# The Impact of Supraclavicular Irradiation on Thyroid Function and Size in Postoperative Breast Cancer Patients by Comparing 2D versus 3D-CRT

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**Abstract: Background:** Post mastectomy supraclavicular (SC) nodal irradiation is recommended in addition to whole breast or chest wall irradiation for the adjuvant treatment of patients with locally advanced breast cancer, where it improved locoregional control and overall survival.[(1)]Thyroid dysfunction is usually underestimated in patients with breast cancer who had SC irradiation (RT). **Aim:** To determine the radiation impact on the thyroid function and size in patients with breast cancer receiving radiotherapy (RT) to the SC nodes by comparing 2 techniques of irradiation, in relation to total dose and irradiated volume of the thyroid gland. **Results:** Twenty patients were included in this study (age range from 25 to 70 years, mean age (45±2.81),all had breast cancer and treated surgically with mastectomy or breast conserving surgery followed by adjuvant irradiation to SC lymph nodes and breast or chest wall. Patients were divided into 2 groups. Group A (10 patients) received irradiation through 2D technique were compared to group B (10 patients) who received irradiation through 3D-CRT technique, for a total dose of 50Gy/25 fractions. The size of the thyroid gland was measured, and thyroid function tests, including serum thyroid stimulating hormone, free thyroxine, free triiodothyronine, were analyzed before RT and 3, 6, 9, 12, 18 and 24 months after RT. **Conclusion**: The 3D conformal radiotherapy technique of SC nodal irradiation is superior to 2D conventional radiotherapy technique in case of breast cancer patients regarding the impact on thyroid function.

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## Introduction

Radiotherapy has frequently been used as adjuvant therapy following mastectomy for patients with locally advanced breast cancer (LABC) or as palliative irradiation for local recurrence (LR) in the supraclavicular (SC) nodes. The routine post operative irradiation of breast cancer patients involves irradiation of the breast or chest wall, ipsilateral SC and internal mammary nodes with 50 Gy /25 fractions.[(2)] It is well known that, thyroid dysfunction is a late effect after radiotherapy to the neck region in patients with head and neck cancers.[(3)] This dysfunction results from including the whole thyroid gland within the high dose level of radiation fields, while in breast cancer patients receiving irradiation to the SC field, only a part of the thyroid gland may be included in the irradiation field.

Prior studies showed that SC nodal irradiation in patients with breast cancer was associated with a higher incidence of hypothyroidism (HT)[(4-7)]and reduction in the size of the gland. Similar studies in patients with head and neck cancer emphasized on long term routine thyroid function tests as part of the follow-up after radiation therapy. [(8 & 9)]

However, the most common type of radiation induced thyroid dysfunction was subclinical HT followed by clinical HT. [(10)]

HT is defined biochemically as a normal free serum thyroxine hormone (fT4) level in the presence of an elevated thyroid stimulating hormone (TSH), with no clinical symptoms, whereas clinical HT is characterized by a high serum TSH level and low fT4 level, in which patient may present with clinical symptoms such as weight gain, fatigue, slow mentation and cold intolerance.(10)Hypothyroidism after RT develops at a median interval of 1.4-1.8 years, but it has been reported even 3 months or 20 years after RT. [(11,12,13)]

With conventional fractionation, the critical absorbed dose for radiation induced HT has been estimated to vary between 26 to 40 Gy. [(14,15)]In the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) report, dose-volume data for HT were not included.[(16)]Some authors suggest that the percentage of thyroid volume receiving ≥30 Gy (V30) is a possible predictor of HT. [(17,18)]Till now no clear threshold dose or dose-volume factors for the development of radiation induced HT has been determined.

The purpose of this study was to evaluate the effects of SC lymph node irradiation upon the thyroid functions and size, of post operative breast cancer patients.

**Patients and Methods**

Twenty patients with breast cancer were enrolled in this study, and treated in Clinical Oncology & Nuclear Medicine Department, Faculty of Medicine, Zagazig University Hospitals, in the period from January 2012 to February 2014.

**Exclusion criteria:-**

1-Patients with primary thyroid disease.
2-Previous thyroid surgery.
3-Previous radiotherapy included hypothalamic pituitary axis or lower neck nodes.

