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Thyroid function post supraclavicular lymph node irradiation in patients with breast cancer

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ABSTRACT

INTRODUCTION: In East Africa, the estimated incidence of breast cancer is second only to cervical cancer. Supraclavicular irradiation post-modified mastectomy is crucial to breast cancer management, as it improves local control and overall survival. However, this is associated with adverse effects, including hypothyroidism (HT), which is usually under-reported. This study aim was to evaluate radiation-induced thyroid gland functional changes following treatment of supraclavicular lymph nodes in breast cancer patients.

METHODS: This was a prospective descriptive study of patients with breast cancer from May 1, 2017, to May 30, 2018. Pre and post-treatment TSH, fT4, and fT3 values were compared using a Wilcoxon signed-rank test.

RESULTS: A total of 42 patients were recruited for this study, with a mean age of 55.7 years (32-71). The mean baseline TSH level was 2.90 (±6.37), with a normal range of 0.27-4.2 uIU/mL. The mean T4 and T3 level were 15.77 (±4.83), with normal ranges of 10.16-22 pmol/l for T4, and 3.46 (±6.22), with a normal range of 1.06-3.3 nmol/l for T3. A Wilcoxon signed-rank test indicated that there was a statistically significant increase in mean TSH levels over baseline when measured at three, six-, and nine-months post-treatment, with p-values of 0.0047, 0.0002, and <0.0001, respectively. In total, four patients (10%) had thyroid function tests outside the normal ranges. Zero patients developed clinical HT during the time period studied.

CONCLUSION: As hypothesized, supraclavicular radiation led to subclinical HT, but the incidence of clinical HT over time remains unknown.

Keywords: Breast Cancer, Radiotherapy, Radiation Toxicity, Low-Income Populations, Hypothyroidism

INTRODUCTION

Radiotherapy has frequently been used as adjuvant therapy following mastectomy for patients with locally advanced breast cancer (LABC) or as palliative therapy for local recurrence (LR) and supraclavicular (SC) lymph nodes (SCLN) involvement [1].

The routine post-operative irradiation for locally advanced breast cancer patients involves

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irradiation of the breast or chest wall, ipsilateral SC, and internal mammary nodes using 50 Grays Gy/25 fractions [2].

Many studies have been conducted regarding the effects of radiation therapy on thyroid function in patients with head and neck cancers [3]. In these cases, the whole thyroid gland is often in the radiation field [3]. Prior studies also showed that SC nodal irradiation in patients with breast cancer was associated with a higher incidence of hypothyroidism (HT) and a reduction in gland size [1].

It is important to note that supraclavicular irradiation is directed in the same axial plane as the thyroid gland. However, little is actually known about how much radiation the gland receives. Studies show that doses between 26 Gy to 40 Gy have been associated with hypothyroidism [4,5]. In the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) report, dose-volume data for the thyroid gland and resulting HT was not included [6]. However, some authors suggest that the percentage of thyroid volume receiving ≥30 Gy (V30) is a possible predictor of HT [7,8]. Until now, no clear threshold dose or dose-volume factors for developing radiation-induced HT have been determined.
Radiotherapy (RT) induced hypothyroidism has been reported at different periods after radiotherapy treatment involving the thyroid gland, ranging from three months to 20 years [9,10,11]. As a result, some clinical protocols recommend routine follow-up tests of thyroid function in patients who are irradiated to the neck [12,13]. The few studies that did report on the effect of radiation therapy on the thyroid gland used advanced technology with three-dimensional conformal RT (3D-CRT), which is able to delineate the thyroid gland as an organ at risk (OAR) and this helps with knowing how much radiation doses that go to the thyroid gland. It was found that in 44% of the 122 breast cancer patients who underwent 3D-CRT treatment, the thyroid gland was exposed to considerable doses of RT, which put these patients at risk of developing thyroid abnormalities [14].
This study aimed to identify the magnitude of hypothyroidism following RT to the supraclavicular lymph node region using 2D planning and a cobalt 60 machine.

