Clinical and Translational Radiation Oncology 39 (2023) 100566

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Thyroid volume changes following adjuvant radiation therapy for breast cancer

John Roberson [a,1], Huakang Huang [b,1], Collin Noldner [a], Wei Hou [c], Kartik Mani [a,d], Edward Valentine [a], Samuel Ryu [a,e], Alexander Stessin [a,e,*]

[a] Department of Radiation Oncology, Renaissance School of Medicine, Stony Brook University, Stony Brook, NY 11794, USA
[b] Renaissance School of Medicine, Stony Brook University, Stony Brook, NY 11794, USA
[c] Department of Family, Population, and Preventive Medicine, Renaissance School of Medicine, Stony Brook University, Stony Brook, NY 11794, USA
[d] Department of Biomedical Informatics, Renaissance School of Medicine, Stony Brook University, Stony Brook, NY 11794, USA
[e] Department of Pharmacology, Renaissance School of Medicine, Stony Brook University, Stony Brook, NY 11794, USA

ARTICLE INFO

Keywords:
Breast Neoplasms
Retrospective studies
Cancer survivors
Thyroid evolution
Hypothyroidism
Radiotherapy dosage
Radiotherapy, conformal
Radiotherapy, intensity-modulated

ABSTRACT

Background and purpose: Incidental thyroid gland irradiation frequently occurs in breast cancer patients who receive regional nodal irradiation (RNI) to the supraclavicular (SCV) region. Recent studies suggest hypothyroidism (HT) is a complication of radiation therapy (RT) that includes SCV fields. We retrospectively analyzed patients who received RNI to evaluate thyroid gland evolution following RT as well as its association with the development of HT.

Materials and methods: 61 breast cancer patients received SCV-directed RT between 2007 and 2019 and met inclusion criteria. Thyroid glands were retrospectively contoured on CT simulation and follow-up images. Individual dose-volume histograms were analyzed to determine thyroid volume within and outside specific isodose lines. Relative thyroid volume changes based on different radiation doses were estimated by fusing post-RT scans with CT simulation. Logistic regression was performed to assess thyroid volume changes as a factor in the development of HT.

Results: Median pre-treatment thyroid volume was 11.8 cc (range: 6.3–74.1 cc) with a median of 42.2 % within the 20 Gy and 23.2 % within the 40 Gy isodose lines. A significant decrease in thyroid volume was noted by 1-year post-treatment ($p < 0.0001$) and thereafter. By 4 years post-treatment, average thyroid volume was decreased by 29.7 % (range: 2.3–64.4 %). Thyroid volume receiving 40 Gy or higher demonstrated a greater decrease compared to those receiving lower irradiation dosage. HT occurred in 17 patients (27.9 %). Patients who developed HT displayed a larger decrease in the thyroid volume receiving between 20 and 40 Gy at 12 months ($p = 0.033$).

Conclusion: Our study demonstrates for the first time that a reduction in thyroid volume may be seen as early as 6 months after SCV-directed RT for breast cancer, which correlates with development of clinical and subclinical HT. Furthermore, a dose-dependent correlation exists between thyroid subvolume reduction and SCV-directed RT in breast cancer patients. As feasible, efforts should be made to reduce the dose to the thyroid in patients who undergo RNI for breast cancer.

Background

Breast cancer is the most common cancer (excluding skin cancers) and second most common cause of cancer death among US women, with approximately 281,000 new cases and 43,600 breast cancer deaths expected to occur in the US in 2021 [1]. External beam radiation therapy (RT) that involves the breast and regional lymph nodes, including axillary and supraclavicular (SCV) lymph nodes, has been demonstrated to decrease the risk of local recurrence and improve long-term survival in high-risk breast cancer patients [2,3]. However, RT-induced toxicities

Abbreviations: HT, hypothyroidism; RT, radiation therapy; SCV, supraclavicular; RNI, regional nodal irradiation.

* Corresponding author at: Department of Radiation Oncology, HSC T-3, Stony Brook University, Stony Brook, NY 11794-8165.
E-mail address: Alexander.Stessin@stonybrookmedicine.edu (A. Stessin).

[1] Co-first authors.

https://doi.org/10.1016/j.ctro.2022.100566
Received 8 August 2022; Received in revised form 18 November 2022; Accepted 14 December 2022
Available online 16 December 2022

to adjacent normal tissues can lead to serious morbidity in cancer survivors [4].

