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Association Between Thyroid Radiation Dose and Hypothyroidism in Breast Cancer Patients Undergoing Volumetric Modulated Arc Therapy for Regional Nodal Irradiation

HYEON KANG KOH[1*], YOUNGHEE PARK[2*], TAERYOOL KOO[3], KWANG-HO CHEONG[3], ME YEON LEE[3], HAE JIN PARK[4], KYOUNG JU KIM[5], SOAH PARK[5], TAEJIN HAN[6], SEI-KWON KANG[6], BORAM HA[7], JAI-WOONG YOON[7], ME YOUNG KIM[8] and HOONSIK BAE[8]

[1]*Department of Radiation Oncology, Konkuk University School of Medicine and Konkuk University Medical Center, Seoul, Republic of Korea;*
[2]*Department of Radiation Oncology, Ewha Womans University Seoul Hospital, Ewha Womans University College of Medicine, Seoul, Republic of Korea;*
[3]*Department of Radiation Oncology, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Gyeonggi-do, Republic of Korea;*
[4]*Department of Radiation Oncology, Hanyang University College of Medicine, Seoul, Republic of Korea;*
[5]*Department of Radiation Oncology, Hallym University Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Republic of Korea;*
[6]*Department of Radiation Oncology, Kangdong Sacred Heart Hospital, Seoul, Republic of Korea;*
[7]*Department of Radiation Oncology, Hallym University Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Gyeonggi-do, Republic of Korea;*
[8]*Department of Radiation Oncology, Hallym University Chuncheon Sacred Heart Hospital, Hallym University College of Medicine, Gangwon-do, Republic of Korea*

Abstract. *Background/Aim: To investigate the association between the thyroid dysfunction and thyroid radiation dose in regional nodal irradiation (RNI) using volumetric modulated arc therapy (VMAT) for breast cancer. Patients and Methods: We reviewed medical data of 67 patients with breast cancer who underwent curative surgery followed by adjuvant radiotherapy, including RNI using VMAT, between 2018 and 2021. All patients had normal thyroid functional test results, including thyroid stimulating hormone (TSH), T3, and free-T4. We defined subclinical hypothyroidism as increased TSH with or without decreased levels of free-T4 and T3 after the completion of VMAT. We calculated dose-volume histogram parameters (DVHPs), including the mean dose and relative thyroid volume receiving at least 10, 20, 30, and 40 Gy. Results: The median follow-up time was 23.2 months. The 3-year locoregional failure-free survival, progression-free survival, and overall survival rates were 96.3%, 94.7%, and 96.2%, respectively. The mean thyroid dose was 21.4 Gy (range=11.5-29.4 Gy). Subclinical hypothyroidism was noted in 14 patients (20.9%) and the median time to the event was 4.1 months. Among the DVHPs, the relative volume receiving ≥20 Gy (V_{20Gy}) was associated with subclinical hypothyroidism. The 2-year rates of subclinical hypothyroidism were 24.8% and 59.1% in patients with V_{20Gy} ≤46.3% and >46.3%, respectively. Conclusion: A significant proportion of patients with breast cancer developed subclinical hypothyroidism after undergoing VMAT for RNI. Our findings highlight the importance of considering the thyroid as an organ at risk for VMAT planning, and suggest that V_{20Gy} could be a useful dose-volume constraint.*

*These Authors contributed equally to this study.

Correspondence to: Taeryool Koo, MD, Ph.D., Department of Radiation Oncology, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, 22, Gwanpyeong-ro 170beon-gil, Dongan-gu, Anyang-si, Gyeonggi-do, 14068, Republic of Korea. Tel: +82 313803901, Fax: +82 313803913, e-mail: kootaeryool@hallym.or.kr

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After breast-conserving surgery (BCS) or total mastectomy (TM), the commonly used radiotherapy (RT) technique for the breast and chest wall (CW) is tangential-field RT, which includes two opposing angles. Regional node irradiation (RNI) can be selectively performed in breast cancer patients with large primary tumors or extensive nodal involvement (1). To irradiate the supraclavicular lymph node (SCL), which is the main component of regional nodes, additional fields are needed, which share one-isocenter with the tangential-field (2).

The one-isocentric technique is a relatively simple manner to irradiate the breast/CW and SCL, as they are located anteriorly. However, a single anterior field would provide inadequate dose coverage for the posterior SCL region (3), which is a major site of nodal failures with geographic missing (4). Although combining anterior and posterior fields could offer improved dose distribution for SCL, it may result in unnecessary irradiation to normal tissues or excessively high doses in the RT fields (3).

