Original Article

Hypothyroidism Evaluation after Radiotherapy of Breast and Supraclavicular in Patients with Breast Cancer

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Abstract

Background: This study aims to evaluate the risk of hypothyroidism (HT) after radiotherapy (RT) of breast and supraclavicular in patients with breast cancer (BC).

Materials and Methods: In a historical cohort study, the records of all patients with BC who had been referred to the Mahdieh radiotherapy Center of Hamadan from 2017 to 2019 were reviewed. Demographic characteristics, clinical information, previous and current used treatment methods (surgery, radiotherapy, chemotherapy), number of RT sessions and doses, and HT (TSH >5 mIU/L) were extracted from the patient's documents. Data were analyzed using SPSS software version 16.

Results: Out of 304 patients referred to the Center, 266 patients were investigated. The mean TSH was 6.3 ± 7.9 ml/L (1.5 to 65.4). Approximately half of the patients were in Stage 2 of the disease. 37 (16.4%) patients were diagnosed with HT, of which 8.8% were clinical, and 7.5% were subclinical. The mean total dose of HT patients (5621.62 ± 491.67) was significantly higher than other patients (5304.76 ± 937.98). 21 patients (56.8%) in Stage 3 and 4 and 16 (43.2%) patients in Stages 1 and 2 had HT ($P = 0.006$). Spearman correlation coefficient showed that there was a significant relationship between total dose and TSH hormone ($r = 0.624$), the number of RT sessions with TSH hormone ($r = 0.237$), and total dose with T4 hormone ($r = -0.232$).

Conclusion: The findings of this study showed that the risk of HT increases significantly in patients with BC who undergo RT of breast and supraclavicular. Patients with higher stage, more radiation, and more RT sessions are at higher risk of HT.

Keywords: Breast cancer, radiotherapy, hypothyroidism, thyroid hormones

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Introduction

Radiotherapy (RT) is considered one of the most effective cancer treatment methods.[1] RT plays an important role in the management of patients with breast cancer (BC), ranging from early-stage to advanced and metastatic cases.[2]

RT uses ionizing radiation to control or kill malignant cells, which is inevitably associated with early and late effects and damage to normal tissues. These damages are the most important obstacles to administering an effective dose to the patient. On the other hand, late and acute side effects are especially the primary concern in treated patients.[1,3]

The thyroid is the largest endocrine gland of the human body and is responsible for producing free triiodothyronine (T3) and free thyroxin (T4) hormones.[4] One of the thyroid disorders is HT, which can occur due to various reasons. HT is divided

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into two categories: clinical and subclinical HT. In clinical HT, Thyroid-Stimulating Hormone (TSH) is high, and T4 is low, and in subclinical HT, TSH is high, and T4 is normal. Usually, symptoms such as fatigue, weakness, weight gain, cognitive disorders, swelling, intolerance to cold, muscle pain, anxiety, hearing loss, dry skin, etc., are detected in patients with these disorders.[3]

Laboratory tests such as T4 and TSH measurements can be used to detect HT. The TSH level should be between 0.5 and 5 mIU/L, and the T4 level should be between 8 and 12 mIU/L in normal thyroid.

The thyroid is one of the sensitive organs against ionizing radiations. During RT of the breast and supraclavicular, parts of the thyroid, which are near the radiation field, exposes and makes the possibility of abnormalities in the thyroid of BC patients, and cause disorders in its function.[3,5,6]

Few studies have examined whether patients receiving breast and/or supraclavicular RT have a higher risk of developing HT, but the results have been very different and contradictory in terms of study conditions.

It is essential to evaluate the risk of infection in these patients to determine whether regular monitoring of their thyroid function after RT is necessary and important. Therefore, this study aimed to measure the level of T4 and TSH in BC patients referred to Mahdieh Radiotherapy Center of Hamadan, Iran, from 2017 to 2019, who had been under RT of breast with or without supraclavicular after one year of treatment. Demographic and Radiotherapy specifications of patients such as the number of sessions, dose per session, and total dose, also the absorbed dose of thyroid measured by the treatment planning system, and the risk of hypothyroidism after one year of RT evaluated.