The thyroid gland is an important endocrine organ located next to the SCV nodal area, which is typically included in the irradiation field for locally advanced breast cancers. The thyroid gland regulates the body's metabolism via producing thyroxine (T4) and triiodothyronine (T3) hormones. As the thyroid is sensitive to RT, radiation-induced thyroid disorders have been reported in cancer patients who received radiation in the cervical or SCV regions [5,6]. In patients that received RT for head and neck tumors, the average incidence of primary hypothyroidism (HT) was reported as over 20 %, with median clinical latency of 3 years [7]. In breast cancer patients, RT to the SCV area has been associated with a higher incidence of HT, particularly in younger patients [8,9]. This complication may be associated with radiation-induced thyroid volume reduction. Recent studies, mostly relatively small, have reported a significant decrease in thyroid volume (14–30 %) in patients with laryngeal cancer or nasopharyngeal carcinoma (NPC), suggesting an association between the development of HT and post-RT thyroid atrophy [10,11]. In breast cancer patients, smaller thyroid volume has been associated with a higher incidence of radiation-induced HT [12]. However, little is known about the changes of thyroid gland volume based on local thyroid gland radiation dose and its correlations with incidence of HT.

We retrospectively analyzed the changes in thyroid volume of breast cancer patients who received RT to the SCV nodal area, to evaluate RT-induced thyroid gland evolution based on local radiation dose. We then assessed the association between thyroid volume changes and the incidence of post-RT HT in breast cancer patients. Fig. 1.

Materials and methods

Patient population

We reviewed the records for all patients with breast cancer treated at our institution between October 2007 and March 2019. Patient data were obtained from our institution's electronic health records. Inclusion criteria for our study included: histopathologically-proven breast cancer; treatment with conventionally fractionated RT that included the SCV; age $\geq$ 18 years old; female; available RT planning records; available pre- and post-radiation imaging that included the entire thyroid gland; available thyroid dose-volume histograms (DVHs); no known pretreatment primary thyroid disease or dysfunction; no prior thyroid surgery; and no prior RT that involved the hypothalamic-pituitary axis or thyroid. Follow-up CTs were obtained only as part of regular follow-up and not for the purpose of this study; as such, this study necessitated a prolonged study interval. While the use of intensity-modulated radiation therapy (IMRT) increased throughout the study period, the use of image-guidance remained essentially the same, using kV and MV imaging. This study was approved by our Institutional Review Board (IRB) and conducted according to the ethical principles of the Belmont Report.

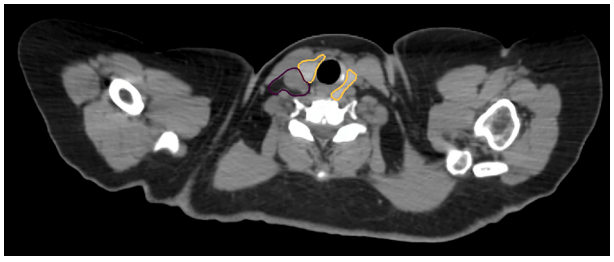

Fig. 1. Example axial slices displaying the relationship of the SCV volume to the thyroid volume. Purple indicates SCV volume while yellow represents thyroid. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Treatment

All patients underwent standard adjuvant RT for patients with breast cancer in whom RNI is clinically indicated. Following initial consultation, patients underwent treatment-planning computed tomography (CT) scans with axial image thickness of 2–5 mm (median: 2.5 mm). These CT images were imported into our 3D treatment planning system (Eclipse, Varian, Cary, NC). Thereafter, target volumes including the breast or chest wall (depending on prior surgery) and regional lymph nodes including the SCV were contoured according to RTOG guidelines. Neighboring organs-at-risk, including the heart, lungs, contralateral breast or chest wall, and spinal cord, were also contoured. A treatment plan was subsequently created using either three-dimensional conformal radiation therapy (3D-CRT) or IMRT with 6-MV, 15-MV, or both 6- and 15-MV photon energy. Patients were treated to 44–50.4 Gy in 1.8–2 Gy per fraction. For patients treated with 3D-CRT, the gantry angle for the SCV fields was set at 5–30 degrees (median: 15 degrees), individualized to the patient's anatomy and set-up. The majority of patients also received a photon or electron boost to the tumor bed (with prior breast-conservation surgery) or the scar (with prior mastectomy) with doses ranging from 8 to 32 Gy (median: 10 Gy in 5 fractions; one received a 32 Gy stereotactic boost for gross disease). Photon boosts were delivered using 6- and/or 15-MV, and electron boosts were delivered using energies between 6- and 20-MeV. The overall treatment time ranged from 29 to 70 days (median: 43 days).