Volumetric modulated arc therapy (VMAT) is one of the latest techniques of rotational Intensity-modulation RT (IMRT) that uses rotational arcs, allowing for shorter treatment times. VMAT can achieve improved dose conformity, target coverage, and normal tissue sparing (5). VMAT is actively adopted to spare organs-at-risk (OARs) for patients with breast cancer indicated for RNI (6). A reliable guideline should be established to categorize dose-volume histogram parameters (DVHPs) to minimize toxicity (7).

Hypothyroidism is a common side effect of RT in patients with head and neck cancers, as the entire thyroid gland is typically located within the irradiated field. Clinical and subclinical hypothyroidism have been reported in up to 33% and 53% of cases, respectively (8). In several studies of RT in head and neck cancers, the relative thyroid volume receiving at least 45 Gy (V_{45Gy}) or 50 Gy (V_{50Gy}) <50%, or mean thyroid dose (D_{mean}) <45-50 Gy is suggested as important cutoff of DVHPs for minimizing the risk of hypothyroidism (9-11).

However, in breast cancer patients receiving VMAT, the unilateral lobe of the thyroid is adjacent to the RNI field and the prescribed dose is typically lower than that in head and neck cancers. Therefore, dose constraints derived from studies in head and neck cancers may not be as helpful for patients with breast cancer, considering the differences in anatomical location and irradiated dose. In the present study, we evaluated the association between thyroid dysfunction and thyroid radiation dose in RNI using VMAT for breast cancer.

Patients and Methods

Between May 2018 and June 2021, a total of 89 patients with breast cancer received BCS or TM followed by VMAT for RNI at the Department of Radiation Oncology of Hallym University Sacred Heart Hospital. We excluded six patients with a history of other malignancies or those who received RT for palliative purposes. Two patients who did not have baseline thyroid functional test (TFT) results and seven patients who had results outside the normal limits were also excluded from the study after checking TFTs. In addition, seven patients who had no follow-up TFT results were excluded. Finally, we included 67 patients and reviewed the medical records including information on patient and tumor characteristics, as well as treatment details.

Baseline TFTs were routinely performed before the start of primary treatments, such as surgery or neoadjuvant systemic therapy. Follow-up TFTs were recommended at six months to one year. The study collected the dates and results of the TFTs performed after the completion of RT, including serum levels of thyroid-stimulating hormone (TSH), T3, and free-T4 (fT4). The upper limit of the normal range was 5.0 μIU/ml for TSH, and the lower limit of the normal range was 0.93 ng/dL for fT4 and 83.2 ng/dl for T3.

We defined subclinical hypothyroidism as increased TSH levels with or without decreased levels of fT4 and T3. We calculated the time interval between the end of RT and the date of TFT results showing subclinical hypothyroidism. In addition, we reviewed the follow-up sonography results to evaluate the presence of thyroid nodules or thyroiditis.

We have previously reported details regarding RT simulation and planning (12). Briefly, all patients underwent RT simulation in the supine position under free-breathing respiration. Non-enhanced computed tomography (CT) with a slice thickness of 3 mm was acquired for RT planning using a Brilliance CT Big Bore (Philips Healthcare, Cleveland, OH, USA) or a Somatom Confidence (Siemens Healthiness, Erlangen, Germany).

The target volumes were delineated by a single radiation oncologist (TK), based on atlases suggested by the Radiation Therapy Oncology Group (13) and the European Society of Radiation Oncology (14). The clinical target volumes (CTVs) included glandular tissue or the CW anterior to the ribs. For RNI, the supraclavicular, infraclavicular, and axillary lymph nodes were routinely delineated, while the internal mammary lymph nodes were selectively delineated in involved cases. A margin of 6 mm in all directions was drawn from the CTVs to obtain the planning target volumes (PTVs). The CTVs and PTVs were cropped to a thickness of 3 mm under the skin surface. In addition, we contoured the contralateral breast, heart, lungs, liver, and thyroid gland.