Materials and Methods

Selection criteria

In this retrospective cohort study, 304 patients with BC who were definitively diagnosed with BC between 2017 and 2019 and treated at Mahdieh Radiotherapy Center of Hamadan, Iran, were entered the examination. Patients were given written consent to participate in the study. The designed checklist has no name, and the information was published in general.

Inclusion criteria were definitive diagnosis of primary BC, and consent to participate in the study. Exclusion criteria were the patient's other thyroid diseases or thyroid abnormalities before starting RT, incomplete data recorded in the patient's medical record, history of thyroid disorders in the family, and lack of access to records related to treatment outcome. Totally, out of 304 patients, who were referred to the RT center between 2017 and 2019, 266 patients were investigated.

Demographic data acquisition

Required data include demographic variables such as age, location of the tumor, stage and grade, the extent of lymph node involvement, primary and following used treatment methods such as surgery, radiotherapy, brachytherapy, and chemotherapy extracted from the patients' documents.

Thyroid investigation

All patients were contacted and asked about thyroid function, thyroid medication, and clinical signs of HT such as fatigue, weakness, weight gain, cognitive disorders, edema, cold intolerance, muscle pain, anxiety, hearing loss, and dry skin. Also, free TSH and T4 tests were done for all patients.

Radiotherapy data

All patients were treated by ELECTA machine, with the MONACO treatment planning system. All information of RT used for each patient such as used treatment methods, the number of RT sessions, the applied dose of RT, treatment or no treatment of supraclavicular, The number of weekly sessions, total radiation dose, and dose per session were extracted from the MONACO treatment planning system. CT scans of all treated patients were available in the treatment planning system. The software could calculate the absorbed dose of intended organs. To measure the absorbed dose of thyroid, the thyroid of patients contoured in CT scans of patients and calculated by the software.

Finally, treatment outcomes (recovery, recurrence, metastasis, etc.) were extracted from patients' medical records and recorded in a checklist. In the case of patients' death, the time and cause of death were asked.

All data of each patient was written in the Questionnaire form that has shown in Figure 1.

Statistical analysis

SPSS software version 16 was used to analyze the data. A statistically significant level of less than 5% was considered. The Chi-square test (or Fisher's exact test) was used to compare the outcome of the disease in terms of nominal and rank qualitative variables. Student t-test was used to compare in terms of quantitative variables.

Results

Demographic results

In this historical cohort study, out of 304 patients included in the training, 266 patients were investigated. The mean age of the patients was 48.34 ± 5.42 years (35 to 68 years). 76 patients (33.6%) of the studied patients had a history of underlying disease (hypertension or diabetes or both). For 73 (32.30%) patients, Modified Radical Mastectomy (MRM), and for 153 (67.70%) patients, Breast Conserving Therapy (BCT) was used.

Examination of patients in terms of frequency in different stages showed that out of 226 patients, 29 (12.8%) patients were in stage 1, 114 (50.4%) patients were in stage 2, 79 (35%) patients were in stage 3, and 4 (1.8%) patients were in stage four, based on which, most of the patients were in stage 3.

Thyroid investigation results

TSH and T4 levels were measured and analyzed. Mean TSH in patients was 6.3 ± 7.9 (1.5 to 65.4), and the mean of examined T4 was 8.8 ± 6.6 mIU/L (1.5 to 100).

According to the results of Table 1, a total of 16.4% of patients had HT, of which 8.85% were clinical, and 7.52% were subclinical.