Thyroid evaluation

Once patients were identified for inclusion into this study, the thyroid glands were retrospectively contoured (as such, no thyroid constraints were prospectively used in treatment planning). The dose volume histograms (DVHs) for each patient were analyzed to determine the maximum (Dmax), minimum (Dmin), and mean (Dmean) doses to thyroid gland. The absolute volume of the thyroid gland was calculated. Isodose lines were generated to encompass the volume receiving 20 Gy (V20) and 40 Gy (V40) to represent moderate and high dose regions respectively. Overlaying respective isodose lines with available images allowed for subdividing the thyroid gland based on the dose delivered. Follow-up imaging was assessed for each patient, and 137 scans met inclusion criteria: 11 at 3 months (range: 1.6–4.0 months), 27 at 6 months (range: 4.5–8.9 months), 25 at 1 year (range: 9.1–14.7 months), 12 at 18 months (range: 15.1–20.8 months), 17 at 2 years (range: 21.6–27.0 months), 11 at 30 months (range: 27.1–33.2 months), 19 at 3 years (range: 33.4–39.8 months), and 15 at 4 years (range: 44.0–53.2 months) post-RT. Post-RT scans were subsequently fused with CT simulation scans to best approximate the relative changes in thyroid volume based on different radiation doses. DVH statistics have been recorded as per TG 263 [13].

Patient's records, including inpatient and outpatient notes and laboratory tests, were reviewed to assess for the development of clinical HT, defined as documented clinical diagnosis, treatment with levothyroxine or other thyroid supplementation, or an elevated TSH in the presence of a low free T4 concentration. Subclinical HT was defined as an elevated TSH in the absence of meeting the definition for clinical HT. The time to the development of HT was defined as the interval between the last RT treatment and the initial diagnosis of clinical or subclinical HT. Patients were censored at last clinical follow-up, further RT that affected the thyroid, or death.

Statistical analysis

Descriptive statistics (e.g., median and range for continuous variables and frequencies and percentages for categorical variables) were calculated for patient, tumor, and treatment characteristics. The medians of dose-volume parameters were compared between IMRT and 3D-CRT treatment modalities using Wilcoxon rank sum tests. Logistic

regression models were used to evaluate the association between thyroid volume and development of HT. A $p < 0.05$ was considered statistically significant in two-tailed statistical tests. Analysis was conducted using either SPSS Statistics version 26 (IBM SPSS, Chicago, IL) or SAS version 9.4 (SAS Institute, Cary NC).

Results

HT incidence

A total of 61 patients met inclusion criteria for our study. Median follow-up duration was 48.3 months (range: 6.5–135.7 months). Patient, tumor, and treatment characteristics are included in Table 1. Of note, two patients had treatment times that were prolonged beyond eight weeks. One of these had a prolonged treatment time of 70 days with a 3-week break prior to starting her boost, due to significant moist desquamation that was slow to heal. In addition, one patient had a prolonged treatment time of 68 days with multiple treatment days missed due to transportation issues and "no shows". Seventeen patients (27.9 %) were identified as having HT, with 11 having clinical HT (18.0 %) and 6 subclinical HT (9.8 %). The median time to develop post-RT HT was 38.7 months (range: 3.2–135.7 months). The median age at diagnosis of HT was 61 years (range: 41–89 years).

Changes of thyroid volume and sub-volumes

The median pre-treatment thyroid volume was 11.8 cc (range: 6.3–74.1 cc), with a median of 42.2 % thyroid volume receiving at least 20 Gy and 23.2 % at least 40 Gy. A time-dependent decrease in thyroid volume was observed in patients who received SCV-directed RT. As demonstrated in Fig. 2, a significant decrease in thyroid volume was noted by 12 months post-radiation ($p < 0.0001$) and remained significant thereafter. By 48 months post-radiation, the mean thyroid volume decrease was 29.7 % (range: 2.3–64.4 %).