For VMAT, two arcs in the 210˚ range were planned. We used RayStation (RaySearch Laboratories, Stockholm, Sweden) version 4.7, 8A, 8B, and 9B by applying the Collapsed Cone algorithm for the final dose calculation. Optimization constraints for the OAR were based on the Radiation Therapy Oncology Group 1005 protocol (15). We controlled D_{mean} not to exceed 20 Gy. D_{mean} and the relative volume of the thyroid receiving at least 10 Gy (V_{10Gy}), 20 Gy (V_{20Gy}), 30 Gy (V_{30Gy}), and 40 Gy (V_{40Gy}) were calculated as DVHPs from the dose-volume histograms. Figure 1 presents the axial and coronal views of the VMAT planning.

For categorical variables, either Pearson's chi-square test or Fisher's exact test was used to determine any associations. The Cox proportional hazard model was performed to identify variables that were associated with subclinical hypothyroidism in both categorical and continuous variables. Candidate-DVHPs were divided into two groups using the maximally selected rank method. Categorized DVHPs were then tested using the Kaplan-Meier method to estimate

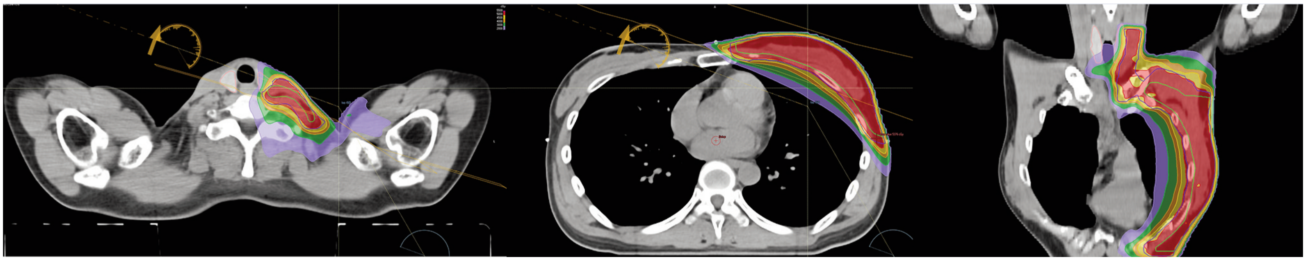

Figure 1. *The axial and coronal views of the volumetric modulated arc therapy planning.*

the probability of subclinical hypothyroidism. The curves of the probability of subclinical hypothyroidism were compared using the log-rank test. Any results with a *p*-value of <0.05 were considered statistically significant.

The statistical analysis was conducted using R 4.1.1 (R Development Core Team, Vienna, Austria). The Institutional Review Board of Hallym University Sacred Heart Hospital approved this study and waived the requirement for informed consent.

Results

Patient characteristics, systemic therapy, and RT. Details of patient and tumor characteristics are listed in Table I. The median age of the patients was 50 years (range=29-81 years). Among them, 53.7% received BCS and 46.3% underwent TM. Neoadjuvant systemic treatments were administered in 11 patients, with the majority of the regimens consisted of four cycles of doxorubicin and cyclophosphamide followed by docetaxel (AC-D) and six cycles of docetaxel and cyclophosphamide (TC). Other patients underwent adjuvant systemic treatments, with four cycles of AC-D and six cycles of docetaxel, doxorubicin and cyclophosphamide (TAC) being the most common regimens.

Of the hormone receptor-positive patients (N=41), 23 received tamoxifen and 18 received aromatase inhibitors. Nineteen patients who were human epidermal growth factor receptor 2 (HER2)-positive received HER2-targeted therapy.

The radiation dose of postmastectomy RT in 31 patients was 50 Gy in 25 fractions. After BCS, 36 patients received 50 Gy in 25 fractions for the whole breast and regional node areas, with a median booster dose of 10 Gy (range=10-14 Gy) in 5 fractions.

Treatment outcomes. The median follow-up time was 23.2 months (range=9.4-47.5 months) for all patients. Two patients died during the follow-up period, resulting in a 3-year overall survival rate of 96.2%. The 3-year progression-free survival rate was 94.7%. Two patients experienced locoregional failures, resulting in a 3-year locoregional failure-free survival rate of 96.3%. Three patients developed distant metastases, leading to a 3-year distant metastasis-free survival rate of 94.3%.