Radiotherapy results

The photon energy used in RT of all patients was 18 MeV, and the dose of all patients in each session was 200 Monitor units (MU). The mean total dose was 5356.63 ± 887.48cGy (3000-6000), and the average number of sessions was 28.20 ± 2.53. The mean absorbed dose of thyroid for patients with HT was 24.22 ± 6.45 Gy, while V40% and V50% were 27.62 ± 7.12, and 36.76 ± 9.66, respectively, but in the group without HT were 21.01 ± 4.55, 22.12 ± 6.25, and 30.27 ± 8.36, respectively.

Table 1: Characteristics of hormones examined based on thyroid status

Status	Hormone (mIU/L)	Mean	SD	Minimum	Maximum
Normal *n*=189	TSH	4.2	1.0	1.5	5
	T4	9.5	6.9	4	100.0
Clinical *n*=20	TSH	25.5	17.5	4	65.6
	T4	2.6	0.9	1.5	1.4
Subclinical *n*=17	TSH	7.3	1.9	4	10
	T4	8.4	7.5	7.5	10

SD: Standard Deviation

Questionnaire Form

1. Document Number:
2. Age (years):
3. Stage of tumor:
   1- ?☐ 2- ? A ☐ 3- ? B ☐ 4-? ☐ 5-? A☐ 6-? B☐
4. Size of the tumor
   1- T1☐ 2- T2a☐ 3- T2b☐ 4- T3☐ 5- T4☐
5. Lymph nodes involvement
   1-N0 ☐ 2- N1 ☐ 3- N2 ☐ 4- N3a☐ 5- N3b☐
6. The primary treatment methods MRM☐ BCT☐
   1-surgery ☐ 2- Radiotherapy☐ 3- Brachytherapy☐ 4-chemotherapy ☐
7. Following treatment methods
   1-surgery☐ 2- Radiotherapy☐ 3- Brachytherapy☐ 4-chemotherapy☐
8. Radiotherapy information:
   Total Dose: Dose per session: Number of sessions:
   type of radiation: Energy of radiation: Absorbed dose of Thyroid:
   Treatment of supraclavicular yes ☐ no☐
9. Treatment outcome: recovery☐ recurrence☐ metastasis☐ death☐
10. Clinical signs of HT exactly after Radiotherapy:
    Fatigue☐ weakness☐ weight gain☐ cognitive☐
    disorders edema☐ cold intolerance☐ muscle pain☐ anxiety☐
    hearing loss☐ dry skin ☐
    Mean TSH test result: Mean T4 test result:
11. Clinical signs of HT 6 months after Radiotherapy:
    Fatigue☐ weakness☐ weight gain☐ cognitive☐
    disorders edema☐ cold intolerance☐ muscle pain☐ anxiety☐
    hearing loss☐ dry skin ☐
    Mean TSH test result: Mean T4 test result:
12. Clinical signs of HT 12 months after Radiotherapy:
    Fatigue☐ weakness☐ weight gain☐ cognitive☐
    disorders edema☐ cold intolerance☐ muscle pain☐ anxiety☐
    hearing loss☐ dry skin ☐
    Mean TSH test result: Mean T4 test result:

Figure 1: Questionnaire form

Statistical analysis results

Table 2 shows the results of the Kruskal-Wallis and Mann-Whitney tests to examine the relationship between HT and the number of sessions, based on which, there was no statistically significant relationship between HT and the number of sessions. Data show that the radiation reception was higher in clinical and subclinical form, and People with HT were exposed to higher levels of radiation, although these relationships were not statistically significant. Also, there was no significant relationship between the number of RT sessions and the incidence of HT.

Table 3 shows the relationship between the presence of underlying disease, surgery, and the tumor stage on the incidence of HT. Based on the results, patients with HT had more underlying disease history with a significant difference. Also, the relationship between HT and the stage was statistically significant.