**Pretreatment evaluation:**

Medical history, complete physical examination complete blood count **,**liver and kidney functions tests**,** thyroid function tests**,** chest x-ray**,** ultrasound to pelvi-abdominal region and thyroid gland, ,bone scan, and echocardiography. Measurements of the dimensions of the normal thyroid gland ultrasonography before irradiation involves measuring the distance between the medial border of the common carotid artery and the lateral border of the trachea.

Patients were divided into 2 groups (A & B) each consisted of 10 patients. All patients underwent surgery (mastectomy or breast conserving surgery), followed by adjuvant radiotherapy to the whole breast or chest wall and SC lymph nodes to a total dose of 50 Gy/25 fractions,(2Gy/fraction/day, 5 fractions per week), using conventional radiotherapy technique 2D for group A, and 3D-CRT technique for group B. Patients were positioned supine, with both arms extended above the head and immobilized using a breast board. The irradiation delivered, using CT planning system (Linac, Electa,151204, Presice Plan Release (2.12) machine with photon beams energy 6 and 15 MV.

In both techniques, a portion of thyroid gland is often included in the treatment fields.

**Radiotherapy**

For 2D technique, determination of the SC nodal target volume based on clinical and radiologic landmarks to determine the borders of the single anterior-oblique field as follow:, superior border placed 1-cm superior to skin profile, inferior border at the lower border of the ipsilateral clavicular head, medial border at the lateral aspect of the vertebral pedicles, and lateral border at the junction of medial 2/3 and lateral 1/3 of the clavicle. The gantry angled 15 degrees away from the spinal cord. A half-beam block was used. The dose to the SC nodes was prescribed to a depth of 1.5 cm. While for 3D-CRT, opposed anterior and posterior-oblique fields were used. Also, angled off-cord with adjustments of beam energies (6 and 15 MV), weightings, and utilization of wedges techniques may be used. They were manually optimized to cover the PTV within 95%-107% of the prescribed dose as per International Commission on Radiation Units and Measurements 50 (ICRU 50) prescribing guidelines. [19] Thyroid gland dosimetric measures were evaluated including**,** mean dose (Gy), maximum dose (Gy), and V5, V20, V30, V40, and V50 (percentage of thyroid volume receiving ≥5 Gy, ≥20 Gy, ≥30 Gy, ≥40 Gy, and ≥50 Gy, respectively).

**Treatment evaluation and follow up:**

Patients were evaluated after finishing radiotherapy by thyroid function tests, including serum thyroid stimulating hormone (TSH), free triiodothyronine(fT3),and free thyroxine (fT4). A diagnosis of Hypothyroidism is based on TSH value greater than the maximum value of laboratory range and/or fT3 and/or fT4 values lower than the minimum value of laboratory range, regardless of whether any symptom was present. Also, we evaluated changes in the dimensions of the thyroid gland size annually. The size of the thyroid gland was measured ultrasonographically, and the measurements were compared pre and post irradiation. Thyroid gland size was calculated from its greatest diameter in the axial plane from the lateral border of the trachea to the medial border of common carotid artery. The thyroid functions and size, were analyzed every 6 months in the first $2^{nd}$ years, then annually thereafter.

**Statistical analysis**

Statistical analysis was performed with a Statistical Package for the Social Scienses for Windows (SPSS). All values are expressed as means and Standard deviations (SD). Pretreatment TSH, fT4 and fT3 values were compared with the corresponding values obtained after treatment by Wilcoxon test, and paired t test with repeated measures. Categorical data were analyzed by using Chi-square and Fisher-Exact test. In univariate analysis, P values < 0.05 were considered significant.

**Results**

All 20 patients completed the study; the median age was 45 years (range 25-70 years). Patients characteristics are shown in table (1).HT was detected in 4 patients (20%) in both groups, of whom, 3 patients (15%) had subclinical HT (2 patients in group A, and 1 patient in group B), while 1 patient (5%) had clinical HT in group A.

However, HT developed after 4-18 months post irradiation of SC nodes (median time 8 months).

Table (2) showed the mean (±SD) for each thyroid function test before irradiation and every 6 months post irradiation for 2 years. The difference in TSH level between baseline and 6 months was statistically significant (P<0.05). There was a significant decrease in the mean fT4 levels after the 9th month on completion of RT compared with baseline levels (p= 0.05). The fT3 level was steady throughout the 2 years of follow-up.