Table I. *Patient and tumor characteristics.*

Variable		N	(%)
Age	Median 50		(29-81)
Laterality	Left	37	(55.2)
	Right	30	(44.8)
Surgery	Conserving	36	(53.7)
	Mastectomy	31	(46.3)
Histology	Ductal	59	(88.1)
	Others	8	(11.9)
T	Tis	1	(1.5)
	T1	20	(29.9)
	T2	38	(56.7)
	T3	8	(11.9)
N	N0	7	(10.4)
	N1	27	(40.3)
	N2	24	(35.8)
	N3	9	(13.4)
Histologic grade	1	3	(4.5)
	2	28	(41.8)
	3	34	(50.7)
Molecular subtypes	ER/PR-positive	41	(61.2)
	HER2-Positive	19	(29.4)

ER: Estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2.

Subclinical hypothyroidism and thyroid DVHPs. The mean thyroid dose was 21.4 Gy (range=11.5-29.4 Gy) in all patients. Subclinical hypothyroidism was observed in 14 patients (20.9%). The median time to the event was 4.1 months (range=2.4-17.1 months) in patients who experienced subclinical hypothyroidism (Figure 2). The 1-year and 2-year rates of subclinical hypothyroidism were 23.6% and 38.5%, respectively. The synthetic thyroid hormone was prescribed in seven patients with clinical hypothyroidism.

Underlying diseases, including hypertension (*p*=1.000) and diabetes (*p*=0.630), were not found to be related to subclinical hypothyroidism, and systemic therapy, including hormone therapy (*p*=1.000) and trastuzumab (*p*=0.176), did not show any significant association either.

Among the continuous DVHPs, there was a trend towards an association between V_{20Gy} and subclinical hypothyroidism

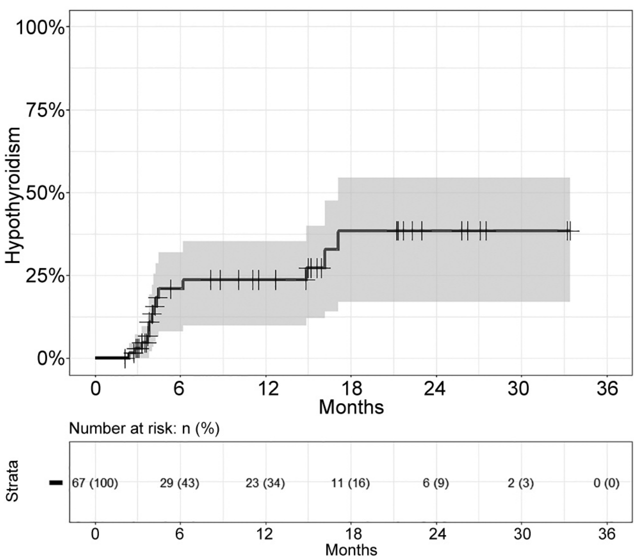

Figure 2. *The probability of subclinical hypothyroidism in all patients. The 1-year and 2-year rates of subclinical hypothyroidism were 23.6% and 38.5%, respectively.*

Table II. *Univariate analysis for continuous dose-volume histogram parameters.*

	HR	95%CI	*p*-Value
Thyroid volume (ml)	1.02	(0.920-1.13)	0.716
D_{mean} (Gy)	1.00	(1.00-1.00)	0.120
V_{10Gy} (%)	1.03	(0.990-1.06)	0.160
V_{20Gy} (%)	1.05	(0.999-1.09)	0.054
V_{30Gy} (%)	1.02	(0.976-1.08)	0.325
V_{40Gy} (%)	1.03	(0.970-1.09)	0.369

HR: Hazard ratio; CI: confidence interval; Dmean: mean thyroid dose; V_{10Gy}: the relative volume of the thyroid receiving at least 10 Gy; V_{20Gy}: the relative volume of the thyroid receiving at least 20 Gy; V_{30Gy}: the relative volume of the thyroid receiving at least 30 Gy; V_{40Gy}: the relative volume of the thyroid receiving at least 40 Gy.

(p=0.054; Table II). We categorized V_{20Gy} into two groups using the threshold of 46.3%, with 26 patients having V_{20Gy} >46.3% and 41 patients having V_{20Gy} ≤46.3%. There was a significant difference in the rate of subclinical hypothyroidism between the two groups (p=0.013). The 2-year rates of subclinical hypothyroidism were 24.8% and 59.1% in the higher and lower V_{20Gy} groups, respectively (Figure 3).

Discussion

VMAT, a rotational IMRT technique, is a valuable tool for delivering radiation dose quickly and precisely to the breast and regional nodes while sparing critical OAR (16, 17). However, in the absence of dose constraints, VMAT can scatter low doses to a relatively larger volume of OAR and administering unwanted higher doses above the prescription in OAR (18, 19).

