radiation therapy and chemotherapy at the routine 6, 12, and 18-month follow-up exams. Follow-up ended at the 18-month visit and the last blood sample was drawn in November 2019. Blood samples during radiation therapy were omitted. Blood samples were centrifuged at 2000G for 10 minutes at room temperature, then fractionated into serum aliquots of *ca.* 0.5mL and stored at -80°C on the day of collection. A technician thawed the blood samples and

used accredited (ISO15189) methods to measure thyroid function (TSH, fT4, and baseline anti-TPO, which is an early indicator of developing autoimmune thyroid disease).

Our primary endpoint was subclinical hypothyroidism defined as TSH exceeding 4mIU/l which is the typical upper reference level for normal TSH.^{9,20–23} As a secondary endpoint, we used a TSH threshold value defined by a 20% event occurrence in the study population.

Statistical Analyses

We tabulated descriptive characteristics of the study cohort outlining continuous variables as means and standard deviations (SD) and categorical variables as numbers and percentages. Odds ratios (OR) and 95% confidence intervals (95% CI) are presented for all statistical analyses showing the association between mean radiation dose to the thyroid and subclinical hypothyroidism.

Our primary analysis focused on subclinical hypothyroidism following breast cancer treatment. We used mixed logistic regression models as used in a study by Rønjom et al,⁹ which included an estimate of the time profile of the appearance of the endpoint. We performed variable selection based on the best-subset selection using a 5-fold cross-validation, including mean dose to the thyroid, thyroid volume, chemotherapy, smoking, BMI, baseline TSH level, patient age at baseline, and a multiplicative interaction term between radiation dose and thyroid volume. We selected the multivariable model with the fewest parameters where the log-likelihood was within one standard error of the log-likelihood of the best-performing model—as recommended by James et al.²⁴ We used this “one-standard-error” rule to obtain as simple a model as possible with almost the same prediction power as “the best performing” model. The analysis software was validated on demo data with known predictors and time-dependence correlation with the endpoint. We estimated the OR of subclinical hypothyroidism and associated 95% CI based on bootstrap sampling using 2000 samples. The 95% CI were defined as the lower and upper 2.5% percentiles of the bootstrapped values. In the secondary analysis based on a 20% event occurrence, we used a similar approach as in the primary analysis. In post hoc analyses, we assessed the endpoints in unadjusted models including only the mean dose as a predictor. In a subsequent secondary analysis, we employed a multiple linear regression approach. The primary focus was on assessing the changes in TSH for each follow-up session compared to the baseline value. The analysis encompassed the following parameters: mean dose to the thyroid, thyroid volume, chemotherapy, smoking status, BMI, and the patient’s age at the time of treatment. These variables were included without resorting to any variable selection methods. Additionally, the potential influence of an interaction term between thyroid volume and thyroid mean dose was explored. This interaction term was examined for significance at the 5% level, and if found statistically significant, it was included in the analysis. All analyses were defined in a statistical analysis plan prepared before any analysis on the primary endpoint.

Results

We recruited 156 patients for the study. We excluded patients who had no recorded information on mean radiation dose to the thyroid (n=28), abnormal thyroid volume (n=1), no baseline visit (n=3), no visit after the end of radiation therapy (n=7), and no blood sample between the end of chemotherapy and the start of radiation therapy (n=12). In the primary analysis, we also excluded patients with TSH >4mIU/l before the start of radiation therapy (n=3). [Supplementary Figure 1](#) shows a flowchart of inclusion and exclusion criteria for the study population. In the secondary analysis, we excluded patients with TSH >2.5mIU/l (n=29) corresponding to a 20% event occurrence in the study cohort.