Mean thyroid doses were 35 Gy (22-50 Gy) in group A, and 25 Gy(19-43) in group B. The mean thyroid volumes were 33 cc (14-60 cc) in group A, and 29 cc (13-59cc) in group B. The maximum thyroid doses were 50 Gy, and 43Gy in groups A, and B, respectively. Median values of the percentage of thyroid gland volume V5, V20, V30, V40, andV50, receiving from 5-50 Gy were 69%, 62%, 58%, 54%, and 50%in group A, while these values were 65%, 57%, 55%, 49% and 45%, in group B. It was found that V20 (OR= 10, 95% CI= 1.15-86.88, p= 0.05), V30 (OR= 10, 95% CI=1.15-86.88, p= 0.05) and V40 (OR= 21, 95% CI= 1.61-273.34), (p= 0.04). Themean thyroid doses that cause HT are≥36 Gy and ≥34 Gy in groups A, and B respectively. However, mean volume of thyroid was not associated with development of HT (p= 0.14).

**Table (1):Patient Characteristics**

| | Group (A) | Group (B) |
|---|---|---|
| **Sex** | 10 | 10 |
| **Age (years)** | | |
| Median | 45 | 43 |
| Range | (25-70) | (27-69) |
| **Stage** | | |
| IIIa | 3 | 4 |
| IIIb | 7 | 6 |
| **Nodal status (+ve)** | | |
| 4 | 6 | 5 |
| ≥5 | 4 | 5 |
| **Surgery** | | |
| MRM | 7 | 6 |
| BCS | 3 | 4 |
| **Radiotherapy** | | |
| 2D | 10 | - |
| 3D-CRT | - | 10 |
| **Chemotherapy** | | |
| FAC | 2 | 3 |
| 4AC→4T | 8 | 7 |
| **Hormonal therapy** | | |
| Tamoxifen | 6 | 7 |
| Letrozole | 4 | 3 |

**Abbreviations:** MRM=modified radical mastectomy, BCS= breast-conserving surgery, FAC= 5-fluouracil, adriamyicin, cyclophosphamide, AC= adriamycin, cyclophosphamide, T=Taxotere (paclitaxel).

**Table (2) The mean (±SD) for TSH and fT4 values pre and post irradiation, 6,12,18 and 24 months, in all patients.**

| | Baseline | 6 months | 12 months | 18 months | 24 months |
|---|---|---|---|---|---|
| **TSH** | 1.8±1.47 | 3.8±7.42 | 3.29±3.49 | 5.6±6.92 | 4.23±3.72 |
| **fT4** | 10.82±1.76 | 10.3±4.07 | 9.45±1.76 | 8.76±2.09 | 9.58±2.01 |

After 1 year follow up, there were 9 patients (45%)had increase in the size of the thyroid gland, 8 patients(40%) had decrease in the size of the gland, while 3 patients (15%) showed no change in the size compared to preirradiation size of the thyroid gland.

After 2 years follow up, 13 patients (65%) showed a reduction in the size of thyroid gland. The reduction occurred in 7 patients (70 %) in group A, versus 6 patients (60%) in group B, without statistically significant differences. Of them, 9 patients showed a reduction of ≥3mm. Four patients (20%) showed an increase in the size,(2 in group A, and 2 in group B) and 3 patients (15%) (1 in group A, and 2 in group B) showed no changes in the size of the thyroid gland after SC irradiation in patients with locally advanced breast cancer.

Therefore, the majority of breast cancer patients after SC irradiation, showed a reduction in the size of thyroid gland, as shown in table (3).

**Table (3): The size of thyroid gland after 1 and 2 years follow up post sc irradiation**

| | **1-year follow-up** | | **2-year follow-up** | |
|---|---|---|---|---|
| | No. of patients | % | No. of patients | % |
| **Increase** | 9 | 45 | 4 | 20 |
| **Decrease** | 8 | 40 | 13 | 65 |
| **No change** | 3 | 15 | 3 | 15 |

**Table(4):Comparison between both groups as regard size of thyroid gland and HT after 2 years follow-up**

| | **Group A (2D)** | | **Group B (3D)** | |
|---|---|---|---|---|
| | No. of patients | % | No. of patients | % |
| **Size of thyroid gland in 2 year follow-up** | | | | |
| Increased | 2 | 20 | 2 | 20 |
| Decreased | 7 | 70 | 6 | 60 |
| No change | 1 | 10 | 2 | 20 |
| **Hypothyroidism** | 3 | 30 | 1 | 10 |
| Subclinical | 2 | 20 | 1 | 10 |
| Clinical | 1 | 10 | - | - |