Hypothyroidism is a common side effect observed after RT for head and neck cancers, as the thyroid gland is adjacent to the regional neck nodes which are routinely irradiated with a high dose as risky areas (8, 20). Before the era of IMRT, the incidence of hypothyroidism, defined as elevated serum TSH levels, had been reported to be about 20-50% in patients with head and neck cancer receiving curative RT (21). Although IMRT was introduced, similar incidences of hypothyroidism up to 50% have been reported (10, 22, 23), indicating the lack of generally accepted dose-volume constraints for the thyroid.

The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) is a widely used guideline for analyzing the dose-volume effects on OAR (7). However, currently there is no QUANTEC data specifically focusing on the thyroid, and there are no reliable dose thresholds established for the thyroid. Instead, studies on head and neck cancers have suggested D_{mean}, V_{45Gy}, or V_{50Gy} as potential dose-volume constraints (9-11).

However, these constraints are not clinically applicable for breast cancer patients receiving RNI in terms of prescribed doses. Therefore, establishing dose-volume thresholds for the thyroid in VMAT planning for breast cancer treatment is becoming increasingly important to avoid hypothyroidism as a side effect.

This study is the first to evaluate the association between thyroid radiation dose and hypothyroidism in patients with breast cancer receiving RNI using VMAT, contributing valuable information for optimizing treatment planning and reducing the incidence of hypothyroidism.

Kanyilmaz *et al*. (24) conducted a study analyzing DVHPs and their effects on hypothyroidism in 243 patients with breast cancer who received RT. The patients were treated with a total dose of 50 Gy to the breast, CW, and SCL, and with an additional 10 to 16 Gy to the tumor bed. The authors reported that 51 patients (21%) developed hypothyroidism. The study found that D_{mean} >21 Gy was associated with the development of hypothyroidism. However, it is important to note that this study included 80 patients who did not receive RNI, and therefore the estimation of hypothyroidism may increase if calculated in patients who received RNI. Additionally, the study used three-dimensional conformal RT (3D-CRT) as the RT technique, which may result in less conformal irradiation of the SCL region using a single anterior field or combined anterior and posterior fields.

Choi *et al*. (25) performed a study comparing the incidence rates of hypothyroidism among patients with breast cancer who received RT for the whole breast alone (n=2,468), RNI up to the subclavian artery (RNI-Lv4; n=215), and RNI up to the

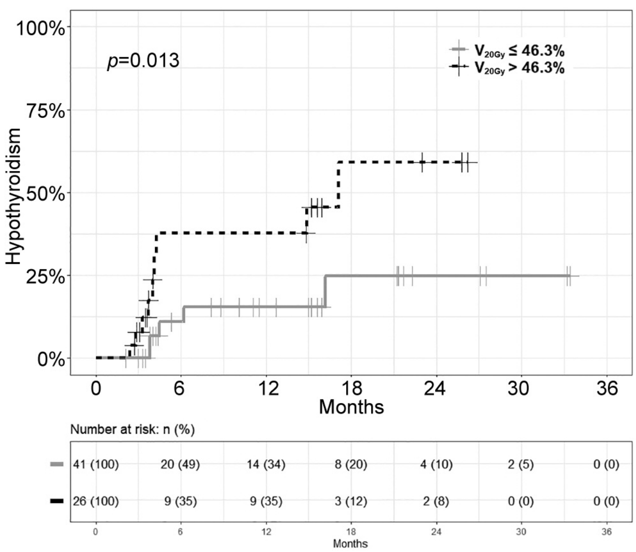

Figure 3. *The probability of subclinical hypothyroidism according to* V_{20Gy}*. The 2-year rates of subclinical hypothyroidism were 59.1% and 24.8% in the higher and lower* V_{20Gy} *groups, respectively.*

cricoid cartilage (RNI-SCL; n=1,390). Both conventional (50 Gy in 25-28 fractions) and hypofractionation (40.05-42.56 Gy in 15-16 fractions) schedules were used during the study period. During the study period, 51.6% of the patients underwent TFTs, and hypothyroidism was diagnosed in 102 patients (2.5%), with 3-year incidence rates of 0.8%, 0.9%, and 2.2% for the whole breast alone, RNI-Lv4, and RNI-SCL groups, respectively. The low proportion of the RNI-SCL group (34%) could be a cause of the low incidence rates of hypothyroidism, as other groups received significantly lower doses than the RNI-SCL group. The D_{mean} of the thyroid was 7.89 Gy for the RNI-SCL group and 0.23-1.93 Gy for the other groups in this study. Regarding the DVHP, patients with hypothyroidism had a higher D_{mean} than patients without hypothyroidism, 12.33 Gy *vs*. 2.90 Gy (p=0.017). The authors predicted that the possibility for hypothyroidism was 50% with a D_{mean} of 26.27 Gy. However, 3D-CRT as well as IMRT was used in this study, and the proportion of RT techniques was not specified.