The effect of RT on thyroid volume decrease appears dose dependent. As shown in Fig. 3, a substantial difference in thyroid sub-volume changes was observed between the thyroid subvolumes receiving low dose (VS20, or "volume spared 20", defined as thyroid volume receiving <20 Gy) and the portions receiving higher dose (V20, defined as thyroid volume receiving at least 20 Gy), starting as early as 6 months post-radiation. A significant decrease in V20 was noted by 6 months post-treatment ($p < 0.0001$) and remained significant thereafter. However, a small increase was found in VS20 at 6 months ($p = 0.031$) that returned to baseline by 1 year and ultimately decreased by 36 months ($p = 0.024$). This dose-dependent response is further delineated in Fig. 4, where the changes of thyroid sub-volume were compared between three groups based on radiation dose, separated by the 20 Gy and 40 Gy isodose lines. As expected, the sub-volume receiving the highest dose (40 Gy or higher, V40) demonstrated the greatest reduction in percentage at all time points, compared to the other two groups.

HT and thyroid atrophy

The association between radiation-induced thyroid volume decrease and the development of HT was also evaluated. In our study, HT occurred in 17 patients (27.9 %), much higher than the primary HT incidence in the general population (4.6 %) [14]. As shown in Table 2, patients who developed HT demonstrated a larger decrease in thyroid volume at 12 months post-RT compared to patients who remained euthyroid. Such difference also appeared to be dose-dependent. Specifically, the hypothyroid group had a significantly greater decrease in the thyroid volume receiving between 20 and 40 Gy (28.6 % vs 9.8 %, $p = 0.033$).

Other variables included in this study were also assessed using univariable analysis. As shown in Supplemental Table 1, thyroid irradiation dosage, postmenopausal status, aromatase inhibitor use, and initial thyroid volume are suggested as independent risk factors for the development of HT in these patients on univariate analysis. These were analyzed in greater detail in our prior manuscript. Interestingly, on multivariate analysis neither post-menopausal status, nor aromatase inhibitor use were found to be significant predictors of HT [12].

Discussion

The thyroid is among the most radiosensitive tissues in the body, and thyroid toxicity can happen with both occupational and medical radiation exposure, in children or adults [15,16]. It is well known that for cancer patients who receive RNI to the cervical or SCV nodal regions, incidental thyroid gland irradiation occurs and may cause various thyroid complications, the most common being RT-induced HT. Previous clinical studies have shown that high-dose head and neck radiation increases the risk of HT in nasopharyngeal cancer patients [17,18]. However, the effect of SCV-directed RNI for patients with locally advanced breast cancer hasn't been properly studied. Based on the results of our analysis of 61 breast cancer patients who received radiation to the SCV lymph nodes, the incidence of post-SCV RT HT in these patients is 27.9 %, with a median time to onset of 38.7 months. Our results are consistent with recent studies that suggest an association between

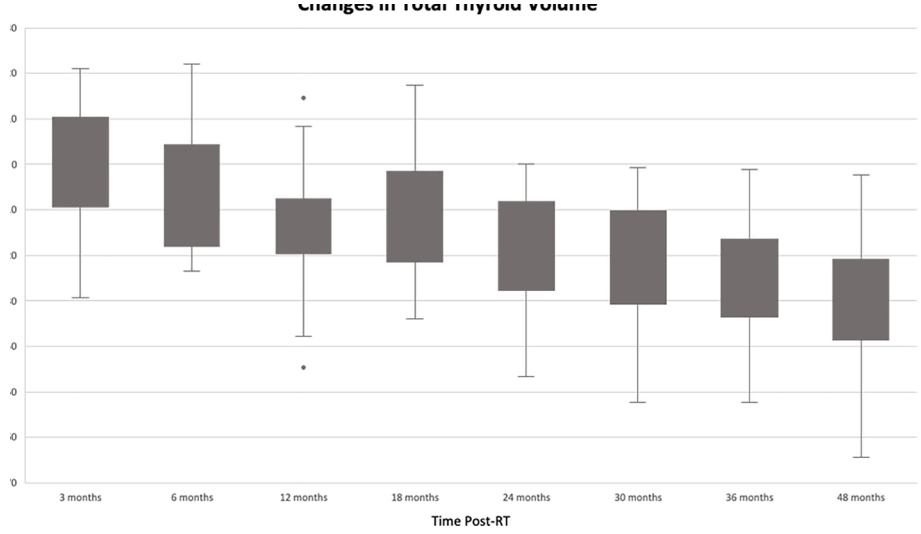

Fig. 2. Changes in total thyroid volume (%) among patients who received RT to SCV region, up to 48 months post-treatment.