Figures 2, 3, and 4 show the correlation between total dose and TSH, the number of RT sessions and TSH, and total dose and T4, respectively. A significant direct correlation was observed between TSH, the number of RT sessions, and the total dose, which showed that when the number of sessions and total dose increase, the TSH also increases. An indirect correlation was observed between total dose and number of sessions with T4, indicating that T4 had a significant relationship with dose, but still, no significant relationship was observed between T4 and the number of RT sessions.

Discussion

In recent decades, the survival rate of patients with BCs has increased significantly.[7] Therefore it is essential that the

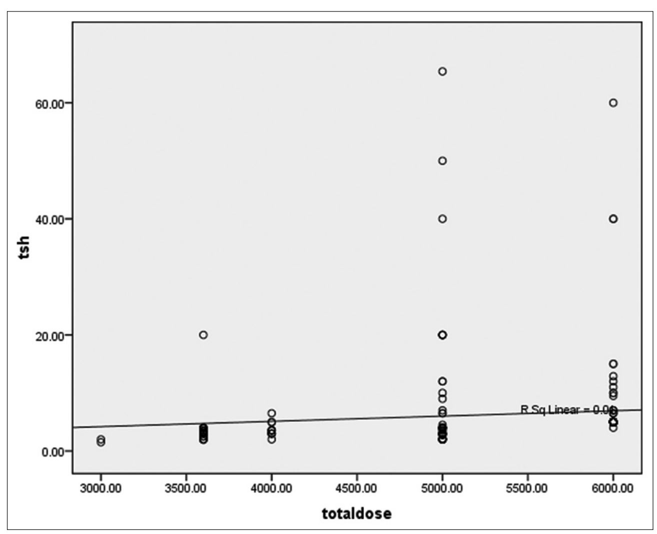

Figure 2: Correlation between total dose and TSH

Table 2: Comparison of mean radiotherapy parameters in patients with thyroid disease

Variable	Hypothyroidism Mean±SD	Normal Mean±SD	Subclinical Hypothyroidism Mean±SD	*P* (Kruskal-Wallis)
Number of Sessions (Days)	2.5±28.0	2.5±28.3	3.1±27.9	0.760
Total Dose (cGy)	651.8±5380.0	930.1±5443.9	624.2±5470.5	0.830
Variable	**CAT (TSH normal) Mean±SD**		**CAT (TSH high) Mean±SD**	***P* (Mann-Whitney)**
Total Dose (cGy)	5343.9±930.1		5421.6±632.1	0.664
Number of Session	28.3±2.5		28.0±2.7	0.478