In total, 102 breast cancer patients were included in our primary analysis of whom 84 patients were followed for up to 18 months, 13 patients for up to 12 months, and 5 patients for up to 6 months. In [Table 1](#), we present characteristics of the study population included in the primary analysis stratified by the receipt of radiation therapy to the lymph nodes (lymph node-positive) or breast only (lymph node-negative). Patients in the lymph node-positive group were younger (58 years, SD=11) compared with lymph node-negative patients (63 years, SD=8). Mean radiation doses to the thyroid were higher in those receiving radiation to the lymph nodes (11.4Gy, SD=4.9) compared with those who received radiation to the breast only (0.3Gy, SD=0.2). Two prescriptions were used for the lymph node-positive patients: 40 Gy in 15 fractions (16 patients) and 50 Gy in 25 fractions (51 patients). For the lymph node-negative patients, only the 40Gy in 15 fractions prescription was used (35 patients). Thyroid volumes were similar between the two groups at 14cm³ (SD=7) in the lymph

Table 1 Patient Characteristics of 102 Patients Diagnosed With Early-Stage Operable Breast Cancer Presented Separately by Receipt of Radiation Therapy to the Lymph Nodes (Lymph Node-Positive) and Breast Only (Lymph Node-Negative)

	Adjuvant Radiation Therapy	
	Lymph Node-Positive	Lymph Node-Negative
Total, n	67	35
Patient characteristics		
Age (years), mean (SD)	58 (11)	63 (8)
BMI (kg/m ²), mean (SD)	26 (5)	26 (5)
Married/cohabiting at diagnosis, n (%)		
Yes	48 (74)	31 (89)
No	17 (26)	4 (11)
Missing	2	
Total score of Charlson comorbidity Index (points), n (%)		
0	59 (88)	32 (91)
≥1	8 (12)	3 (9)
Baseline TSH (mU/l), mean (SD)	1.8 (0.9)	1.8 (0.9)
Thyroid volume (cm ³), mean (SD)	14 (7)	15 (8)
Clinical characteristics		
Tumor size (mm), mean (SD)	24 (16)	17 (7)
Malignancy grade, n (%)		
Grad I	16 (26)	6 (19)
Grad II	29 (47)	13 (41)
Grad III	17 (27)	13 (41)
Missing	5	3
HER-2 status, n (%)		
Negative	60 (90)	29 (83)
Positive	7 (10)	6 (17)
Ki67, mean (sd)	38 (29)	40 (32)
Estrogen receptor status, n (%)		
Negative (0)	11 (16)	3 (9)
Poor (1–10)	1 (1)	3 (9)
Positive (10+)	55 (82)	29 (83)

(Continued)

Table 1 (Continued).

	Adjuvant Radiation Therapy	
	Lymph Node-Positive	Lymph Node-Negative
Cancer treatments		
Chemotherapy, n (%)		
Yes	49 (73)	14 (40)
No	18 (27)	21 (60)
Mean thyroid radiation dose (Gy), mean (SD)	11.4 (4.9)	0.3 (0.2)
Radiotherapy regimen, n (%) ^a		
40 Gy in 15 fractions	16 (24)	35 (100)
50 Gy in 25 fractions	51 (76)	0 (0)
Adjuvant Endocrine therapy, n (%)		
No	12 (18)	4 (12)
Yes	55 (82)	31 (89)
Type of endocrine therapy, n (%)		
Tamoxifen	17 (31)	5 (17)
Letrozole	38 (69)	25 (83)
Missing		1
Type of primary surgery, n (%)		
Lumpectomy	33 (50)	35 (100)
Mastectomy	33 (50)	0 (0)
Missing	1	
Number of lymph nodes removed, mean (SD)	17 (8)	2 (1)

Notes: ^aRadiotherapy regimen refers to the prescribed dose for the breast or chest region, as well as the lymph node region in patients with lymph node-positive disease.

Abbreviations: BMI, body mass index. TSH, serum thyroid-stimulating hormone. HER-2, human epidermal growth factor receptor 2. Ki67, Antigen KI-67.

node-positive group and 15cm³ (SD=8) in the lymph node-negative group. The proportion of patients requiring adjuvant chemotherapy was 73% in lymph node-positive patients and 40% in lymph node-negative patients. BMI and baseline TSH were similar in the two patient groups (Table 1).

The variable selection based on the best-subset selection using 5-fold cross-validation showed that the best-performing model included no parameters and had a likelihood within one standard error of the likelihood of the best-performing model. Thus, the null model (the model with no predictors, and fixed event probability for all patients) had a prediction power similar to the best-performing model. Thus, for the primary (TSH >4mIU/l) and secondary (TSH >2.5mIU/l) endpoints, there was no observable dependence on dosage or any of the other parameters included in the best-subset selection, as shown in [Supplementary Figure 2](#). For the endpoint of TSH >4mIU/l, the best-performing model included thyroid volume, baseline TSH level, and BMI. For the endpoint of TSH >2.5mIU/l, the best-performing model included baseline TSH level and BMI.