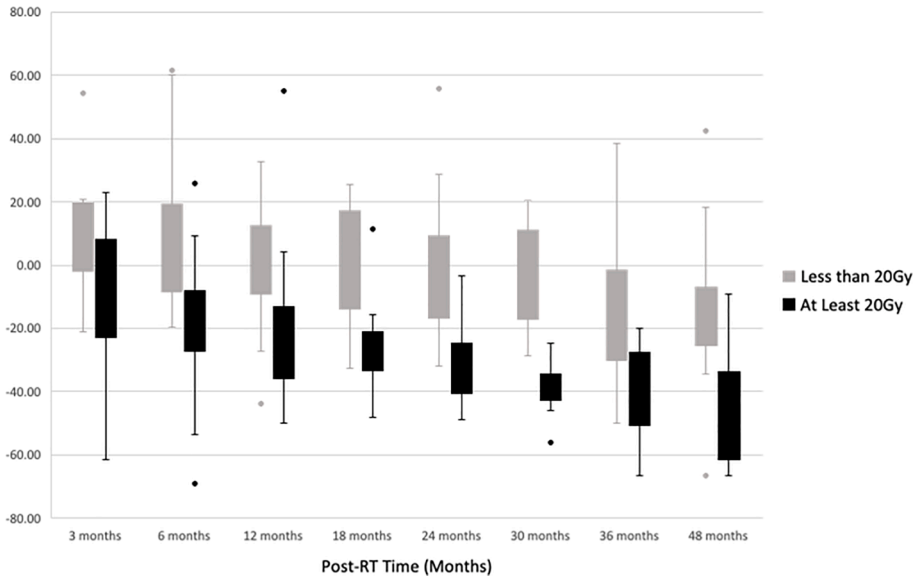

Fig. 3. Changes in thyroid subvolumes (%) among patients who received RT to SCV region, up to 48 months post-treatment.

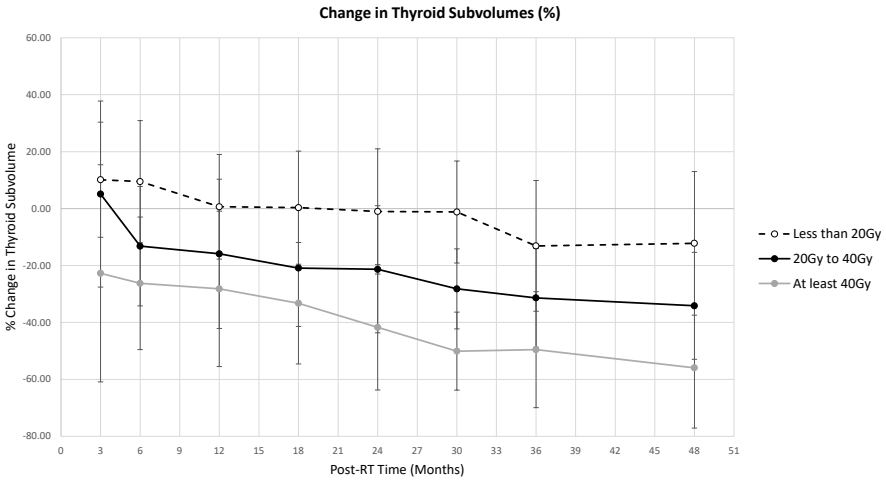

Fig. 4. Changes in thyroid subvolumes (%) among patients who received RT to SCV region, up to 48 months post-treatment.

SCV-directed RT and higher incidence of HT in cancer patients compared to the general population [9,12,14].