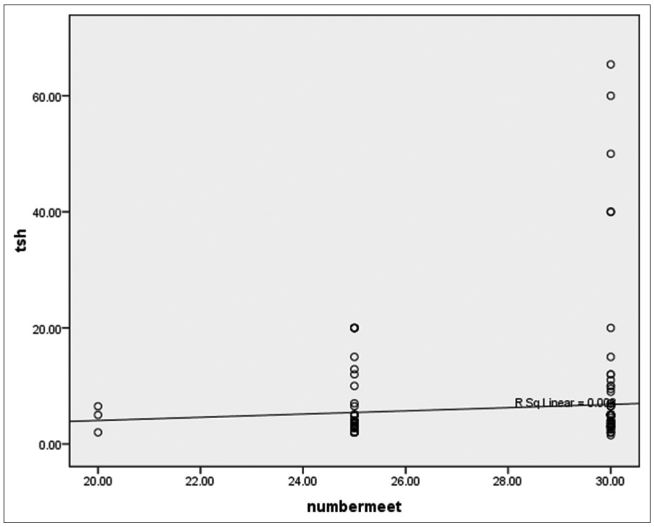

Figure 3: Correlation between the number of RT sessions and TSH

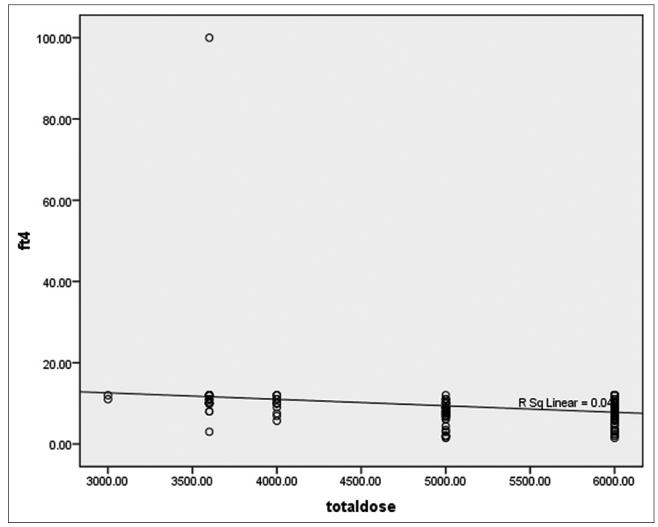

Figure 4: Correlation between total dose and T4

side effects of the treatments, such as HT following RT, be appropriately diagnosed, and treated.

In this historical cohort study, the possibility of HT after RT of breast and supraclavicular was investigated in patients with BC.

Results of the study showed that approximately 16.5% of patients developed HT, six months after RT, of which approximately half were subclinical HT. It can be concluded that HT is due to the effect of radiation absorbed by the thyroid.

As opposed to our claims, few studies asserted that HT had been shown to occur not only in patients with BC who have received RT but also happens in patients receiving systemic medications. However, these studies are associated with limitations, such as the small sample size.[3] On the other hand, two studies with a relatively large sample size (more than 1600 women) have shown that the incidence of HT in patients who have survived BC is higher than in the group who did not develop BC.[8,9] Although the effect of chemotherapy can be attributed to these abnormalities,[10] few studies have examined the effect of chemotherapy on thyroid function. Other results that bolsters the idea about the effect of RT aside from chemotherapy on thyroid function, was a relationship between HT and the number of RT sessions or the dose received by the patient. It was shown that in both clinical and subclinical HT radiation was higher. Some other studies also confirm our results. A study done by Akyurek *et al*.[11] showed that out of 28 patients with BC undergoing RT, 6 (21%) developed HT, which is lower than this article's results (16.5%). While another similar study by Kanyilmaz *et al*.[3] showed a higher rate of HT (21%) compared to the results of the present study. The probable reason for this increase is attributed to a higher amount of radiation to the supraclavicular region, differences in the selected population, the region and geography influencing the incidence of HT, and the different follow-up times of the patients. In a study done by Tunio *et al*.,[12] 40 patients with BC were divided into two groups. The first group received only breast RT, but the second group received supraclavicular RT. Results showed that 5% of patients in the first group and 15% of patients in the second group developed HT, which is consistent with the findings of the present study.[12]

Park *et al*.[13] investigated the incidence of HT after RT of about 117135 Korean BC patients with a follow-up time of 4 to 8 years. For patients treated with RT the rate of HT at 1, 5, and 8 years were 1.4, 6.2, and 9.3%, respectively, and for patients treated without RT were 1.2, 5.5, and 8.6%, respectively. They concluded that the risk of HT after RT increases after treatment up to 9 years, although they reported a lower rate

Table 3: Relationship between cancer history and type of surgery and hypothyroidism

Variable	No Hypothyroidism n=189 (TSH normal) Abundance (percent)	Hypothyroidism n=37 (TSH high) Abundance (percent)	*P* (chi2)
Underlying Disease			
yes	51 (27.0)	25 (67.6)	0.001
no	138 (74.0)	12 (32.4)	
Surgery			
MRM	56 (29.6)	17 (45.9)	0.06
BCT	133 (70.4)	20 (54.1)	
Stage			
1, 2	127 (67.2)	16 (43.2)	0.006
3, 4	62 (32.8)	21 (56.8)	

MRM: Modified Radical Mastectomy. BCT: Breast Conserving Therapy

of HT incidence than ours, which could be due to different demographic and treatment specifications.