Table 2 Associations Between Mean Radiation Dose to the Thyroid and Subclinical Hypothyroidism

	Events/Patients (proportion)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Mean radiation dose to the thyroid ^a	4/102 (3.9%)	0.99 (0.95–1.03)	^c 1.02 (0.91–1.15)
Mean radiation dose to the thyroid ^b	16/76 (21.1%)	1.11 (1.01–1.20)	^d 1.22 (1.01–1.38)

Notes: ^aSubclinical hypothyroidism defined as thyroid stimulating hormone (TSH) >4mIU/l ^bSubclinical hypothyroidism defined as TSH >2.5mIU/l in accordance with the 20% event criteria ^cBest-performing model analysis: Adjusted for thyroid volume, baseline TSH level, body mass index, and interaction between mean radiation dose to the thyroid and thyroid volume ^dBest-performing model analysis: Adjusted for baseline TSH level, body mass index, and interaction between mean radiation dose to the thyroid and thyroid volume.

Abbreviations: OR, odds ratio. 95% CI, 95% confidence interval.

From the model including no parameters, we identified four patients (3.9%) with subclinical hypothyroidism (TSH >4mIU/l) at any visit after completion of radiation therapy—two in the lymph node-positive group and two in the lymph node-negative group (Table 2). In the model forcing radiation dose into the mixed logistic regression models with a >4mIU/l TSH threshold, the OR for subclinical hypothyroidism was 0.99 (95% CI: 0.95–1.03) per increase Gray of mean radiation dose to the thyroid. In the best-performing model, the OR was 1.02 (95% CI=0.91–1.15) (Table 2).

We included 76 patients in our secondary analysis using a TSH threshold of >2.5mIU/l corresponding to 20% event occurrence in the study cohort. Sixteen patients developed subclinical hypothyroidism during follow-up using this lower threshold (Table 2). In mixed logistic regression models, the unadjusted analysis yielded an OR of 1.11 (95% CI: 1.01–1.20) and an OR of 1.22 (95% CI=1.01–1.38) in the best-performing model (Table 2).

Using multiple linear regression analysis, we investigated TSH level changes relative to baseline during follow-up. For the association between mean dose to the thyroid and change in TSH levels, we observed a regression coefficient of –0.003 (95% CI: –0.02 to 0.02). We found no statistically significant interaction between mean dose to the thyroid and thyroid volume.

Discussion

In this prospective study of women with early-stage breast cancer treated with CT-guided radiation therapy, we were unable to detect an increased risk of subclinical hypothyroidism associated with increasing radiation dose to the thyroid, based on the current reference TSH level of >4.0mIU/l. In a secondary analysis using a TSH threshold of >2.5mIU/l, we observed a positive association between increasing mean radiation dose to the thyroid and the incidence of subclinical hypothyroidism.

Our results on subclinical hypothyroidism after radiation therapy agree with some published studies. Akyurek et al analyzed thyroid function before radiation therapy, and at 3, 6, 9, 12, 18 and 24 months post-treatment in 28 breast cancer patients.²⁵ Despite a higher TSH threshold (5.6mIU/l) than in our study, they found 7% incidence of *subclinical* hypothyroidism and 14% incidence of *clinical* hypothyroidism (TSH>5.6mIU/l and decreased ft4). Compared with our findings, their higher incidence may be attributable to their higher mean radiation dose to the thyroid (31Gy) or to chance given the small sample size. Among 4073 breast cancer patients, Choi et al reported a risk of hypothyroidism of 0.8% after radiation therapy to the breast only (mean thyroid dose of 0.23Gy), but 2.2% after radiation therapy to the supraclavicular lymph nodes (mean thyroid dose of 7.89Gy).²⁶ Compared with our findings, their lower incidence of hypothyroidism may reflect a lower mean radiation dose to the thyroid compared with our study and a higher TSH threshold (4.69mIU/l). Still, Choi et al based the mean dose to the thyroid on random samples from the two groups rather than the actual thyroid irradiation in individual patients.²⁶

Other studies report higher incidence of subclinical (and clinical) hypothyroidism than our findings. Yet, these studies had longer follow-up (median follow-up of 24–53 months and maximum follow-up of 130 months).^{27–29} A Norwegian study of 403 women found an increased incidence of hypothyroidism (18%) in breast cancer patients compared with the general population (6%).⁶ Among the patients with hypothyroidism, 59% received CT-guided radiation therapy (no part of the thyroid gland received less than 12Gy) while 31% had standardized field arrangements (typically 1–4Gy). While the radiation dose to the thyroid was comparable to that in our study, hypothyroidism was self-reported and based on a wide range of criteria, which could potentially lead to overestimation of the incidence.