The development of HT in cancer patients seems to be associated with small thyroids. In patients undergoing hemithyroidectomy, low post-operative thyroid volume (<3.2 cc) has been associated with thyroid dysfunction and HT during follow-up [19]. Multiple studies have indicated that head and neck cancer patients with smaller pre-treatment thyroids are at a significantly higher risk for developing post-RT HT, although the cutoff value varies among different studies [17,20–22]. Little is known if such association also exists in breast cancer patient population. A retrospective study at our institution identified smaller thyroid volume to be associated with the development of HT based on univariable analysis among a larger population of breast cancer patients [12]. The evidence that HT is associated with both thyroid volume and volume spared from receiving at least 20 Gy (as we previously demonstrated) appears validated by this study demonstrating no significant difference in the change in the volume that received <20 Gy at 1 year between patients who remained euthyroid or developed HT (see Table 2) and provides further evidence to support the goal of maximizing the thyroid volume spared from receiving at least 20 Gy in an effort to minimize the risk of post-RT HT.

Radiation-induced decrease in thyroid volume may also be associated with a higher incidence of post-radiation primary HT [18,23]. Reduction of thyroid volume may occur with local thyroid gland dose of 2 Gy or higher, possibly due to radiation-induced microvascular and parenchymal damage [24]. A recent analysis by Lin and colleagues showed that patients with nasopharyngeal cancer demonstrated a 40 % decrease in thyroid volume by 30 months post-RT, including nearly 30 % within the first 12 months [10]. A separate study by Miller-Thomas and colleagues demonstrated a mean reduction of 13.8 % in thyroid width at an average of 25 months post-XRT in patients with laryngeal cancer. However, no significant difference in absolute and percentage change of thyroid size was found between the hypothyroid and euthyroid groups [25]. To assess thyroid evolution following RT to SCV lymph nodes in breast cancer patients, we tracked changes in size of thyroid in these patients based on pre-treatment and follow-up CT images. Our results, indicate a time-dependent decrease in thyroid volume in these patients, with a significant decrease in thyroid volume starting from 12 months post-radiation ($p < 0.0001$). The greatest percent change in total thyroid volume was found at 48 months post-RT, with a mean reduction of 29.7

% (range: 2.3–64.4 %), suggesting that thyroid atrophy may continue to occur for years after radiation treatment. In addition, we found a trend towards a larger percent decrease in total thyroid volume in patients who developed HT compared to those that remained euthyroid during the follow-up period ($p = 0.055$), suggesting that total thyroid atrophy may be an independent risk factor for risk of HT. This association seems to be driven by changes in thyroid tissue receiving doses greater than 20 Gy. These findings are in accordance with a recent retrospective study by Ishibashi and colleagues, where decrease in CT densities of the thyroid gland occurred in 73.9 % patients after radiation for head and neck tumors, while a larger decrease in thyroid density was significantly associated with higher serum TSH level, suggesting a higher risk of HT development [23].

Although multiple RT-induced thyroid complications have been shown in previous studies, little is known about the association between RT dose and post-RT thyroid evolution. Here, we evaluated the difference in thyroid volume decrease based on different local thyroid dose regions through assessing changes in thyroid sub-volume separated by isodose lines of 20 Gy and 40 Gy on CT images. Our results, as demonstrated in Fig. 3, indicated a significantly larger decrease in thyroid tissue that received 20 Gy or higher compared to the rest of thyroid organ, starting 6 months post-RT ($p < 0.0001$). Furthermore, the sub-volume receiving the highest dose (40 Gy or higher, V40) demonstrated the greatest reduction in percentage at all time points, compared to the other two sub-volumes (<20 Gy and 20–40 Gy), suggesting a dose-dependent effect of radiation on thyroid volume decrease.

Interestingly, our results also showed a small increase in thyroid sub-volume after low dose radiation (<20 Gy, VS20) at 6 months ($p = 0.031$), which returned to baseline by 1 year and ultimately decreased by 36 months ($p = 0.024$). A similar finding of thyroid volume increase was found in a recent study by by Miller-Thomas and colleagues, where 15 % (9/61) patients had measured increase in the size of the thyroid gland following XRT for laryngeal cancer [25]. Possible explanations include radiation-mediated damage inducing temporary enlargement or compensatory hypertrophy of the thyroid gland responding to hormonal stimulation from the feedback system [17,25]. Such physiological compensation may not be commonly observed in other head and neck cancer studies, as the hypothalamic-pituitary-thyroid dysfunction is more common in NPC patients [26].