Based on the results of such articles, it is predictable that with longer follow-up of patients, a higher rate of HT among the patients of the current study might be seen.

In another similar study Falstie-Jensen *et al*.[14] also found that radiation to the thyroid gland increased the risk of HT in BC patients. A recent study by Pillai *et al*.[15] in India confirmed that HT in BC patients was 14.86%. A Norwegian study also found that women with BC were twice as likely to develop HT.[16] One of the reasons for the difference in HT prevalence in these patients is the difference in the way HT is assessed. In some studies, the test result is considered HT, and in others, levothyroxine is prescribed and considered HT.

In the present study, it was observed that one of the factors that could increase the chances of developing HT in patients with BC was patients' received dose, which increased with growing the dose and the number of sessions. Results showed that TSH increased with the increasing number of sessions and total dose. The relationship between T4 and total dose was significant but this relation was not significant between T4 and the number of sessions.

Other studies have also shown that increasing the amount of radiation received by patients raises the risk of damage to adjacent tissues, including the thyroid.[5,17] In addition to the amount of radiation and the number of sessions, another factor in the incidence of HT after RT in BC patients is the amount of thyroid volume placed in the radiation field. Previous findings show that patients with higher thyroid volume underexpose have a higher risk of developing HT.[5] Tunio *et al*.[12] observed that the most critical risk factor for happening HT was more received radiation (V30 >50%) in patients with BC. Therefore, it is recommended that for patients with more RT sessions and doses, thyroid hormones and thyroid volume be measured before starting RT and regular follow-ups are done to ensure proper thyroid function during and after treatment. Some investigations concluded that V50 was a high-risk factor inducing hypothyroidism (HT), such that patients with a V40 > 80% had a higher risk of HT than those with V40 <80%.[18,19] mean absorbed dose of thyroid, also V40 and V50 of our results were in correlation with the results of such similar studies.[18]

The demographic results of this study showed that patients with HT had more underlying disease history with a significant difference, and the relationship between HT and the higher stage was statistically significant. However few studies have investigated the influence of such parameters on thyroid function with or without the effect of used treatment methods. In this regard, Falstie-Jensen *et al*.[14] showed that patients with the underlying disease were more likely to develop HT. Therefore, it is further added that having sufficient information about the lifestyle, smoking status, obesity, and physical activity of patients as other factors that may affect the incidence of HT can be accurate conclusions about the effect of radiation on the incidence of thyroid disorders.

It seems that to investigate and control the HT in treated BC patients the effect of underlying disease, as well as chemotherapy, should be investigated more wildly, to determine the exact role of RT on thyroid function.

Conclusions

In total, it is essential to pay attention to its late complications, including HT. Therefore, screening and follow-up of these patients would be beneficial to detect and treat HT as soon as possible.

Declarations

Ethics approval

This study was performed based on the dissertation approved by Hamadan University of Medical Sciences with the number 99010571 with the ethics code of IR.UMSHA.REC.1398.793 approved on 21 Dec 2019.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