A US-based study of 38,255 breast cancer patients, found a 5-year incidence of hypothyroidism of 14% compared with 11% in an age-matched general population. Yet, they found no evidence of elevated risk of hypothyroidism after radiation therapy to the lymph nodes versus the breast only. Still, they did not assess the mean radiation dose to the thyroid.³⁰ Furthermore, their study cohort had a higher mean age (75 years) and longer median follow-up (4.6 years) compared with our study.

Several issues should be considered when interpreting our findings. Our study had a small sample size leaving the possibility of imprecise estimates. Participation in our study was voluntary, but patients had no information on radiation dose or thyroid function at enrolment, reducing the risk of selection bias. Among those recruited, one-third of the study population was excluded due to a lack of information on mean radiation dose to the thyroid, or insufficient follow-up. However, baseline characteristics of these excluded patients were similar to those of the included patients, so this is unlikely to have introduced substantial selection bias. Still, blood samples had to be drawn before 9 a.m. potentially precluding participation from, for example, patients living far away from the hospital or those with comorbid diseases. However, severe comorbidity is not associated with increased risk of subclinical hypothyroidism after radiation therapy^{30–32} and seems unlikely to be associated with mean radiation dose to the thyroid.

We anticipate that misclassification of mean radiation dose to the thyroid is minimal as we estimated the mean radiation dose to the thyroid using CT scans. Only a minor degree of inter-observer variation is expected when delineating organs at risk.^{33–35} Misclassification of TSH levels seems unlikely as blood samples were drawn before 9 a.m. to ensure minimal daily variation,^{17–19} and all samples were analyzed in accordance with the relevant guidelines. Patients were not asked to fast before blood draw as this is not a requirement according to Danish clinical guidelines.³⁶ However, fasting may increase thyroid hormone levels compared with non-fasting.^{37,38} If this led to misclassified TSH values, it would not be related to radiation dose, so such misclassification would be non-differential. Overall, we do not believe our findings can be explained by selection or information bias.

In our study, the overall mean radiation dose to the thyroid gland was low even for women receiving radiotherapy to the lymph nodes, with a mean value of 11.4Gy in this group. On one hand, this is reassuring to patients and providers of radiation therapy. On the other hand, findings from our secondary analyses using the lower TSH threshold supported by other studies reporting long-term effects after radiation therapy,^{27,28,39,40} suggest the need for enhanced clinical awareness of hypothyroidism among breast cancer patients after radiation therapy to the lymph nodes, and/or potentially those with elevated TSH >2-2.5mIU/l after radiation therapy. We note that research investigating the long-term effects of elevated TSH and subsequent development of hypothyroidism shows a TSH value of 2.0mIU/l was associated with a high risk of developing hypothyroidism 20 years later.^{39,40}

Conclusion

We could not confirm that increasing mean radiation dose to the thyroid was associated with an increased incidence of subclinical hypothyroidism when using a TSH threshold level of >4mIU/l. However, the elevated risk of subclinical hypothyroidism using a TSH threshold of >2.5mIU/l supports further large-scale studies evaluating various TSH threshold levels and longer follow-up.

Data Sharing Statement

In accordance with Danish law, individual-level data cannot be made publicly available to protect patient privacy.

Ethics Approval and Informed Consent

This study was approved by the Regional Ethical Committee of the South Denmark Region (S-20150187) and registered with the Danish Data Protection Agency (Aarhus University, journal number 2016-051-000001, number 437). The project complied with the General Data Protection Regulation. Informed consent was obtained from all individual participants included in the study.

Author Contributions

All authors made significant contributions to the work reported, whether in the conception, study design, execution, data acquisition, analysis, or interpretation. They took part in drafting, revising, and critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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