METHODS

Patients and Setting: A total of 42 patients with a diagnosis of breast cancer treated with local radiation, including the supraclavicular lymph node region, were enrolled and followed up for a period of nine months. Other inclusion criteria were a good performance status (Eastern Cooperative Oncology Group (ECOG) performance scale of 0-2) and patients treated with curative intent. The study period ran from May 2017 to June 2018.
The study was conducted at the Ocean Road Cancer Institute, one of Tanzania's oldest health institutions, founded in 1895.The center offers cancer prevention and screening programs, radiation therapy, medical oncology, and palliative care.

Radiotherapy: Cobalt machine and 2D planning technique were used in treating this cohort of patients. Clinical and radiological landmark borders were determined for the supraclavicular lymph node radiation field. The borders of this single anterior, slightly oblique field were the following: a skin flash of approximately 0.5-1.5 cm superiorly, the inferior border at the lower border of the ipsilateral clavicular head, the medial border at the lateral midline, and the lateral border at the junction of the medial 2/3 and lateral 1/3 of the clavicle (Figure 1 and 2). The gantry was angled 15 degrees away from the spinal cord. A half-beam block was used to match the field tangent to the chest wall. The dose to the SC nodes was prescribed to a depth of 3 cm.

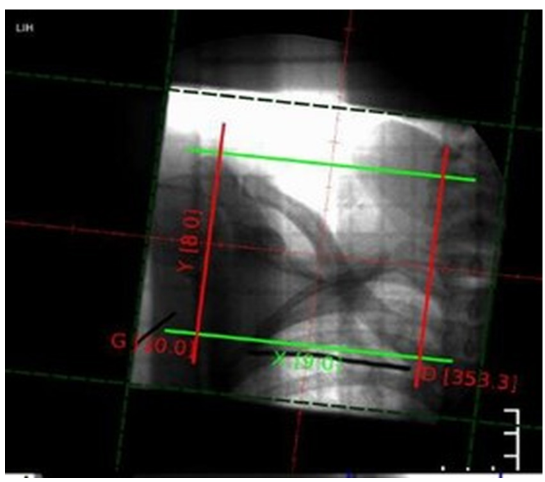

Figure 1: Digital Reconstructed image of supraclavicular field

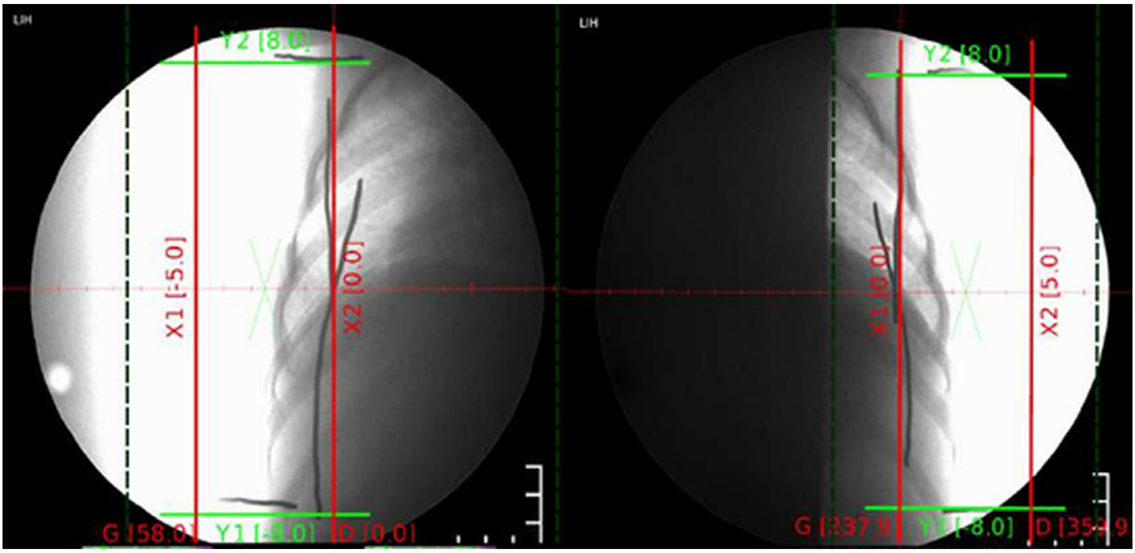

Figure 2: Digital reconstructed image of the chest wall/tangential field

The chest wall and SCLN regions each received 50 Gy of radiation given in twenty-five fractions. The dose and radiation fields used were conducted in accordance with the Ocean Road Cancer Institute protocol and clinical radiation oncology protocol given by Gunderson et al. [15,16].