In our previous work, we had found through NTCP modeling that thyroid volume receiving <20 Gy was a significant predictor of developing hypothyroidism [12]. Specifically, greater than 8.5 cc thyroid volume receiving <20 Gy was supported by our NTCP modeling as a reasonable dosimetric guideline to minimized HT risk in breast cancer patients receiving SCV-directed RT.

In recent studies, younger age, adjuvant chemotherapy and higher mean thyroid dose were suggested to increase risk of post-RT HT in breast cancer patients [8,10,27]. In this study, post-menopause status, aromatase inhibitor, and mean thyroid dose were also suggested as risk factors for HT incidence in breast cancer patient following SCV RT. Age is known to be correlated with HT risk in general population due to thyroid epithelium degeneration [28]. A recent study suggested that breast cancer patients at younger age (<60 years) are more prone to radiation-induced HT [8]. However, this association was not observed in our study. Univariate analysis did show that post-menopausal status was associated with an increased risk of HT; however, this did not stay significant on multivariate analyses, as indicated in our previous manuscript [12].

Conclusion

Radiation-induced thyroid atrophy is an important side effect of SCV-directed RT for patients with locally advanced breast cancer. Our study shows for the first time that changes in the thyroid volume may be seen as early as 6 months after RNI for breast cancer, which may ultimately be associated with the development of clinical and subclinical HT. We further demonstrated a dose-dependent correlation between irradiation to the thyroid and thyroid volume reduction as a significant decrease in thyroid volume is associated with radiation dose of 20 Gy or higher. In addition, our data shows that smaller pre-treatment thyroid volumes can translate into higher risk of RT-induced HT. As feasible, careful assessment of pre-treatment thyroid volume and effort to reduce the dose to thyroid should be made in order to reduce risk of long-term RT-induced thyroid toxicity in patients who undergo regional nodal irradiation for breast cancer.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2022.100566.

References

[1] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin 2021;71(1):7–33.
[2] Early Breast Cancer Trialists' Collaborative Group. (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;366(9503):2087–106.
[3] Van de Steene J, Soete G, Storme G. Adjuvant radiotherapy for breast cancer significantly improves overall survival: the missing link. Radiother Oncol 2000 Jun;55(3):263–72.
[4] Bucci MK, Bevan A, Roach 3rd M. Advances in radiation therapy: conventional to 3D, to IMRT, to 4D, and beyond. CA Cancer J Clin 2005;55(2):117–34.
[5] Alterio D, Jereczek-Fossa B, Franchi B, D'Onofrio A, Piazzi V, Rondi E, et al. Thyroid disorders in patients treated with radiotherapy for head-and-neck cancer: a retrospective analysis of severty-three patients. Int J Radiat Oncol Biol Phys 2007;67:144–50.
[6] Smith GL, Smith BD, Giordano SH, et al. Risk of hypothyroidism in older breast cancer patients treated with radiation. Cancer 2008 Mar 15;112(6):1371–9.
[7] Bhandare N, Kennedy L, Malyapa R, Morris C, Mendenhall W. Primary and central hypothyroidism after radiotherapy for head-and-neck tumors. Int J Radiat Oncol Biol Phys 2007;68:1131–9.
[8] Choi SH, Chang JS, Byun HK, Son NH, Hong CS, Hong N, et al. Risk of Hypothyroidism in Women After Radiation Therapy for Breast Cancer. Int J Radiat Oncol Biol Phys 2021 Jun 1;110(2):462–72.
[9] Darvish L, Ghorbani M, Teshnizi SH, et al. Evaluation of thyroid gland as an organ at risk after breast cancer radiotherapy: a systematic review and meta-analysis. Clin Transl Oncol 2018 Nov;20(11):1430–8.
[10] Lin Z, Yang Z, He B, Wang D, Gao X, Tam SY, et al. Pattern of radiation-induced thyroid gland changes in nasopharyngeal carcinoma patients in 48 months after radiotherapy. PLoS One 2018 Jul 9;13(7).
[11] Rivas AM, Larumbe-Zabala E, Diaz-Trastoy O, et al. Effect of chemoradiation on the size of the thyroid gland. Baylor University Medical Center Proceedings 2020;33(4):541–5.
[12] Huang H, Roberson J, Hou W, Mani K, Valentine E, Ryu S, et al. NTCP model for hypothyroidism after supraclavicular-directed radiation therapy for breast cancer. Radiother Oncol 2021 Jan;154:87–92.
[13] Mayo CS, Moran JM, Bosch W, Xiao Y, McNutt T, Popple R, et al. American Association of Physicists in Medicine Task Group 263: standardizing nomenclatures in radiation oncology. Int J Radiat Oncol Biol Phys 2018;100(4):1057–66.
[14] Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T4, and Thyroid Antibodies in the United States Population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002;87(2):489–99.
[15] Park S, Lee DN, Jin YW, Cha ES, Jang WI, Park S, et al. Non-cancer disease prevalence and association with occupational radiation exposure among Korean radiation workers. Sci Rep 2021 Nov 17;11(1):22415.
[16] Sinnott B, Ron E, Schneider AB. Exposing the thyroid to radiation: a review of its current extent, risks, and implications. Endocr Rev 2010;31(5):756–73.
[17] Lertbutsayanukul C, Kitpanit S, Prayongrat A, Kannarunimit D, Netsawang B, Chakkabat C. Validation of previously reported predictors for radiation-induced hypothyroidism in nasopharyngeal cancer patients treated with intensity-modulated radiation therapy, a post hoc analysis from a Phase III randomized trial. J Radiat Res 2018 Jul 1;59(4):446–55.
[18] Lin Z, Wu VW, Lin J, Feng H, Chen L. A longitudinal study on the radiation-induced thyroid gland changes after external beam radiotherapy of nasopharyngeal carcinoma. Thyroid 2011 Jan;21(1):19–23.