**Table (5): Dosimetric measures of thyroid gland in both groups**

| | **Group A(2D)** | **Group B(3D)** |
|---|---|---|
| **Mean thyroid dose(Gy)** | 35 | 25 |
| **Maximum thyroid dose(Gy)** | 50 | 43 |
| **Median thyroid volume receiving %** | | |
| ≥5 Gy | 69 | 65 |
| 20 Gy | 62 | 57 |
| 30 Gy | 58 | 55 |
| 40 Gy | 54 | 49 |
| 50 Gy | 50 | 45 |
| **Mean thyroid dose that cause HT (Gy)** | 36 | 34 |
| **Mean thyroid volume (cc)** | 33 | 29 |
| Range | (14-60) | (13-59) |

**Discussion**

Several reports upon thyroid function after the exposure of a large portion of the thyroid gland during irradiation of the chest wall and SC nodes in postoperative breast cancer patients, have been published. These authors, reported radiation-induced HT in 40% of patients after 4-5 years.[(20)]

Some reports revealed HT after irradiation in postoperative breast cancer patients. [(21-23)]

**Samaan et al**, evaluated thyroid dysfunction after radiotherapy and noted 43.6% incidence of HT after a period of 1-26 years in irradiated breast cancer patients[(24)].

In our study, the overall incidence of HT was 20% in patients with breast cancer who had SC irradiation, these results were similar to the results of other studies which reported that the incidence of HT varies 6% and 21% [(22,23,25)]. The median time to the development of HT was 8 months (range, 4-18 months). **Bruning et al**. concluded that HT was significantly more frequent in patients with breast cancer, who had received radiotherapy to SC field to non-irradiated breast cancer patients[(23)].

In this study TSH, fT4 and fT3 were monitored prior to RT and every 6 months for 2 years after irradiation. We found V20-40 (thyroid volume receiving over 20-40 Gy) and mean thyroid dose ≥34 Gy had a significant impact on development of HT. Similarly, Cella et al. reported the V30 was the only independent predictive factor for HT.[(17)]

**Yoden et al.** also used DVHs to evaluate the correlation between percentage of the thyroid gland volume absorbing a defined dose and thyroid function. They found that V10, V20 and V30 have significant impact of serum TSH to be possible risk factor for HT.[(18)]

Other studies revealed that this dose-volume parameters, including percentage of thyroid gland volume absorbing V10-60,were not associated with HT.[(26,27)]

However, recent studies published a normal tissue complication probability (NTCP) model based on mean thyroid dose and thyroid volume for radiation induced HT in patients with head and neck cancer. According to these studies, thyroid gland volume and mean thyroid dose were the only independent risk factors for HT.[6,28]

In our study, the mean TSH levels were stable through the 1st6 months, then increase to significant higher levels than baseline levels. While mean fT4 levels were stable throughout the 1st 6 months, then decreased slightly at 6, 12, 18, and 24 months. Many trials had been conducted to define the time to development of HT [5,13,29-31]. The time to development of HT ranged from 16 to 20 months. [11,13]. Other studies reported that, this time ranged from 3 months to 20 years.[(11,12,32]. In our study, the median time to the development of HT was 8 months (range, 4-18 months).

Many reports similarly indicate that radiation-induced changes in thyroid function initially manifested within 3 to 6 months after radiotherapy.[20,32,33]

**Mercado et al**. described the incidence of HT was 48% at 5 years and 67% at 8 years.[13]In our trial there was a correlation between follow-up period and incidence of HT, where it was16% at 12 months and 23% at 24 months.

**McHardy-Young**[34] and **Glatstein et al**,[35] found a slight reduction in the thyroid gland reserve without distinct HT after radiotherapy of tumors of head and neck.

## Conclusion

HT, and reduction in the size of thyroid gland were observed in postoperative breast cancer patients following SC irradiation. The majority of changes in thyroid function recorded after 6 months post irradiation. We found mean thyroid dose ≥ 34 Gy and V20-40 had a significant impact on the development of HT. 3D conformal radiotherapy technique of SC nodal irradiation is superior to 2D conventional radiotherapy technique in postoperative breast cancer patients regarding the impact on thyroid function.so close follow-up is warranted to avoid thyroid complications.

Further studies including larger number of patients, needed to confirm our results and to determine the relation between thyroid gland size and function in postoperative breast cancer patients.

Also, the size of the thyroid gland was found to be considerably reduced after 2 years of irradiation.

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