Thyroid function tests and patient follow-up: Patients were evaluated prior to radiation therapy by thyroid function tests, including serum thyroid stimulating hormone (TSH), free triiodothyronine (fT3), and free thyroxine (fT4). The same tests were done every three months post-treatment for a period of nine months, and two laboratories were used to control for the validity of the results. The reference ranges for TSH, T3, and T4 were 0.27-4.2 uIU/mL, 1.06-3.3 nmol/l, and 10.16-22 pmol/l, respectively. Given how impractical it was to assess patients for HT symptoms, a diagnosis of HT was solely based on thyroid hormones. Subclinical HT was defined as TSH values above normal values provided by the laboratory, and/or fT3 and/or fT4 values lower than the minimum value provided by the laboratory, while clinical HT is evidenced by HT signs and symptoms.
Written informed consent was sought and obtained from patients before participating. The MUHAS institutional review board approved this study.

Data analysis: Data was entered into excel and analyzed using STATA version 13. Pre-treatment TSH, fT4, and fT3 values were compared with the corresponding values obtained after treatment by the Wilcoxon test and paired t-test with repeated measures. Categorical data were analyzed by using Chi-square and Fisher-Exact tests. In univariate analysis, p-values <0.05 are considered significant. Variables like histology, hormonal status, disease stage, field size, total dose, and thyroid functions at different periods were applied in the multivariate analysis. The authors have no relevant financial interests to disclose.

RESULTS

The study's patient characteristics are summarized in Table 1. The mean age of patients was 55.7 years (32-71). Regarding tumor stage and biology, 90% of the patients fell under locally advanced classification, 38 % were Stage II, 36% were Stage III, 69% were Estrogen Receptor positive (ER+), and only 24% were human epidermal growth factor receptor 2(HER2). Twenty-two patients (52%) had left breast cancer. Regarding additional prognostic factors that warranted radiation following modified radical mastectomy, 21% had lymphovascular invasion (LVI), 7% had perineural invasion, 36% had positive margins, and 67% had positive lymph nodes. The mean (SD) of harvested lymph nodes was 6.75 (±4.3).

Table 2 shows different treatment modalities. 98% of patients underwent modified radical mastectomies, and only one patient got breast-conserving surgery. Most of the combination chemotherapies administered were anthracycline-

Table 1: Patients Characteristics

Variables	All patients (n=42)
Age	
Mean	55.7
Range	32-71
Histology	
IDC	42
Stage	
I	1
II	38
III	36
Disease site	
Left	22
Right	20
Grade	
1	3
2	16
3	15
Missing	8
Hormonal Status	
ER+/PR+	17
ER+/PR-	12
ER-/PR-	13
HER2+	10
HER2-	32
Prognostic factors	
LVI	9
PNI	3
Positive margins	15
Positive LNs	28
Mean Harvested LNs (SD)	6.75 (±4.3)

IDC: Invasive ductal carcinoma, LVI: Lymph vascular Invasion, PNI: Perineural invasion; LN: Lymph nodes

based, 55% being a TAC (Taxane, Adriamycin, Cyclophosphamide) regimen, and 29% being an AC-T regimen (Adriamycin, Cyclophosphamide, and Taxane). These chemotherapy regimens were given in 76% of patients as adjuvant therapy, following a pattern of surgery - adjuvant chemotherapy - radiation. Among the ER+ patients, 53% received tamoxifen, and 21% received anastrozole. Two patients who were ER+ got neither tamoxifen nor anastrozole.

All recruited patients got 50 Gy of radiation therapy in 25 fractions, with 2 Gy per fraction administered to the chest and supraclavicular lymph node region. Among the 42 patients recruited for this study, only 38 patients completed the nine months of follow-up post-treatment. One patient developed lung and bone metastasis after six months of follow-up, resulting in their dismissal from the study. Three patients (7%) did not come for their last follow-up visit; however, the analysis included all 42 patients. Of the 42 patients, four patients (10%) had thyroid function test values outside normal ranges and

Table 2: Treatment Modalities

Variables	All patients (n=42)
Surgery	
Mastectomy	41
Others	1
Chemotherapy regimen*	
CAF	4
AC	12
CMF	2
TC	1
TAC	23
Endocrine therapy	
Tamoxifen	18
Anastrozole	9
Radiotherapy site	
Breast/Chest wall	42
Supraclavicular	42

**Chemo regimen C: Cyclophosphamide, A: Adriamycin, F: Fluorouracil, T: Taxane*

were considered to have subclinical HT, as detected biochemically at the ninth month of follow-up. Zero of the patients developed clinical HT in the time period studied.