References

1. Pesch AM, Pierce LJ, Speers CW. Modulating the radiation response for improved outcomes in breast cancer. JCO Precis Oncol 2021;5:PO.20.00297.
2. Shah C, Al-Hilli Z, Vicini F. Advances in breast cancer radiotherapy: Implications for current and future practice. JCO Oncol Pract 2021;17:697-706.
3. Kanyilmaz G, Aktan M, Koc M, Demir H, Demir LS. Radiation-induced hypothyroidism in patients with breast cancer: A retrospective analysis of 243 cases. Med Dosim 2017;42:190-6.
4. Voutsadakis IA. The TSH/Thyroid hormones axis and breast cancer. J Clin Med 2022;11:687.
5. Ilic L, Haidinger G, Simon J, Hackl M, Schernhammer E, Papantoniou K. Trends in female breast cancer incidence, mortality, and survival in Austria, with focus on age, stage, and birth cohorts (1983-2017). Sci Rep 2022;12:7048.
6. Mirsadraei M, Seilanian Toosi M, Mohebbi S, Khalili-Hezarjaribi H. Evaluating dose to thyroid gland in women with breast cancer during radiotherapy with different radiation energies at supraclavicular fossa region. J Radiother Pract 2018;17:373-6.
7. Munoz D, Near AM, van Ravesteyn NT, Lee SJ, Schechter CB, Alagoz O, *et al*. Effects of screening and systemic adjuvant therapy on ER-specific US breast cancer mortality. J Natl Cancer Inst 2014;106:dju289.
8. Khan NF, Mant D, Carpenter L, Forman D, Rose PW. Long-term health outcomes in a British cohort of breast, colorectal and prostate cancer survivors: A database study. Br J Cancer 2011;105(Suppl 1):S29-37.
9. Smith GL, Smith BD, Giordano SH, Shih YC, Woodward WA, Strom EA, *et al*. Risk of hypothyroidism in older breast cancer patients treated with radiation. Cancer 2008;112:1371-9.
10. De Groot S, Janssen LG, Charehbili A, Dijkgraaf EM, Smit VT, Kessels LW, *et al*. Thyroid function alters during neoadjuvant chemotherapy in breast cancer patients: Results from the NEOZOTAC trial (BOOG 2010-01). Breast Cancer Res Treat 2015;149:461-6.
11. Akyurek S, Babalıoğlu İ, Köse K, Gokce S. Thyroid dysfunction following supraclavicular irradiation in the management of carcinoma of the breast. Int J Hematol Oncol 2014;2:139-144.
12. Tunio MA, Al Asiri M, Bayoumi Y, Stanciu LG, Al Johani N, Al Saeed EF. Is thyroid gland an organ at risk in breast cancer patients treated with locoregional radiotherapy? Results of a pilot study. J Cancer Res Ther 2015;11:684-9.
13. Park J, Kim C, Ki Y, Kim W, Nam J, Kim D, Park D, *et al*. Incidence of hypothyroidism after treatment for breast cancer: A Korean population-based study. PLoS One 2022;17:e0269893.
14. Falstie-Jensen AM, Esen BÖ, Kjærsgaard A, Lorenzen EL, Jensen JD, Reinertsen KV, *et al*. Incidence of hypothyroidism after treatment for breast cancer-a Danish matched cohort study. Breast Cancer Res 2020;22:106.
15. Pillai US, Kayal S, Cyriac S, Nisha Y, Dharanipragada K, Kamalanathan SK, *et al*. Late effects of breast cancer treatment and outcome after corrective interventions. Asian Pac J Cancer Prev 2019;20:2673-9.
16. Reinertsen KV, Cvancarova M, Wist E, Bjoro T, Dahl AA, Danielsen T, *et al*. Thyroid function in women after multimodal treatment for breast cancer stage II/III: Comparison with controls from a population sample. Int J Radiat Oncol Biol Physics 2009;75:764-70.
17. Akgun Z, Atasoy BM, Ozen Z, Yavuz D, Gulluoglu B, Sengoz M, *et al*. V30 as a predictor for radiation-induced hypothyroidism: A dosimetric analysis in patients who received radiotherapy to the neck. Radiat Oncol 2014;9:104.
18. Wei S, Tao N, Ouyang S, Liu T, Guo Q, Tao F, *et al*. Dosimetric comparisons of intensity-modulated radiation therapy and three-dimensional conformal radiation therapy for left-sided breast cancer after radical surgery. Prec Radiat Oncol 2019;3:80-6.
19. McGowan DR, Pratt BE, Hinton PJ, Peet DJ, Crawley MT. Iodine-131 monitoring in sewage plant outflow. J Radiol Prot 2014;34:1-14.