[19] Lang BH, Wong CKH, Wong KP, Chu KK, Shek TWH. Effect of thyroid remnant volume on the risk of hypothyroidism after hemithyroidectomy: a prospective study. Ann Surg Oncol 2017 Jun;24(6):1525–32.
[20] Huang CL, Tan HW, Guo R, Zhang Y, Peng H, Peng L, et al. Thyroid dose-volume thresholds for the risk of radiation-related hypothyroidism in nasopharyngeal carcinoma treated with intensity-modulated radiotherapy-A single-institution study. Cancer Med 2019 Nov;8(16):6887–93.
[21] Kamal M, Peeler CR, Yepes P, Mohamed ASR, Blanchard P, Frank S, et al. Radiation-Induced Hypothyroidism After Radical Intensity Modulated Radiation Therapy for Oropharyngeal Carcinoma. Adv Radiat Oncol 2019 Sep 7;5(1):111–9.
[22] Zhou L, Chen J, Shen W, Chen ZL, Huang S, Tao CJ, et al. Thyroid V50 is a risk factor for hypothyroidism in patients with nasopharyngeal carcinoma treated with intensity-modulated radiation therapy: a retrospective study. Radiat Oncol 2020 Mar 23;15(1):68.
[23] Ishibashi N, Maebayashi T, Aizawa T, Sakaguchi M, Okada M, Matsushita J. Computed Tomography Density Change in the Thyroid Gland Before and After Radiation Therapy. Anticancer Res 2018 Jan;38(1):417–21.
[24] Lollert A, Gies C, Laudemann K, Faber J, Jacob-Heutmann D, König J, et al. Ultrasound Evaluation of Thyroid Gland Pathologies After Radiation Therapy and Chemotherapy to Treat Malignancy During Childhood. Int J Radiat Oncol Biol Phys 2016 Jan 1;94(1):139–46.
[25] Miller-Thomas MM, Kumar AJ, Sellin RV, Azimpoor S, Ang KK. The shrinking thyroid: how does thyroid size change following radiation therapy for laryngeal cancer? AJNR Am J Neuroradiol 2009 Mar;30(3):613–6.
[26] Huang S, Wang X, Hu C, Ying H. Hypothalamic-pituitary-thyroid dysfunction induced by intensity-modulated radiotherapy (IMRT) for adult patients with nasopharyngeal carcinoma. Med Oncol 2013 Dec;30(4):710.
[27] Mortezaee K, Ahmadi A, Haghi-Aminjan H, et al. Thyroid function following breast cancer chemotherapy: A systematic review. J Cell Biochem 2019;120:12101–7.
[28] Gietka-Czernel M. The thyroid gland in postmenopausal women: physiology and diseases. Prz Menopauzalny 2017 Jun;16(2):33–7.