The mean baseline TSH level was 2.90 (±6.37) uIU/mL, while that for T4 and T3 were 15.77 (±4.83) nmol/l and 3.46 (±6.22) pmol/l, respectively (Table 3).

A Wilcoxon signed ranks test indicated that the rises in mean TSH level between the baseline and those measured at three, six-, and nine months post-treatment was statistically significant with p-values of 0.0047, 0.0002, and <0.0001, respectively. The difference between mean baseline levels for T3 and T4 was not statistically significant at the third month of follow-up (p=0.1225 and p=0.3203, respectively). However, they were statistically significant when measured at the sixth month (T3, p=0.0028; T4, p=0.0018) and ninth month (T3, p=0.009; T4, p=0.0001) follow-up, respectively (Table 4).

DISCUSSION

Breast cancer, especially locally advanced disease, is treated using a multimodality therapy approach, with surgery, chemotherapy, targeted therapy, and radiation being all used in an attempt to cure the patient. For patients who have pathological adverse features such as perineural invasion (PNI), lymphovascular invasion (LVI), Positive lymph nodes, and Positive margins that increase the risk of local recurrence, there is a benefit in radiation therapy treatment to improve local control and overall survival [17]. Despite the benefits of radiation therapy in treating breast cancer, there

Table 3: The mean (±SD) for each thyroid function test before and after completion of RT

	Baseline	3 months	6 months	9 months
TSH [uIU/mL]	2.90 (±6.37)	3.24 (±6.29)	3.63 (±631)	3.96 (±6.68)
T3[nmol/l]	3.46 (±6.22)	3.34 (±6.25)	3.19 (±6.34)	3.19 (±6.6)
T4 [pmol/l]	15.77 (±4.83)	15.77 (±4.68)	14.79 (±4.83)	13.61 (±5.42)

TSH: Thyroid Stimulating Hormone; T4: Thyroxine; T3: Triiodothyronine

Table 4: A Wilcoxon signed ranks test comparison with p values

	Baseline Values	Mean Values(±SD)	Z	P-value
TSH 3 mo vs. Baseline	2.90 (±6.37)	3.24 (±6.29)	2.826	0.0047
TSH 6 mo vs. Baseline		3.63 (±631)	3.706	0.0002
TSH 9 mo vs. Baseline		3.96 (±6.68)	4.081	<0.0001
T3 3 mo vs. Baseline	3.46 (±6.22)	3.34 (±6.25)	-1.544	0.1225
T3 6 mo vs. Baseline		3.19 (±6.34)	-2.987	0.0028
T3 9 mo vs. Baseline		3.19 (±6.6)	-2.61	0.009
T4 3 mo vs. Baseline	15.77 (±4.83)	15.77 (±4.68)	-0.994	0.3202
T4 6 mo vs. Baseline		14.79 (±4.83)	-3.129	0.0018
T4 9 mo vs. Baseline		13.61 (±5.42)	-3.93	0.0001