Zhao *et al*. (26) prospectively analyzed data on hypothyroidism after hypofractionated RT in 500 patients with breast cancer. A total dose of 43.5 Gy was delivered to the breast/CW and SCL area, and 49.5 Gy to the tumor bed, simultaneously, in 15 fractions. Hypothyroidism was developed in 131 patients (26%), while 82 (16.4%) had elevated TSH at baseline. The authors suggested D_{mean} >21 Gy as a threshold value for hypothyroidism, with a 2-year incidence of 17.0% *vs*. 32.2% (p<0.001) for D_{mean} ≤21 Gy and >21 Gy, respectively. However, in this study, not all patients received RNI and several techniques were used for RNI. The SCL area was irradiated in 369 patients (74%) using 3D-CRT (n=81, 16%), IMRT (n=209, 42%), or VMAT (n=79, 16%). The incidence of hypothyroidism was higher in patients who received RNI (31.5% *vs*. 11.4% at 2 years, p<0.001). Furthermore, the study included patients with elevated TSH at baseline.

Previous studies (24-26) have proposed using D_{mean} as a DVHP for predicting hypothyroidism after RT for breast cancer. However, several important factors need to be considered when using D_{mean} as a threshold for the thyroid. First, not all patients included in the studies received RNI (24-26), so the dose to the thyroid would be significantly reduced if it is not irradiated (25), resulting in a lower incidence of hypothyroidism (26). Second, TFT was only performed when hypothyroidism-related symptoms or thyroid nodules were observed during follow-up rather than routine tests (25), which may lead to a bias in the incidence of hypothyroidism. Additionally, patients with elevated baseline TSH were included (26), which may also introduce a bias affecting the incidence of hypothyroidism. Lastly, less conformal RT techniques, such as 3D-CRT, were used for RNI rather than IMRT (24-26), which have inherent limitations in optimizing the balance between target coverage and organ sparing during RT planning.

Our study has several strengths, including more homogeneous patient characteristics and the use of consistent planning techniques. We only included patients who had normal baseline TFT results, and we performed follow-up TFT on all patients. Additionally, we used the VMAT technique to irradiate the SCL region in all patients. As a result, we suggest that V_{20Gy} could be a potential threshold to prevent hypothyroidism after RNI for breast cancer. Our threshold for the thyroid V_{20Gy} ≤46.3% is stricter compared to the D_{mean} 21-26.27 Gy suggested by other studies (24-26). A stricter threshold could contribute to reducing the possibility of hypothyroidism after RNI for breast cancer.

However, our study has some limitations that need to be addressed. First, the study design was retrospective and based on a relatively small sample size. Therefore, the cut-off value of V_{20Gy} ≤46.3% needs to be validated in larger prospective studies involving a more diverse population of patients with breast cancer undergoing RNI. Second, although hypothyroidism was assessed through laboratory tests, clinical hypothyroidism with associated symptoms was not evaluated in this study. Further research is needed to investigate the impact of hypothyroidism on patients' quality of life and to develop strategies for the prevention and management of clinical hypothyroidism after RNI.

In conclusion, our study showed that 20.9% of patients with breast cancer developed subclinical hypothyroidism after undergoing RNI with the VMAT technique. Neither underlying diseases nor systemic therapy were found to be associated with the development of hypothyroidism. We found V_{20Gy} to be a significant DVHP for predicting hypothyroidism, with a cut-off value of 46.3%. Our findings highlight the importance of considering the thyroid as an OAR in VMAT planning and suggest that V_{20Gy} could be a useful dose-volume constraint.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

TK conceptualized and designed this study. HKK, YP, and TK collected and analyzed data. MYL, KHC, HJP, KJK, SP, TH, SKK, BH, JWY, MYK, and HB participated in the interpretation of results. HKK, YP, and TK drafted the article, and TK revised the article. All Authors read and approved the article.

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