TSH: Thyroid Stimulating Hormone, T4: Thyroxine, T3: Triiodothyronine

are adverse effects associated with this treatment modality. These side effects arise from other normal structures that are within the radiation field and thus are affected by treatment, despite not being the primary target. For breast cancer, examples of organs at risk include the heart, lungs, chest bones, and thyroid [18]. Current advances in treatment modalities and imaging technologies have made it possible to minimize the size of radiation fields by constricting the field to only the targeted tumor. These technologies, including three-dimensional radiotherapy (3D-RT), Intensity-modulated radiation therapy (IMRT), Image Guided Radiotherapy (IGRT), and brachytherapy, are expensive assets, and only a handful of African countries have them [19]. As of March 2020, 33 African countries with radiotherapy machines were distributed in a total of 253 centers. Twenty-six countries and 120 RT centers are found in Sub Saharan Africa region, and 51% of centers are found in South Africa [19]. Evidently, most African countries use Cobalt machines with 2D planning, which lack the conformity given by advanced modalities, and 2D planning is associated with high radiation toxicities. Radiation-induced hypothyroidism (RIHT) is a well-known side effect seen in patients after long-term radiation therapy for head and neck cancers [20,21,22]. However, most of these studies evaluated patients undergoing radiation treatment using 3D-CRT. The only article that compared 3D versus 2D planning consisted of only 20 patients (10 treated by 2D and 10 by 3D) and showed that 20% of those treated with 2D planning had subclinical hypothyroidism, compared to only 10% in those who were treated with 3D [1]. Some studies have reported HT in 40% of patients after four to five years of treatment [23,24]. In our study, the incidence of HT after nine months of follow-up was 10%, and this is similar to other studies that reported an incidence of 6-21% [1,5,9,20,21].

Both the QUANTEC and Emami et al. articles, which report on tolerance doses of different organs at risk of radiation, did not report anything regarding the thyroid gland [6,24,25]. Some studies, especially regarding the treatment of head and neck cancer and Hodgkin's lymphoma, have reported different tolerance doses depending on the volume of thyroid irradiated. Cella et al. considered it to be a significant risk factor for the development of HT in Hodgkin's lymphoma if more than 62.5% of the total volume of the thyroid gland was exposed to 30 Gy (V30 >62.5%). [7]. Tunio et al. considered V30>50% as a risk for HT in patients with breast cancer when treated with radiation to the SC area [26]. Some studies have tried to evaluate the effects of different volumes using a dose volume histogram (DVH) of thyroid gland treated. These reveal that on the treatment plan evaluation, V10, V20, and V30 were associated with high levels of TSH and might be considered risk factors for HT [8]. Cella et al. confirmed that V30 can be considered a sole predictor of HT [7].

No study has shown a correlation of irradiated volume using 2D planning, as it is impossible to know how much volume is irradiated using fluoroscopy. This is shown in Figure 1 A & B, where the supraclavicular radiation field's medial border may include one-third of the thyroid gland.

In previous studies of similar nature, biochemical hypothyroidism was found in patients who had received anthracycline-based chemotherapy and tamoxifen [24,27]. This correlates with our study, where all four patients who had subclinical HT had also received anthracycline-based chemotherapy (3 TAC, 1 AC-T), and two of them had received tamoxifen. Combining these two medications with radiation to the supraclavicular region increases the chances of HT, as Reinertsen et al. show [26]. According to our research, there is no study in Africa evaluating HT in breast cancer patients post-treatment, making this the first article to report the status of thyroid function post supraclavicular lymph node region radiation in resource-limited settings.

There are several limitations to this study. First, similar studies have been conducted that include measurements of the thyroid gland size. Studies like the one done by Chyan et al. displayed that the incidence of HT in patients with oropharyngeal cancer treated with RT to the neck was decreased when the initial thyroid volume was 8 cm^3 or more [28]. In our study, measuring the thyroid was not possible, as only one radiologist on-site could perform this test, and it was not consistently available. Thyroid iodine uptake testing was not possible during the study period, as there was a frequent shortage of radiopharmaceutical materials.
Secondly, this study consisted of small sample size and a short follow-up period. The short follow-up was due to limited funds, as it is difficult to follow up with patients for a long period of time in a large country like Tanzania with only one radiotherapy center. However, this study included more patients compared to similar studies on this topic. A period of nine months post-radiation therapy is a short follow-up period to make substantial inferences and conclusions.

CONCLUSION

The incidence of HT in our cohort was 10%, which is comparable to other studies. Here, subclinical HT was detected at the 9-month follow-up, where there was a gradual statistically significant increase of TSH and a decrease of both T3 and T4. Given that this was a short follow-up, there is a chance that if these patients were followed over time, a larger percentage would develop subclinical and clinical HT. However, this remains unknown. Therefore, because of the risk of developing HT in these patients, thyroid function should be evaluated during follow-up visits after radiation therapy of the supraclavicular lymph node region. Further prospective studies should be carried out to confirm the incidence of sub-clinical and clinical hypothyroidism in this patient population within Tanzania.

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